Catalytic Asymmetric Reactions Employing Chiral Cations

Roly Armstrong

A dissertation presented in partial fulfilment of the requirements for the award of the degree of

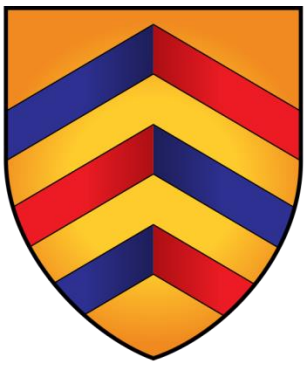
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Dedication

I would like to dedicate this thesis to my grandfather, Professor Frank Stone, on the occasion of his 90th birthday.

Declaration

This dissertation describes work carried out in the Chemistry Research Laboratory at the University of Oxford between October 2011 and September 2015. The dissertation is a result of my own work and includes nothing that is the outcome of work done in collaboration except where specifically indicated in the text.

Roly Armstrong

Acknowledgments

I would like to begin by thanking Martin for his supervision and enthusiasm throughout my time in Oxford. Nobody else could look at a bilogarithmic plot of catalyst concentration *vs* reaction rate that looks like a pointed hat and draw a more positive conclusion. I have learned so much from you over the past four years and I will remain eternally grateful that you suggested to Emily that I should bleed her radiators.

Many thanks also to John Brown for patiently explaining and discussing PTC kinetics.

I would also particularly like to thank Craigo, Pete and Jamie, who have always been there to give advice and guidance throughout my DPhil.

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Most importantly, I'd like to thank Emily for everything over the past four years – It's been fantastic. Don't worry, I won't get too slushy here as you've already told me it would make you queasy, but I really do appreciate how patiently you've tolerated me writing up. I promise that I will devote the rest of my days to washing up Tupperwares in Bristol.

Finally I'd like to thank the late Mr Rochester. Teacher, mentor and friend.



Mr Rochester: Nov 2011- Jan 2015

Abbreviations

18-c-6	18-crown-6
2D	two-dimensional
Å	Ångstroms
Ac	acetyl
acac	acetoacetate
AIBN	azobisisobutyronitrile
aq.	aqueous
Ar	a generic aromatic system
Bn	benzyl
Boc	*tert*-butoxycarbonyl
brsm	based on recovered starting material
Bu	butyl
^{o}C	degrees celsius
cat.	catalytic/catalyst
CBS	Corey-Bakshi-Shibata
COSY	^{1}H-^{1}H correlation spectroscopy
d	days
dba	dibenzylideneacetone
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEPT	distortionless enhancement by polarization transfer
$\Delta G^{\ddagger}$	Gibbs free energy of activation
DCE	1,2-dichloroethane
DME	1,2-dimethoxyethane
DMEDA	*N*,*N'*-dimethylethylenediamine
DMF	*N*,*N*-dimethylformamide
DMFDMA	*N*,*N*-dimethylformamide dimethyl acetal
DMSO	dimethylsulfoxide
dppf	1,1'-bis(diphenylphosphino)ferrocene
d.r.	diastereomeric ratio
E	a generic electrophile
EDG	electron donating group
e.e.	enantiomeric excess

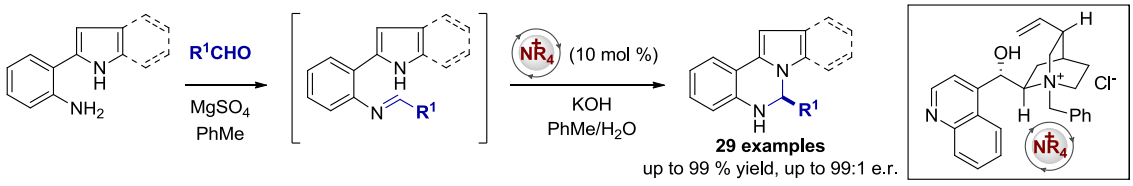
EI	electron-impact ionization
e.r.	enantiomeric ratio
ESI	electrospray ionization
Et	ethyl
eq.	equivalents
EWG	electron withdrawing group
EXSY	exchange spectroscopy
FI	field ionization
FTIR	Fourier-transform infra-red spectroscopy
g	grams
h	hours
HMBC	heteronuclear multiple-bond correlation spectroscopy
HOMO	highest occupied molecular orbital
HPLC	high-performance liquid chromatography
HRMS	high-resolution mass spectrometry
HSQC	heteronuclear single-quantum correlation spectroscopy
Hz	Hertz
i	*iso*
k	a generic rate constant
k_{ent}	rate constant of enantiomerization
k_{rac}	rate constant of racemization
L	litres
LDA	lithium diisopropylamide
LUMO	lowest occupied molecular orbital
µ	micro-
m	milli-
M	moles per litre
*m*CPBA	*meta*-chloroperoxybenzoic acid
Me	methyl
MIDA	*N*-methyliminodiacetic acetate
min	minutes
mol	moles
MOM	chloromethyl methyl ether
m.p.	melting point

MS	molecular sieves
MS	mass spectrometry
n	normal
NBP	*N*-bromophthalimide
NBS	*N*-bromosuccinimide
NMP	*N*-methyl-2-pyrrolidone
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser effect
Nu	a generic nucleophile
Ph	phenyl
ppm	parts per million
Pr	propyl
PTC	phase-transfer catalysed
PyBox	bis(oxazolinyl)pyridine
quat.	quaternary
quant.	quantitative
R	a generic substituent
r.t.	room temperature
S	selectivity factor
s	solid
SM	starting material
SPhos	2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl
t	*tertiary*
T	temperature
t	time
$t_{1/2}^{ent}$	half-life for enantiomerization
$t_{1/2}^{rac}$	half-life for racemization
Tf	trifluoromethanesulfonate
TFP	tri(2-furyl)phosphine
THF	tetrahydrofuran
TLC	thin-layer chromatography
TMS	trimethylsilyl
vs	*versus*
w/w %	weight percent

Abstract

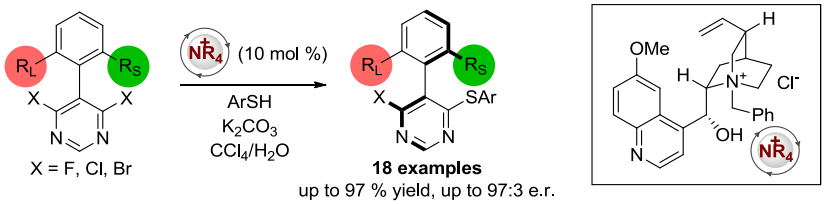
This thesis describes two new phase-transfer catalysed processes, in which asymmetry is mediated *via* ion-pairing with a chiral cation.

Cation-directed enantioselective *N*-functionalization of pyrroles: A number of catalytic asymmetric *C*2-functionalization reactions of pyrroles have been disclosed, but in contrast, enantioselective *N*-functionalization remains a comparatively unexplored area. We were able to develop a one pot procedure for imine formation followed by asymmetric *N*-cyclization (Scheme I). We have probed the steric and electronic requirements of this system, synthesising a total of 29 examples. The utility of the cyclized products was explored by carrying out several derivatization processes.



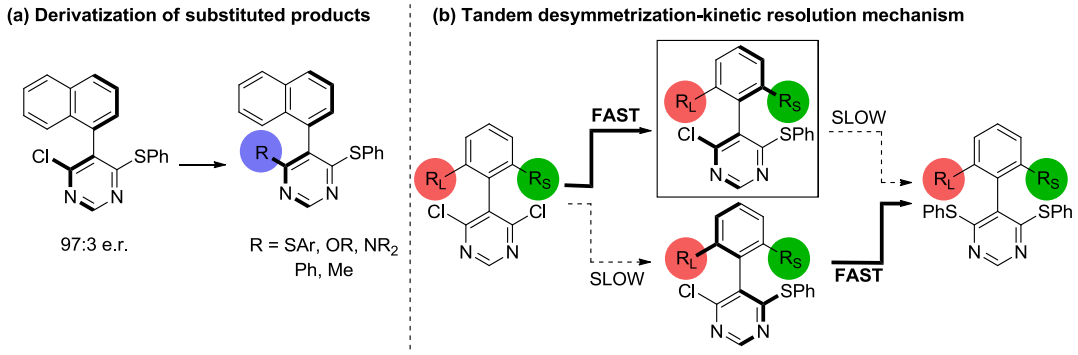
Scheme I. Cation-directed enantioselective *N*-functionalization of pyrroles

Synthesis of axially chiral biaryls *via* a cation-directed S_NAr reaction: Despite the significant synthetic utility of the S_NAr reaction, few asymmetric variants have been disclosed, and to the best of our knowledge no such reactions targeting axially chiral materials have been reported. We have developed a cation-directed desymmetrization of prochiral dihalopyrimidine electrophiles (Scheme II). 18 examples have been synthesised within this series in up to 97:3 e.r.



Scheme II. An atropselective cation-directed S_NAr reaction

A range of derivatization reactions have been carried out (Scheme IIIa). We have demonstrated that the high enantioselectivity observed in this reaction is a result of a tandem desymmetrization-kinetic resolution mechanism (Scheme IIIb). Investigation into the kinetics of the desymmetrization has suggested an extractive mechanism to be operative and implies that catalyst aggregation may play an important role in this reaction.



Scheme III. Derivatization of desymmetrized products and tandem desymmetrization-kinetic resolution mechanism

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1. Introduction

1.1. Chiral counter-ion directed catalysis

Catalytic asymmetric synthesis represents an extremely powerful method for the construction of chiral molecules.[1] Fundamentally, any such reaction relies upon the ability of a chiral additive to mediate the enantioselective transformation of achiral material to a chiral product. In order to achieve efficient transfer of chiral information, a transition state must be formed in which a highly specific interaction between substrate and catalyst is present. Frequently, this has been accomplished by relying upon strong, directional catalyst-substrate interactions such as a covalent or dative bond (for example enamine[2], Lewis base[3] and Lewis acid[4] catalysis) or through a network of hydrogen bonds.[5] An alternative approach relies upon the tight ion-pair formed between an anion and a chiral counter-ion in a non-polar organic solvent. This method is termed chiral counter-ion directed catalysis, and has been demonstrated to be an efficient strategy to mediate asymmetry within reactions involving charged intermediates (Figure 1.1).[6]

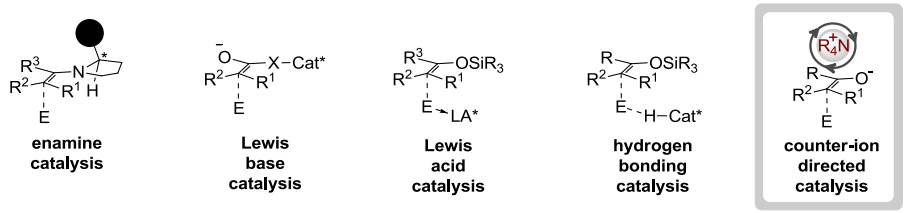
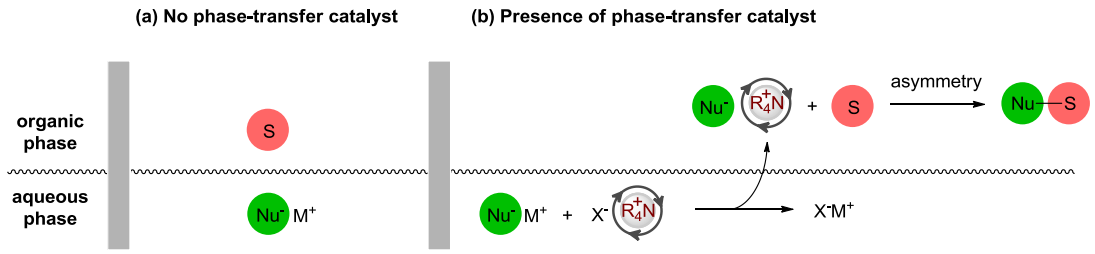


Figure 1.1. General strategies for catalytic asymmetric functionalization – enolate alkylation

1.2. Asymmetric phase-transfer catalysis

Asymmetric phase-transfer catalysis (PTC) represents an attractive method to achieve chiral counter-ion directed catalysis.[7] This approach relies on the ability of a lipophilic ionic catalyst to accelerate reactions in which the reagents are separated between two immiscible phases. In a biphasic mixture of a non-polar organic solvent and water, a neutral organic substrate (S) will almost exclusively occupy the organic phase, whereas a charged nucleophilic reaction

partner (Nu^-) will be preferentially dissolved in the aqueous phase.* These reagents are therefore physically separated and cannot react with each other (Scheme 1.1a). Upon addition of a phase-transfer catalyst, for example a lipophilic quaternary ammonium salt (NR_4^+), counter-ion metathesis takes place leading to the key species $NR_4^+ \bullet Nu^-$ (Scheme 1.1b). This ion pair is now sufficiently lipophilic to dissolve in the organic phase where reaction with the neutral partner can take place. As discussed above, if a chiral cation is employed, then the tight nature of the ion pair $NR_4^+ \bullet Nu^-$ can enable induction of asymmetry in the subsequent reaction.

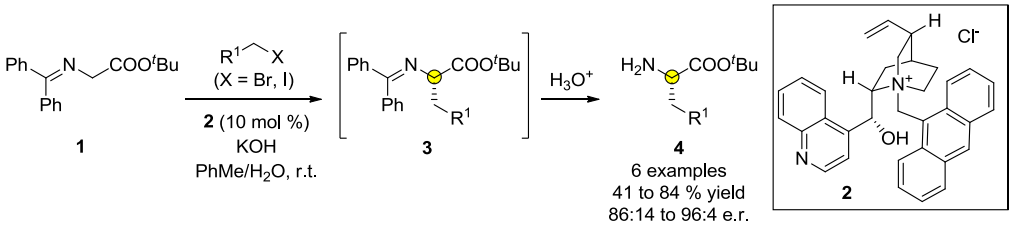


Scheme 1.1. Basic principles of phase-transfer catalysis

1.3. Interfacial phase-transfer catalysed reactions

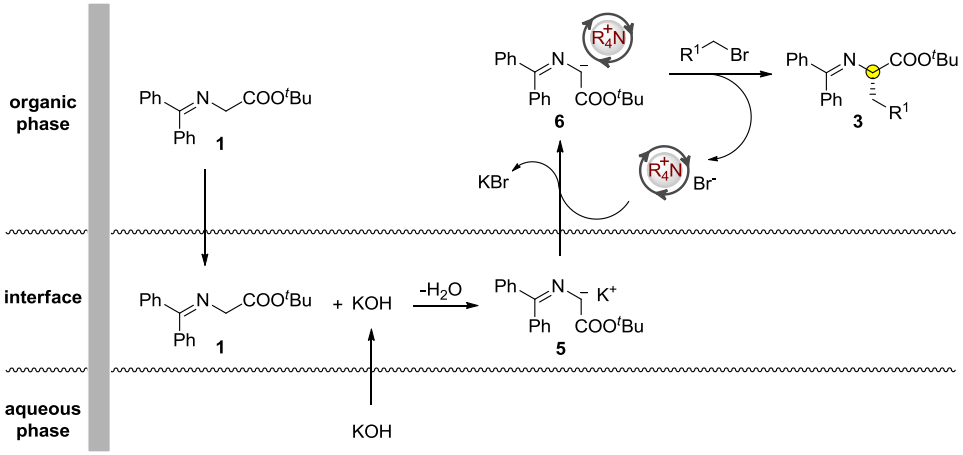
A large number of asymmetric phase-transfer catalysed reactions have been reported in the literature, with a particular focus on the asymmetric functionalization of compounds containing acidic methylene groups. As a representative example, Lygo *et al.* have demonstrated that Schiff base **1** (derived from glycine) can undergo highly enantioselective alkylation in the presence of a chiral cinchona derived phase-transfer catalyst **2**.[8] Following deprotection with aqueous acid, highly enantioenriched non-natural α-amino acids were obtained (Scheme 1.2).

* It is also possible to utilize cationic reagents along with an anionic phase-transfer catalyst. This discussion is focussed only on the role of cationic phase-transfer catalysts.



Scheme 1.2. Asymmetric phase-transfer alkylation of glycine imine Schiff base **1**

It is thought that this reaction (along with other phase-transfer catalysed processes involving alkylation of acidic methylene derivatives) proceeds *via* an interfacial mechanism.[7b] This mechanistic picture was first proposed by Mąkosza and invokes the formation of an interfacial region between the aqueous and organic phases (Scheme 1.3).[9] The acidic substrate (for example Schiff base **1**) is deprotonated by the hydroxide base at the interface forming potassium enolate **5**. Counter-ion exchange then takes place with the phase-transfer catalyst which results in the formation of a lipophilic ion pair **6**, which moves deep into the organic phase and undergoes alkylation, resulting in **3**.



Scheme 1.3. A representative example of an interfacial phase-transfer process

Generally speaking, the interfacial mechanism is operative for reactions involving substrates with relatively low aqueous solubility and with acidity in the approximate range $16 < pK_a < 23$.[10]

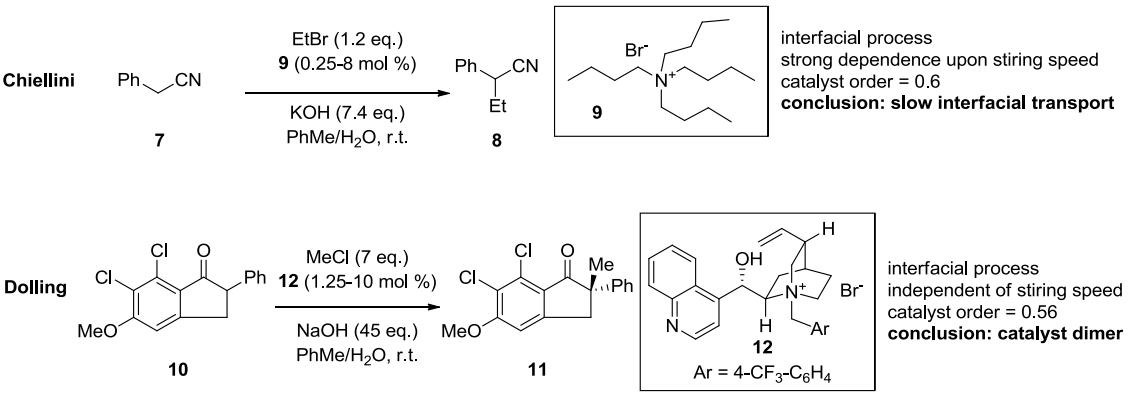
Experimentally, an interfacial phase-transfer catalysed process is usually characterised by the following features:

i. Dependence of the rate of reaction upon stirring speed (in most, but not all cases).

ii. Complex kinetic order with respect to starting materials.

iii. Fractional kinetic order with respect to phase-transfer catalyst.

For the interfacial phase-transfer catalysed ethylation of benzyl cyanide **7**, Chiellini *et al.* have determined the catalyst order to be 0.6.[11] Taken in conjunction with the observation of a strong dependence of the reaction rate upon stirring speed, this fractional kinetic order was interpreted to suggest that interfacial transport occurs at a rate which competes with that of alkylation (Scheme 1.4). However, in the methylation of indanone derivative **10**, Dolling *et al.* have rationalized a catalyst order of 0.56 to be a consequence of aggregation of the phase-transfer catalyst **12** in solution.[12] In this case, slow interfacial transport was ruled out by the observation that the reaction rate is independent of stirring speed.

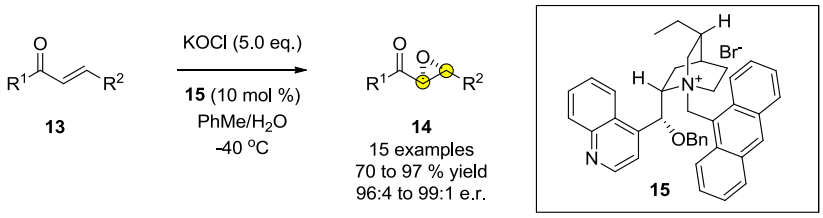


Scheme 1.4. Proposed explanations for fractional kinetic orders with respect to phase-transfer catalyst

1.4. Extractive phase-transfer catalysed reactions

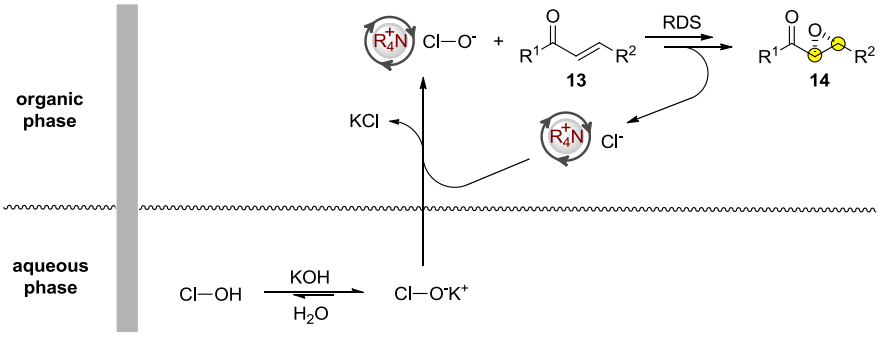
Although comparatively scarce, some asymmetric phase-transfer reactions have been carried out in which a non-prostereogenic anion undergoes attack upon a prochiral electrophile. Often the nucleophiles employed in such reactions are rather acidic, and as a consequence, a

different phase-transfer mechanism is operative, which Starks has coined the extractive mechanism.[13] One particularly important example in this category is the phase-transfer mediated Weitz-Scheffer epoxidation.[7b] For example, Corey *et al*. have demonstrated that *trans*-chalcone derivatives **13** can undergo highly enantioselective epoxidation with potassium hypochlorite in the presence of phase-transfer catalyst **15**.[14]



Scheme 1.5. Phase-transfer catalysed asymmetric epoxidation of chalcone

It is proposed that in an extractive mechanism, the nucleophile (in this case hypochlorite) is fully ionized and dissolved in the aqueous phase (Scheme 1.6). The phase-transfer catalyst - which is partially soluble in the aqueous layer - undergoes a counter-ion exchange with potassium hypochlorite, resulting in a lipophilic tetraalkylammonium hypochlorite. This species is extracted into the organic phase where it undergoes rate determining reaction with **13**.



Scheme 1.6. A representative example of an extractive phase-transfer mechanism

In general, extractive mechanisms are observed with water soluble, acidic nucleophiles ($pK_a < 16$).[10]

The experimental observations made for these reactions differ to those for an interfacial mechanism in the following ways:

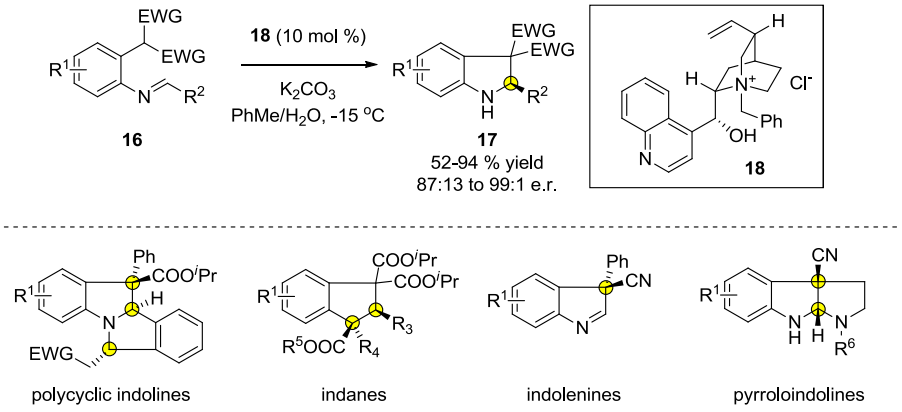
i. Independence of the rate of reaction upon stirring speed (above a key threshold required for mass transfer).

ii. Simple first or second order kinetics with respect to starting materials.

iii. First order dependence upon the phase-transfer catalyst.

1.5. Phase-transfer catalysis in the Smith group

Extensive work in our group has been directed towards the cation-directed synthesis of small chiral molecules. It has been demonstrated that under asymmetric phase-transfer conditions, acidic substrates bearing a tethered electrophile such as **16** can be induced to undergo cyclization, leading to chiral indolines **17** in high yields and with excellent enantioselectivities (Scheme 1.7).[15] The reactive nitrogen of the cyclized products could be engaged in further reactions leading to polycyclic anilines.[16] This asymmetric cyclization methodology has also been extended to the synthesis of indanes,[17] indolenines[18] and pyrroloindolines[19] with excellent levels of stereocontrol in all cases.



Scheme 1.7. Enantioselective synthesis of indolines and expansion to other scaffolds

Mechanistic work carried out in the group has suggested that these cyclization reactions proceed *via* an interfacial mechanism.

1.6. This Work

This thesis describes research involving two reaction manifolds in which asymmetry is mediated by a chiral phase-transfer catalyst. An enantioselective method for *N*-functionalization of pyrroles is discussed in Chapter 2. A phase-transfer catalysed approach to axial chirality *via* a cation-directed S_NAr reaction is discussed in Chapters 3, 4 and 5. It is interesting to note that the former likely represents an interfacial phase-transfer process, whist the latter operates under an extractive regime.

2. N-Functionalization of Pyrroles

2.1. Pyrroles

Pyrroles were first isolated and characterised in 1858 by the high temperature distillation of bone oil.[20-21] Since then, this simple five membered ring structure has been demonstrated to be a privileged motif, present within array of natural products (for example porphyrins such as haem B) and pharmaceutical agents including the blockbuster drug atorvastatin (Figure 2.1).[22-23] Pyrroles are also frequently encountered in important synthetic applications, for example within an asymmetric halide binding catalyst disclosed by Jacobsen *et al.*[24]

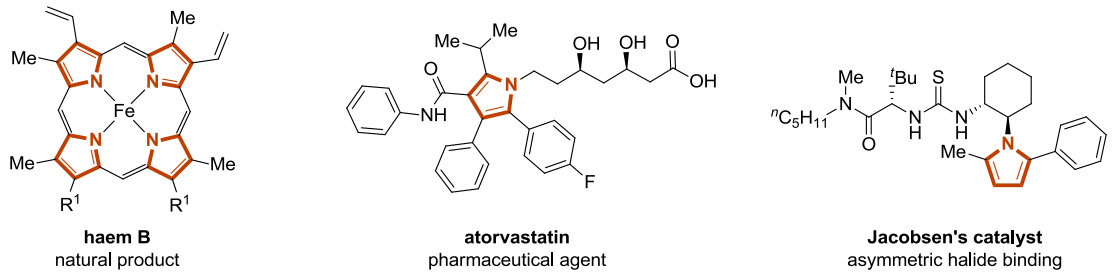


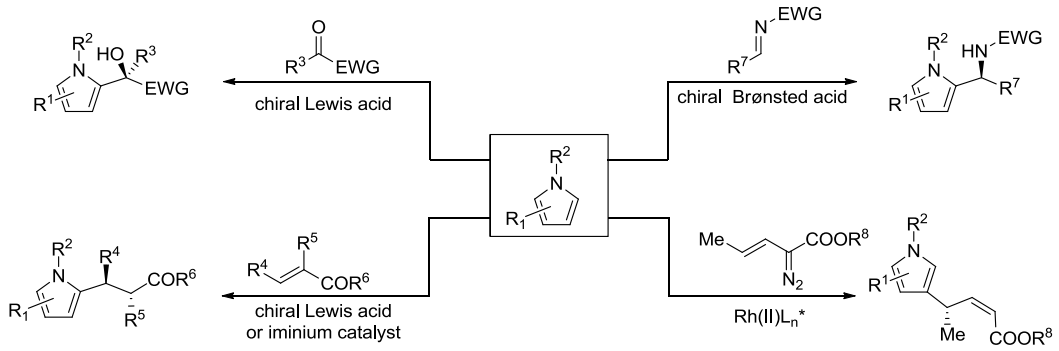
Figure 2.1. Selected examples of pyrrole derivatives

In many important compounds, including two of the three shown above, the pyrrole is substituted with a chiral group. Accordingly, significant effort has been devoted to establishing methods for the catalytic asymmetric functionalization of pyrroles.[25] These approaches can be broadly divided into two categories: firstly, those involving reaction at one of the carbon positions (usually at the *C*2-position); secondly, reactions involving functionalization of the *N*1-position.

2.2. C-Functionalization of pyrroles

The electron rich nature of pyrroles results in high nucleophilicity, particularly at the *C*2-position. As a result, a number of asymmetric *C*-functionalization reactions have been developed relying on this innate reactivity. The enantioselectivity within these reactions is

typically controlled *via* strategies which lower the LUMO of the electrophile, for example through activation with chiral Lewis or Brønsted acids. A variety of electrophiles have been successfully employed, including electron deficient ketones,[26] Michael acceptors,[27] imines[28] and metal carbenoids[29] (Scheme 2.1).

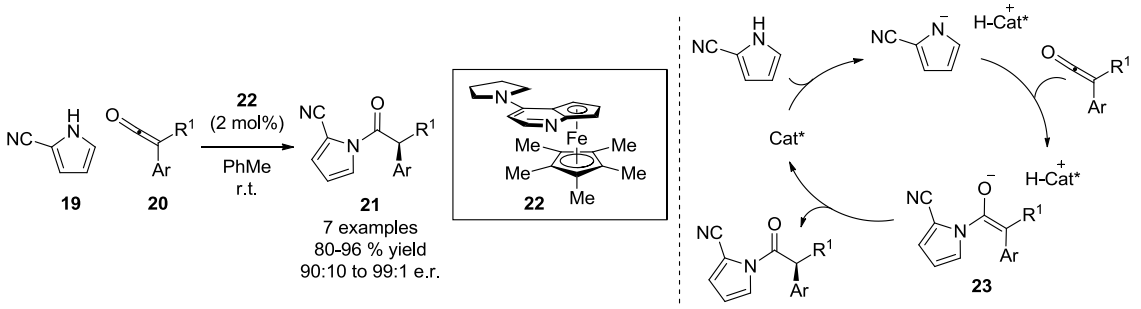


Scheme 2.1. Strategies for asymmetric *C*-functionalization of pyrroles

2.3. N-Functionalization of pyrroles

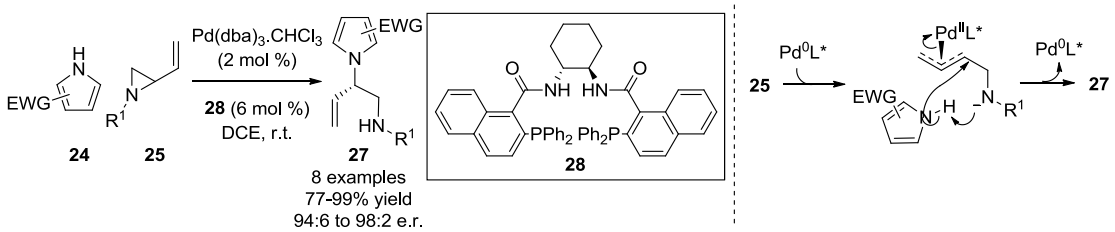
In order to carry out *N*-functionalization of pyrroles selectively, it is usually necessary to deprotonate the pyrrolic N-H. As a result asymmetric approaches to *N*-functionalization normally utilize chiral Brønsted base catalysis as a means to raise the HOMO of the pyrrole nucleophile. However, since this position is relatively non-acidic (the pK_a of pyrrole itself is 23.1 in DMSO),[30] the majority of catalytic asymmetric *N*-functionalization reactions developed to date require the pyrrole to be substituted with an electron withdrawing group.

Fu *et al.* have employed a planar chiral 4-pyrrolidino(pyridine) catalyst **22** to carry out the asymmetric *N*1-addition of 2-cyanopyrrole **19** to disubstituted ketenes (Scheme 2.2).[31] Mechanistic studies have revealed that the catalyst in this system is not operating as a Lewis base, but instead functions as a Brønsted base, initially deprotonating the pyrrole, enabling it to undergo *N*1-selective attack upon the ketene. The enantiodetermining step is the asymmetric protonation of the resulting enolate intermediate **23**.



Scheme 2.2. Fu's catalytic asymmetric addition of 2-cyanopyrrole to ketenes and proposed mechanism

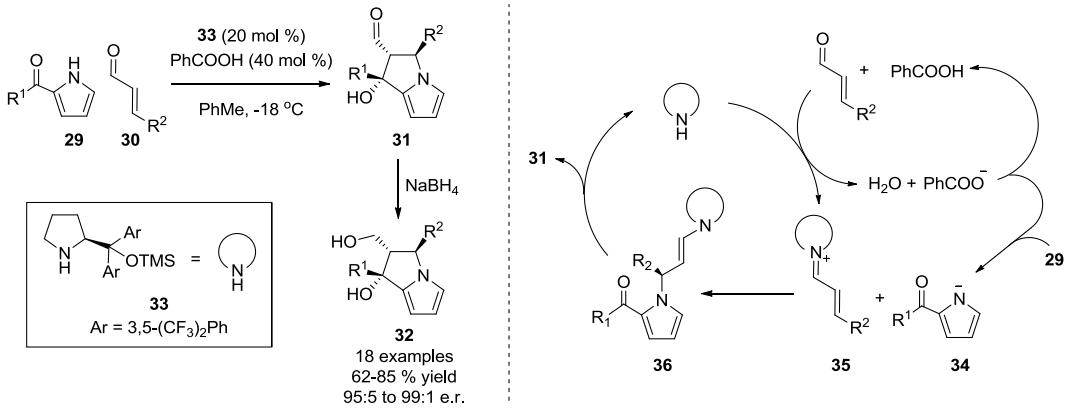
Trost *et al.* have carried out a series of palladium catalysed asymmetric *N*1-allylation reactions of pyrroles. Both *meso*-allylic carbamates[32] and vinyl aziridines[33] have successfully been employed as π-allyl precursors (Scheme 2.3). In the latter case, the authors postulate that nucleophilic attack by the pyrrole is concerted with deprotonation of the pyrrolic N-H by the aziridine nitrogen.[34] It is noteworthy that under these conditions, analogous pyrrole nucleophiles lacking an electron withdrawing group underwent no reaction. This approach has been successfully applied in the synthesis of natural products.[34]



Scheme 2.3. Trost's catalytic asymmetric *N*1-allylation of pyrroles and proposed mechanism

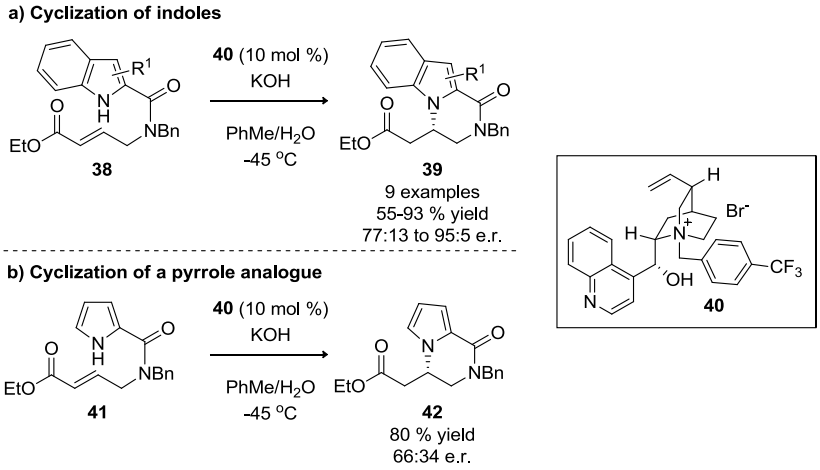
Cho *et al.* have disclosed a conjugate addition–aldol cascade reaction (Scheme 2.4).[35] Mechanistically, it is suggested that benzoic acid catalyses the condensation of secondary amine catalyst **33** with unsaturated aldehyde **30**, resulting in the generation of a reactive iminium intermediate **35** along with concomitant formation of benzoate. It is then proposed that benzoate acts as a base, deprotonating the N-H of activated pyrrole **29**. The resulting pyrrolyl anion **34** then undergoes an enantioselective conjugate addition to the iminium species followed by a diastereoselective aldol cyclization leading to **31** and regenerating the

catalyst**.** In practice, the unstable aldehyde products were reduced to the corresponding alcohols with excess sodium borohydride in order to facilitate analysis.



Scheme 2.4. Cho's catalytic asymmetric conjugate addition-aldol cascade reaction

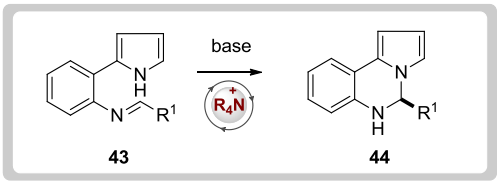
Bandini *et al.* have described a catalytic asymmetric intramolecular aza-Michael reaction of indoles and pyrroles to α,β-unsaturated esters.[36] In this reaction, the enantioselectivity is mediated by a chiral phase-transfer catalyst. The main focus of this work is the *N*-functionalization of indoles **38**, which offers a highly enantioselective route to products **39** containing the biologically important 3,4-dihydropyrazino[1,2-a]indol-1(2H)-one core (Scheme 2.5a). When applied to an analogous pyrrole derived substrate **41**, the cyclization took place with significantly reduced enantioselectivity (Scheme 2.5b).[37] The authors rationalize this observation on the basis of computational modelling, which suggests that a critical π–π interaction with the phase-transfer catalyst is absent in the case of cyclization of **41**.



Scheme 2.5. Bandini's phase-transfer catalysed cyclization of indoles and pyrroles

2.4. Project aims

As discussed previously, hydroxide initiated phase-transfer conditions offer an opportunity to deprotonate relatively non acidic substrates.[10] We therefore hoped that it may be possible to employ a phase-transfer system to deprotonate a comparatively unactivated pyrrole. To explore this idea, we planned to synthesise **43**, consisting of a pyrrole nucleophile substituted with a tethered imine, which we hoped would function as an internal electrophile. Our aim would then be to cyclize this imine, relying upon a chiral cation to control the asymmetry of the process (Scheme 2.6).



Scheme 2.6. This work - cation-directed cyclization of pyrroles

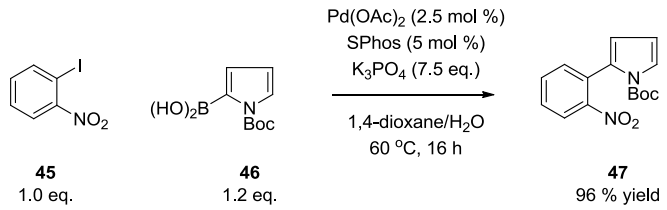
2.5. A note on collaboration

This project was initiated by Dr Melissa D'Ascenzio, then a visiting student in our research group.[38] In the final months of her placement, she developed a first generation route to the desired imine **43** and performed some initial investigations into the asymmetric cyclization

reaction. However, due to time constraints, the optimization carried out at this point was limited to a relatively small set of conditions. My involvement in the project commenced by repeating these results and then moved on to extending the optimization. The two sections which follow below on substrate synthesis and optimization represent our combined findings.

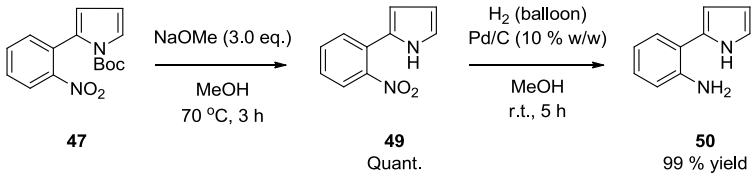
2.6. Substrate synthesis

Our synthesis of target substrate **43** began with a known Suzuki-Miyaura cross coupling of 2-nitro-iodobenzene **45** with commercial boronic acid **46**.[39] The cross coupling reaction could be carried out with as little as 2.5 mol % of palladium acetate, affording **47** in 96 % yield.



Scheme 2.7. Preparation of **47** *via* Suzuki-Miyaura cross coupling

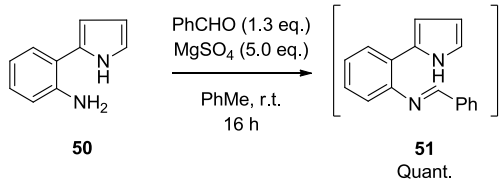
The Boc group was then quantitatively cleaved under basic conditions, thus avoiding any possibility of acid catalysed side reactions, and catalytic hydrogenation of the aromatic nitro group afforded the desired aniline **50** in near quantitative yield.[39] **50** proved somewhat unstable to column chromatography and was therefore used crude in the subsequent imine formation step (Scheme 2.8).



Scheme 2.8. Synthesis of aniline **50**

With this aniline in hand, we were in a position to attempt an imine formation reaction. We were pleased to observe that treatment of aniline **50** with 1.3 equivalents of benzaldehyde

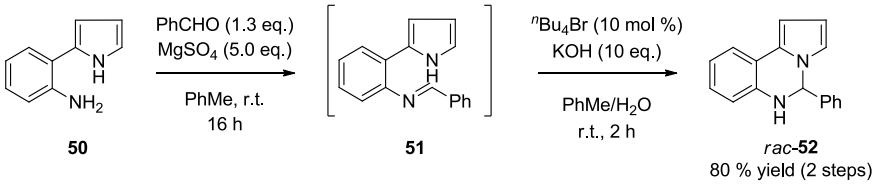
and excess magnesium sulfate led to the desired imine in near quantitative yield (Scheme 2.9).[*] We were unable to crystallise this material and purification by column chromatography resulted in extensive decomposition. As a result, we decided to employ the imine crude in the subsequent cyclization reaction.



Scheme 2.9. Magnesium sulfate catalysed imine formation

2.7. Optimization of cyclization conditions

We initially set out to investigate the cyclization of **51** under phase-transfer conditions using an achiral tetraalkylammonium salt. Upon treatment of crude **51** with tetra-*n*-butylammonium bromide in a biphasic mixture of toluene and aqueous potassium hydroxide, we were pleased to find that the desired cyclization reaction took place (Scheme 2.10). The product *rac*-**52** was formed as a single regioisomer in 80 % yield (over 2 steps).[†]



Scheme 2.10. Racemic phase-transfer catalysed cyclization of **51**

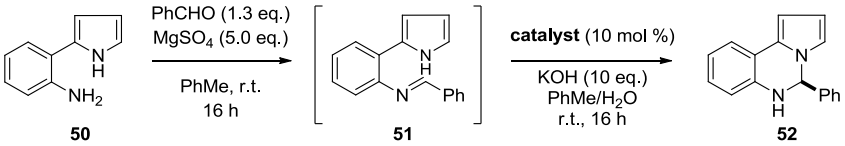
With this result in hand, we turned our attention to the asymmetric variant of this transformation. We were pleased to find that cyclization of **51** in the presence of catalytic *N*-benzylcinchonidinium chloride **18** afforded the product **52** in a promising 32:68 e.r. We next moved on to investigate a range of chiral phase-transfer catalysts (for full details see

[*] We found it is necessary to use freshly distilled benzaldehyde in order to achieve good conversion to imine **51**.

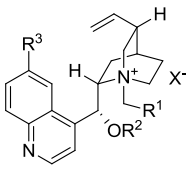
[†] **52** was the only product which could be detected in the crude ^{1}H NMR spectrum.

Appendix A). Protection of the *C*9 hydroxyl group of the catalyst resulted in conversion to essentially racemic **52** (Table 2.1, entries 2-3). This observation is consistent with other observations in the literature and implies that the free alcohol plays an important role in substrate binding.[40] Incorporation of a methoxy substituent to the *C*6' position of the catalyst led to slightly reduced selectivity (Table 2.1, entry 4). Substitution of the pendant *N*-benzyl group of the catalyst had a deleterious effect on enantioselectivity, resulting in seemingly non-systematic variations in enantioenrichment (Table 2.1, entries 5-8).

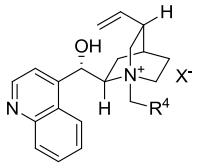
Switching to a pseudoenantiomeric catalyst derived from cinchonine led to an inversion of the absolute sense of stereoinduction along with a significant increase in enantioselectivity, affording the product in 80:20 e.r. (Table 2.1, entry 9). We explored a range of benzyl substituted analogues of this catalyst – varying both the steric and electronic nature of the group; however these changes all resulted in reduced enantioselectivity (Table 2.1, entries 10-15). Phase-transfer catalysts based on biaryl scaffolds pioneered by Lygo and Maruoka also proved effective catalysts for this reaction, although the resulting enantioselectivities were a little lower than those obtained with cinchona derived catalysts (Table 2.1, entries 16-17).[41] Having identified **60** to be the optimal catalyst, we next turned our attention to the identification of alternative reaction solvents.



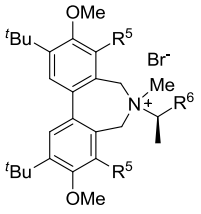
Entry	Catalyst	e.r.
1	**18**	32:68
2	**53**	47:53
3	**54**	51:49
4	**55**	34:66
5	**56**	27:73
6	**57**	30:70
7	**58**	34:66
8	**59**	34:66
9	**60**	80:20
10	**61**	78:22
11	**12**	74:26
12	**62**	64:36
13	**63**	76:24
14	**64**	76:24
15	**65**	74:26
16	**66**	23:77
17	**67**	29:71



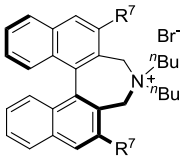
18: R^1 = Ph; R^2 = H; R^3 = H; X = Cl
53: R^1 = Ph; R^2 = allyl; R^3 = H; X = Br
54: R^1 = 9-anth; R^2 = Me; R^3 = H; X = Br
55: R^1 = Ph; R^2 = H; R^3 = OMe; X = Cl
56: R^1 = 4-NO_2-C_6H_4; R^2 = H; R^3 = H; X = Br
57: R^1 = 3-F-C_6H_4; R^2 = H; R^3 = H; X = Br
58: R^1 = 1-naphthyl; R^2 = H; R^3 = H; X = Br
59: R^1 = 2-naphthyl; R^2 = H; R^3 = H; X = Br



60: R^4 = Ph; X = Cl
61: R^4 = 4-NO_2-C_6H_4; X = Br
12: R^4 = 4-CF_3-C_6H_4; X = Br
62: R^4 = 3,5-$(CF_3)_2$-C_6H_3; X = Br
63: R^4 = 4-F-C_6H_4; X = Br
64: R^4 = 3-F-C_6H_4; X = Br
65: R^4 = 2,3,4-F_3-C_6H_2; X = Br



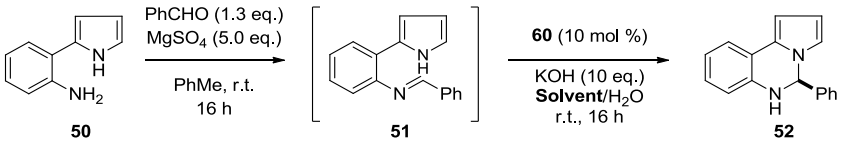
66
R^5 = 3,5-$(CF_3)_2$-C_6H_3
R^6 = 2-naphthyl



67
R^7 = 3,4,5-F_3-C_6H_2

Table 2.1. Catalyst optimization

Alternative aromatic solvents such as benzene or chlorobenzene led to slightly reduced enantioselectivity (Table 2.2, entries 2-3). As expected, more polar solvents such as dichloromethane, 1,4-dioxane and tetrahydrofuran led to **52** with lower levels of enantioenrichment (Table 2.2, entries 4-6). We found that addition of hexane in order to reduce solvent polarity had a deleterious effect upon enantioselectivity (Table 2.2, entries 7-8). A range of ethers also proved effective solvents for this reaction, affording the product with comparable levels of selectivity to toluene (Table 2.2, entries 9-11).

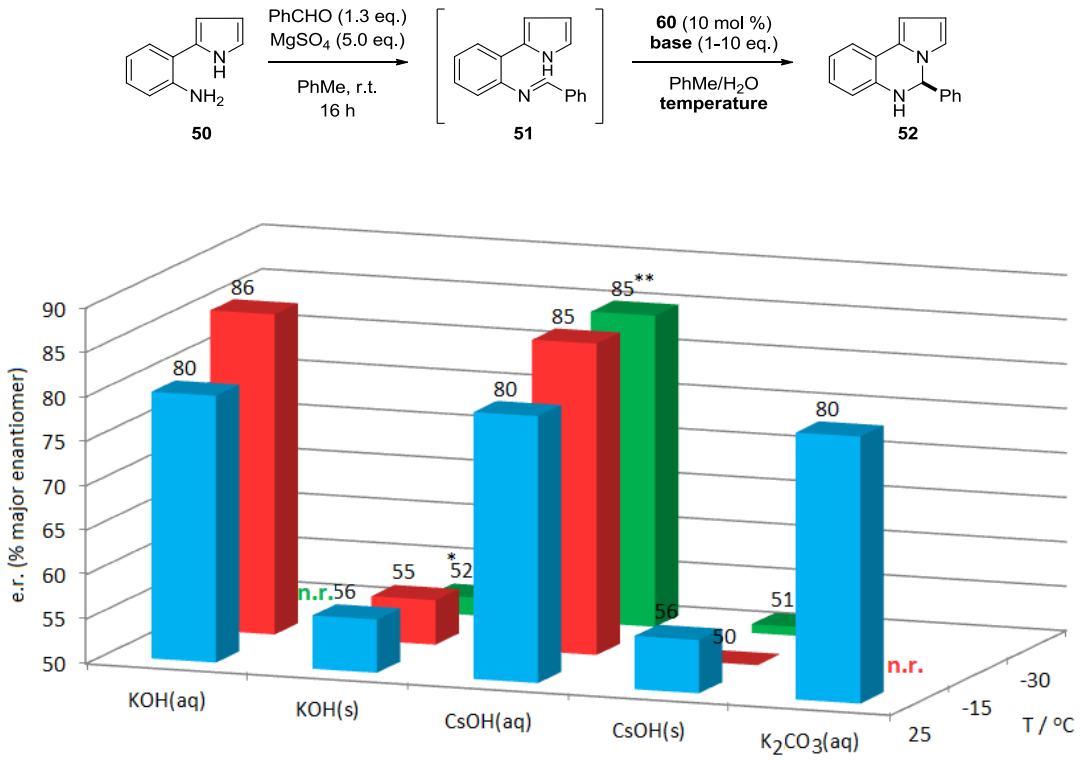


Entry	Solvent	e.r.
1	PhMe	80:20
2	PhH	76:24
3	PhCl	76:24
4	CH_2Cl_2	75:25
5	1,4-dioxane	70:30
6	THF	60:40
7	PhMe/hexane (1:1)	78:22
8	hexane	71:29
9	Et_2O	79:21
10	*t*-BuOMe	79:21
11	cyclopentyl methyl ether	78:22

Table 2.2. Optimization of reaction solvent

Up to this point we had focussed on aqueous potassium hydroxide as a base. We therefore decided to evaluate the performance of a series of aqueous and solid bases at different temperatures (20 ^{o}C, −15 ^{o}C and −30 ^{o}C). The results are summarized graphically in Scheme 2.11 (for full details, see Appendix B). This plot reveals that aqueous bases offered

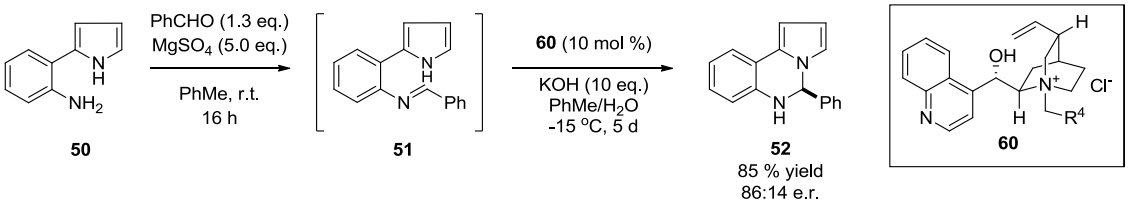
improved enantioselectivity over solid bases (even at low temperature).* At room temperature, there was little difference in the enantioselectivity observed between aqueous hydroxide and carbonate bases. Upon lowering the temperature to −15 °C an increase in selectivity was observed for KOH and CsOH, but no reactivity was observed with aqueous potassium carbonate. Cooling to −30 °C led to reduced conversion and did not result in improved enantioselectivity, so we settled upon optimized conditions of aqueous KOH at −15 °C.



Scheme 2.11. The effect of base and temperature on enantioselectivity**.** (*36:64 ratio **52**:**51**, **26:74 ratio **52**:**51**).

With these optimised conditions in hand, we tested the reaction on a 100 mg scale and were able to isolate the cyclized product in 85 % yield in 86:14 e.r. (Scheme 2.12).

* Solid potassium carbonate was also screened, but only uncyclized imine was detected after 24 h.

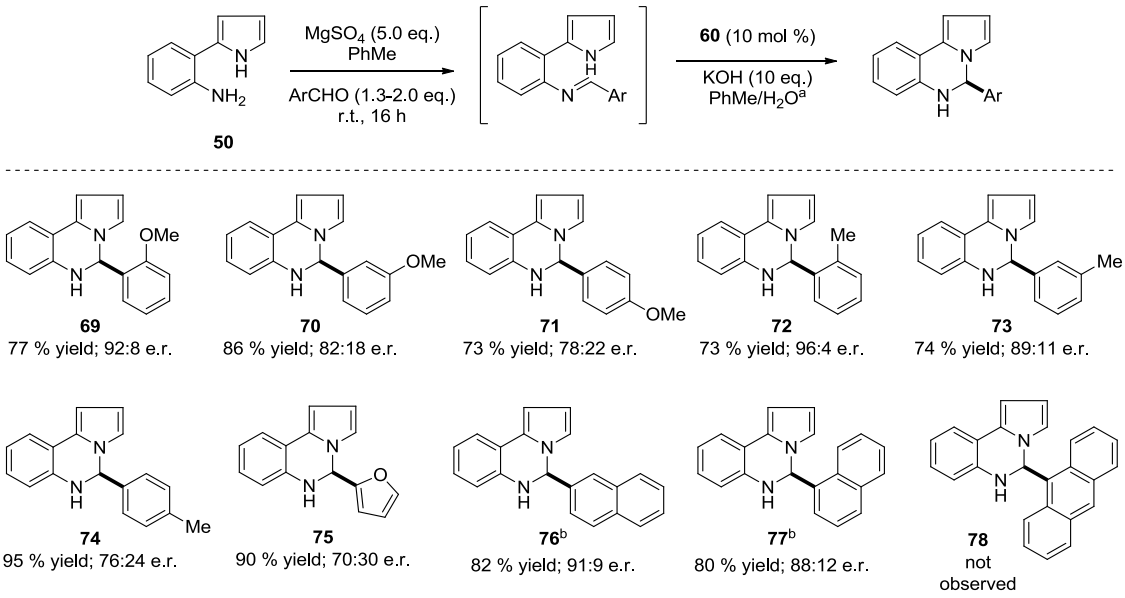


Scheme 2.12. Optimized asymmetric cyclization conditions

2.8. Substrate scope

We set about investigating the generality of this asymmetric cyclization reaction by varying the aldehyde used in the imine formation. A large number of aldehydes are commercially available, and we hoped that this would allow us to probe the steric and electronic requirements of the cyclization reaction. Initially, a range of substituted benzaldehydes were selected and subjected to our optimized conditions for one-pot imine formation/cyclization.[*] We found the procedure to be most effective for electron rich, sterically congested aldehydes - those substituted in the *ortho*- or *meta*- positions proved particularly effective (**69**, **70**, **72**, **73**) (Scheme 2.13). When the electron rich substituent was located in the *para*-position, slightly lower levels of selectivity were observed, although **71** and **74** were still formed in good to excellent yields. An electron rich imine derived from furfural underwent cyclization in excellent yield, but the product **75** was formed with a modest selectivity of only 70:30 e.r. suggesting that high enantioselectivity is not simply related to the electronic properties of the imine. We were also able to condense aniline **50** with hindered 1- and 2-naphthaldehydes, and the resulting imines underwent highly enantioselective cyclization forming **76** and **77** in good yields.[†] However, with the very bulky aldehyde 9-anthracenylcarboxaldehyde we observed no conversion to the desired imine. This may be due in part to the insolubility of the aldehyde in toluene.

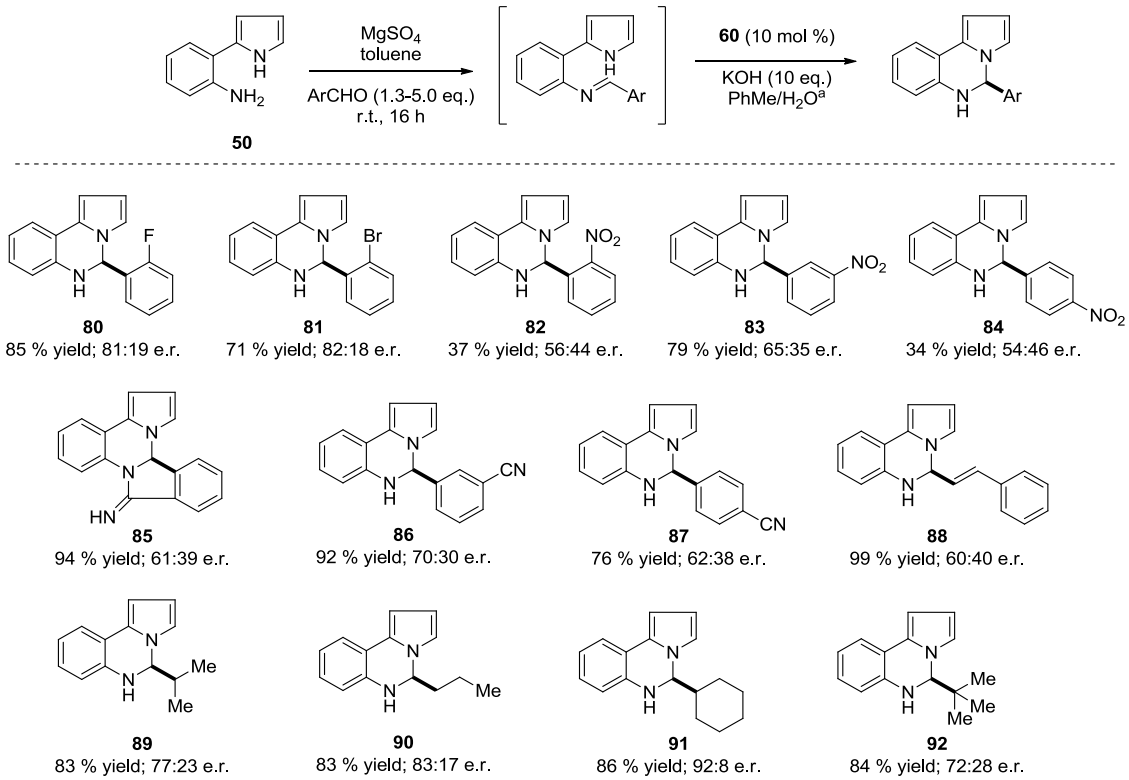
[*] Aldehydes were freshly distilled or recrystallized prior to use.
[†] In order to separate the cyclized products from excess aldehyde, the crude reaction mixtures from the cyclization were treated with excess sodium borohydride.



Scheme 2.13. Cyclization of imines derived from electron rich aldehydes. (a) For cyclization times and temperatures see experimental. (b) Imine formation carried out with 2.0 eq. of aldehyde and 10 eq. of $MgSO_4$ for 48 h.

Next we examined the cyclization of imines derived from electron deficient aldehydes (Scheme 2.14). Products **80** and **81**, substituted in the *ortho*-position with a fluoride or bromide cyclized with good enantioselectivity. Introduction of a more powerful electron withdrawing group, such as nitro or nitrile had a deleterious effect and the corresponding products were obtained in lower levels of enantioenrichment. Interestingly, in the case of cyclization of the imine derived from 2-cyanobenzaldehyde, an unexpected pentacyclic product **85** was observed in 94 % yield. Presumably **85** arises by initial *N*1-fuctionalization followed by 5-*exo*-dig cyclization onto the pendant nitrile group.

Pleasingly, aliphatic aldehydes also proved viable substrates for the reaction. A range of imines were prepared and were found to undergo cyclizations in enantioselectivities that varied from high (92:8 e.r. for **91**) to modest (72:28 e.r. for **92**). The enantioenrichment did not appear to have a straightforward dependency upon the steric or electronic nature of the aldehyde, for example **89** and **91** which are both derived from α-branched aldehydes were formed with significantly differing levels of selectivity. For all of the aliphatic imines investigated, the products were isolated in good yields.

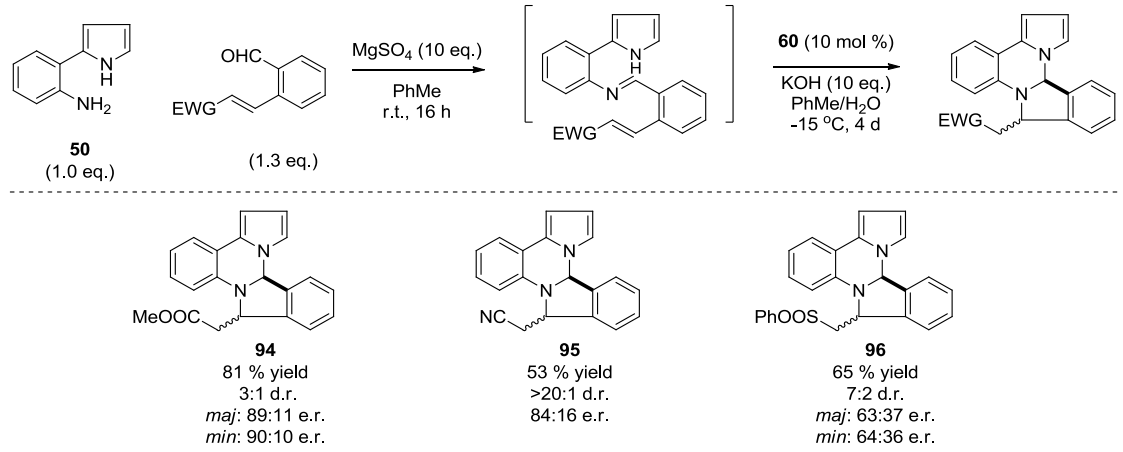


Scheme 2.14. Cyclized products derived from electron deficient and aliphatic aldehydes. (a) For cyclization times and temperatures see experimental.

The observation of unexpected domino reactivity leading to **85** led us to speculate whether other substrates might be amenable to similar cascade processes. As discussed in Chapter 1, our group already has some expertise in this area and we hoped to apply a similar principle, employing *ortho*-functionalized aldehydes to obtain complex polycyclic products in a single step.[16] The requisite aldehydes (kindly provided by Dr Peter Knipe) were condensed with **50** according to our optimized procedure. Following asymmetric cyclization, the products **94**, **95** and **96** were formed in moderate to good yields (Scheme 2.15). The enantioselectivities were high in the case of ester and nitrile substituted products **94** and **95**, but lower for the corresponding sulfone **96**. Interestingly, **95** was formed as a single diastereoisomer, but **94** and **96** were obtained with lower levels of diastereoselectivity.[*] We postulate that this is a result of

[*]In all three cases, we were unable to determine whether the major diastereomer was *anti*- or *syn*-, since nOe correlations were ambiguous and we could not readily grow analytical quality crystals.

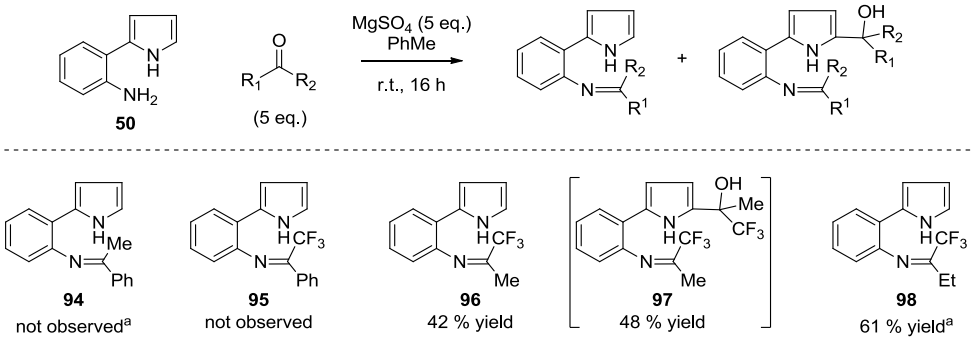
increased reversibility of the conjugate addition to the unsaturated ester and sulfone, resulting in erosion of the diastereoselectivity of **94** and **96**.[16]



Scheme 2.15. Cascade cyclization with functionalised aldehydes

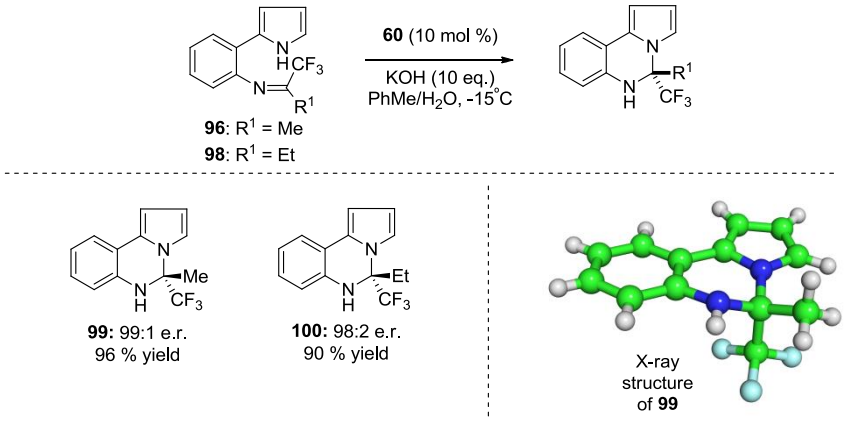
We felt that using ketone derived imines (ketimines) in the place of aldimines would be of great interest, since the cyclized products would contain a quaternary stereogenic centre. We therefore set about investigating the condensation of aniline **50** with a series of aromatic ketones, but only obtained unreacted starting materials (Scheme 2.16).* This is presumably a consequence of the high stability of acetophenones. Pleasingly however, condensation with 1,1,1-trifluoromethylacetone was successful, affording **96** in 42 % yield along with by-product **97**, resulting from condensation and Friedel-Crafts reaction at the *C*2 position. Upon warming to 50 °C successful condensation was also achieved with 1,1,1-trifluoro-2-butanone affording ketimine **98** in 61 % yield. It is noteworthy that unlike the aldimines synthesised previously, ketimines **96**, **97** and **98** were stable to column chromatography and these yields refer to isolated material.

* A variety of other reaction conditions were evaluated - see Appendix C for full details.



Scheme 2.16. Formation of ketimines. (a) Reaction carried out with 15 eq. ketone and 15 eq. $MgSO_4$ for 24 h at r.t. and then 20 h at 50 °C.

Ketimines **96** and **98** were subjected to our previously optimised conditions for phase-transfer catalysed cyclization and we obtained the corresponding products **99** and **100** in excellent yields (Scheme 2.17). Furthermore, we were pleased to find that the quaternary stereogenic centres of **99** and **100** were formed in 99:1 and 98:2 e.r. respectively. An X-ray crystal structure of **99** allowed the regioselectivity of the cyclization reaction to be unambiguously confirmed.*

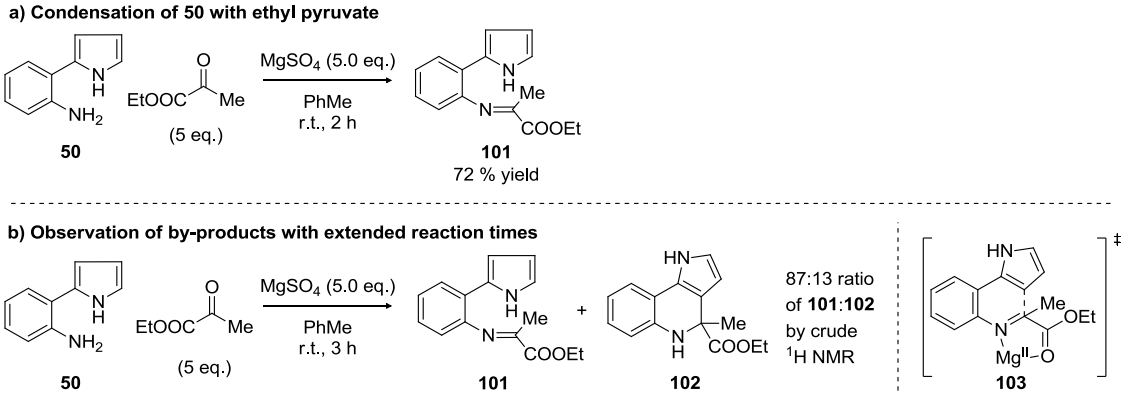


Scheme 2.17. Cyclization of trifluoromethyl ketimines

We hoped that the increased electrophilicity displayed by pyruvates over the corresponding ketones might also render them viable substrates. Accordingly, imine formation with ethyl pyruvate was attempted (Scheme 2.18a). Although this method allowed access to **101**, the reaction proved somewhat capricious and we noticed that with extended reaction times, we began to observe formation of a by-product which we identified as *C*3-cyclized **102**

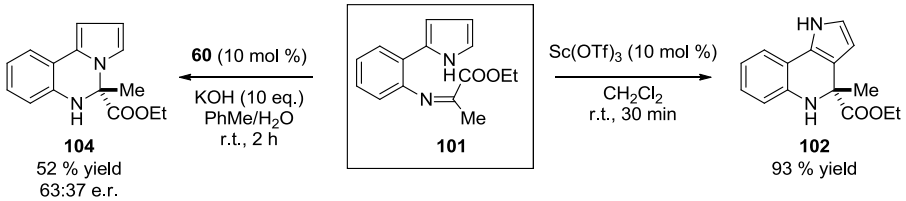
* We are indebted to Dr Russell Driver for his crystallographic expertise.

(Scheme 2.18b). It is possible that **102** is formed *via* a Lewis acid promoted 6π-electrocyclization reaction in which the substrate is activated by bidentate binding with Mg(II) (i.e. transition state **103**).



Scheme 2.18. Synthesis of ketimines from ethyl pyruvate

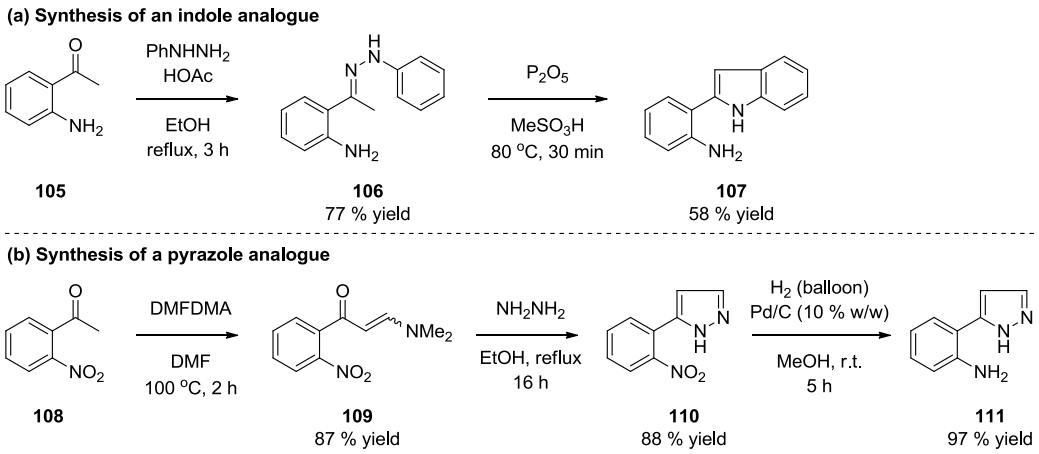
Ketimine **101** was successfully cyclized under asymmetric phase-transfer conditions, leading to quaternary substituted product **104** in 52 % yield and 63:37 e.r. (Scheme 2.19). The observation of small quantities of **102** in the imine formation reaction (Scheme 2.18b) prompted us to speculate whether a Lewis acid might be able to promote a complementary *C*3-selective cyclization reaction. Gratifyingly, treatment of **101** with catalytic scandium triflate in dichloromethane led exclusively to **102** in 93 % yield. We wondered whether this *C*3-cyclization reaction might be rendered asymmetric by the use of a chiral Lewis or Brønsted acid, but a small screen of asymmetric conditions led only to racemic **102** (for details see Appendix D). It is nevertheless interesting that complete regiodivergence could be obtained under these different reaction conditions.



Scheme 2.19. Regiodivergent reactivity of ketimine **101**

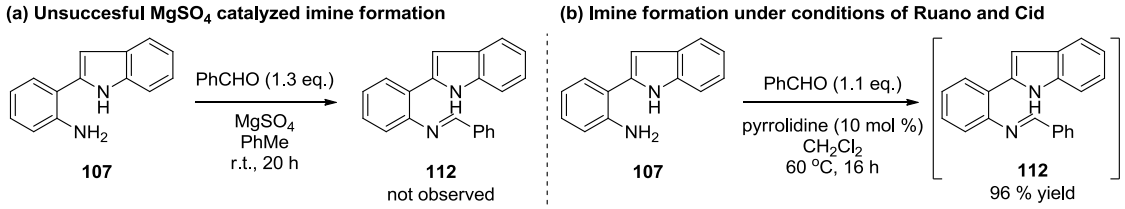
2.9. Heterocyclic analogues

We hoped to extend this methodology to cyclization of compounds containing different heterocyclic cores. An indole derivative **107** was readily synthesised *via* a two-step literature procedure involving condensation of phenylhydrazine with 2'-aminoacetophenone **105** followed by thermal cyclization and dehydration (Scheme 2.20a).[42] Pyrazole **111** was accessed in three steps according to a literature procedure.[43] Condensation of 2'-nitroacetophenone **108** with DMFDMA generated masked 1,3-ketoaldehyde **109**. Reaction of **109** with hydrazine hydrate followed by catalytic hydrogenation of the aromatic nitro group afforded **111** in a good yield over three steps (Scheme 2.20b).



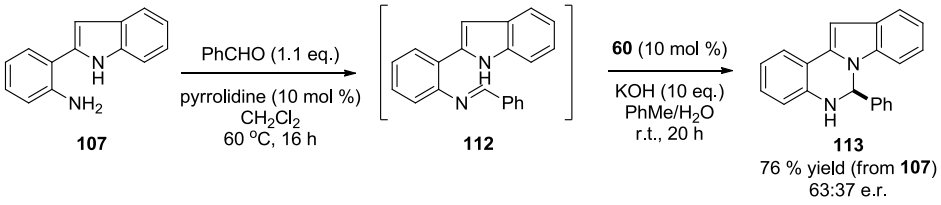
Scheme 2.20. Synthesis of indole and pyrazole analogues

We found that upon subjection of **107** to our previously employed conditions for imine formation with benzaldehyde and excess magnesium sulfate, no conversion to the desired imine was observed – only unreacted starting materials were detected (Scheme 2.21a). Fortunately, conditions recently disclosed by Ruano and Cid, employing catalytic pyrrolidine led to imine **112** in excellent yield which was used in the cyclization step without further purification (Scheme 2.21b).[44]



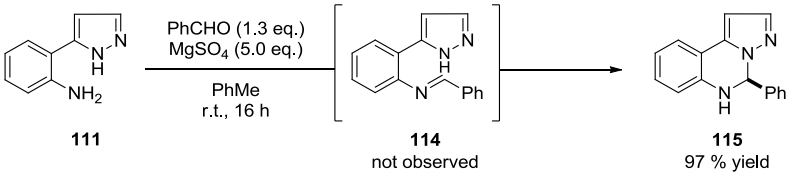
Scheme 2.21. Imine formation with indole derivative

This material was subjected to optimized asymmetric phase-transfer conditions and as anticipated, regioselective cyclization took place to form **113** in 76 % yield (2 steps) (Scheme 2.22). The enantioenrichment of this material was determined to be 63:37 e.r., somewhat lower than the corresponding result of 80:20 e.r. obtained for the analogous pyrrole substrate **52** under identical conditions.



Scheme 2.22. Asymmetric cyclization of an indole derivative

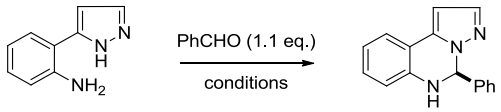
We were surprised to find that treatment of **111** with our standard conditions of 1.3 equivalents of benzaldehyde and excess magnesium sulfate lead not to the expected imine **114**, but instead to **115**, which appears to result from imine formation followed by cyclization (Scheme 2.23).[*45]



Scheme 2.23. Formation of unexpected cyclized material in imine formation

[*] Imine formation followed by *C*2-cyclization has been observed previously by DeStevens *et al.*, although the conditions were more forcing (at reflux in ethanol).

We wondered whether this serendipitous result could be turned to our advantage in the development of a one-pot asymmetric procedure for imine formation/cyclization. A control experiment carried out in the absence of magnesium sulfate resulted in only a low level of conversion to cyclized product, indicating that this additive has an important role in promoting this reaction (Table 2.3, entry 2). Addition of catalytic cinchonidine **116** as a chiral Brønsted base appeared to inhibit the reaction and no **115** was detected after 3 hours (Table 2.3, entry 3). Lewis acids proved more promising catalysts, and in the presence of 10 mol % scandium triflate rapid and complete conversion to **115** took place (Table 2.3, entry 4). This result prompted us to carry out a small screen of chiral Lewis acid catalysts. Disappointingly, although complexes of scandium with PyBox proved effective catalysts for this reaction, only racemic **115** was produced (Table 2.3, entries 5-6). A Lewis acidic BINOL-derived copper(II) catalyst **118** recently disclosed by our group gave a similar result (Table 2.3, entry 7).[46] The reaction also proved amenable to catalysis by chiral Brønsted acids such as TRIP, although again no asymmetry was observed (Table 2.3, entry 8).



Entry	Catalyst [mol %]	Conditions	time	Ratio **115**:**111** [isolated yield]	e.r.
1	$MgSO_4$ [500]	d_8-PhMe, r.t.	3 h	64:36	-
2	none	d_8-PhMe, r.t.	3 h	23:77	-
3	**116** [10]	d_8-PhMe, r.t.	3 h	<5:95	-
4	$Sc(OTf)_3$ [10]	CH_2Cl_2, r.t.	1 h	>95:5	-
5	**117** [10]	CH_2Cl_2, r.t.	3 h	>95:5 [78 %]	50:50
6	**117** [10]	PhMe/THF (1:1), r.t.	3 h	>95:5 [74 %]	50:50
7	**118** [5]	CH_2Cl_2, r.t.	1 h	>95:5	50:50
8	TRIP [5]	CH_2Cl_2, r.t.	1 h	>95:5	50:50

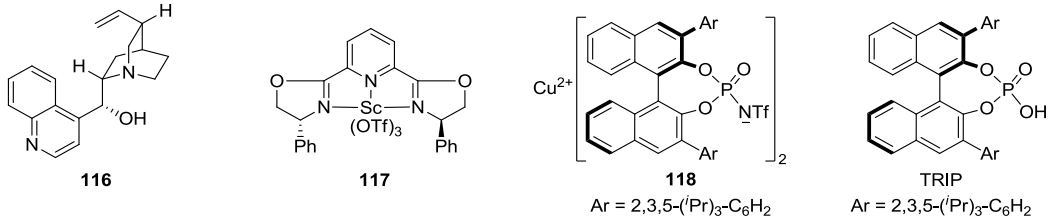
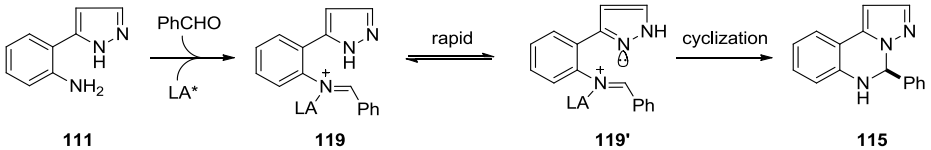


Table 2.3. Asymmetric conditions for one-pot imine formation and *N*1-cyclization

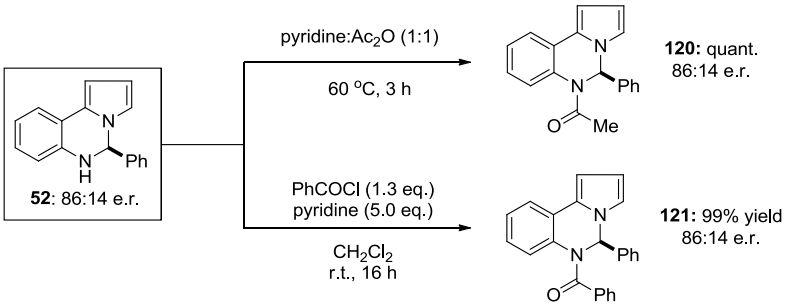
At first sight it seemed puzzling that Lewis acids led to selective *N*-functionalization rather than *C*2-cyclization. However, presumably **119** is in rapid equilibrium with the tautomer **119'** (Scheme 2.24). In this case, the nucleophilic unconjugated sp^2 lone pair would be able to undergo cyclization onto the Lewis or Brønsted activated imine. The developing positive charge would then be stabilized by donation of the adjacent nitrogen lone pair, which after loss of a proton would lead to cyclized product **115**.



Scheme 2.24. Proposed explanation of Lewis acid catalysed *N*-cyclization

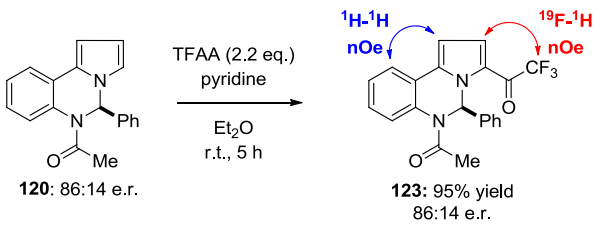
2.10. Product derivatization

To demonstrate the synthetic utility of the cyclized products, we aimed to carry out a series of derivatization reactions. Taking cyclized compound **52** as a representative example, we began by investigating *N*-protection of the product. After some optimization, we found that *N*-acylation could be efficiently achieved by heating to 60 °C in a 1:1 mixture of acetic anhydride and pyridine, leading to **120** in quantitative yield with no loss in stereochemical integrity. Alternatively, treatment of **52** with a slight excess of benzoyl chloride in the presence of pyridine led to **121** in 99 % yield with no enantiomeric erosion (Scheme 2.25).



Scheme 2.25. *N*-functionalization of cyclized products

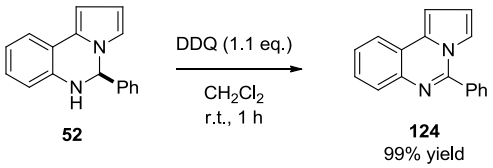
With the reactive benzylic nitrogen suitably protected, we were able to carry out Friedel-Crafts functionalization of the pyrrole with trifluoroacetic anhydride, affording **123** in 95 % yield with no erosion of enantiomeric purity. This reaction took place at the 2-position with complete regioselectivity, as determined by analysis of homo- and heteronuclear nOe correlations. (Scheme 2.26).*



Scheme 2.26. Regioselective *C*2 functionalization and key nOe interactions

* 1D nOe experiments were performed by Dr Barbara Odell.

Treatment of **52** with a slight excess of DDQ resulted in rapid benzylic oxidation to the corresponding aromatized compound **124**, which was obtained in near quantitative yield (Scheme 2.27). Although this oxidation ablates the stereogenic centre installed in the cyclization step, it nevertheless represents an efficient approach for the synthesis of the pyrolloquinazoline core, a heterocycle for which few preparative methods have been described to date.[47]



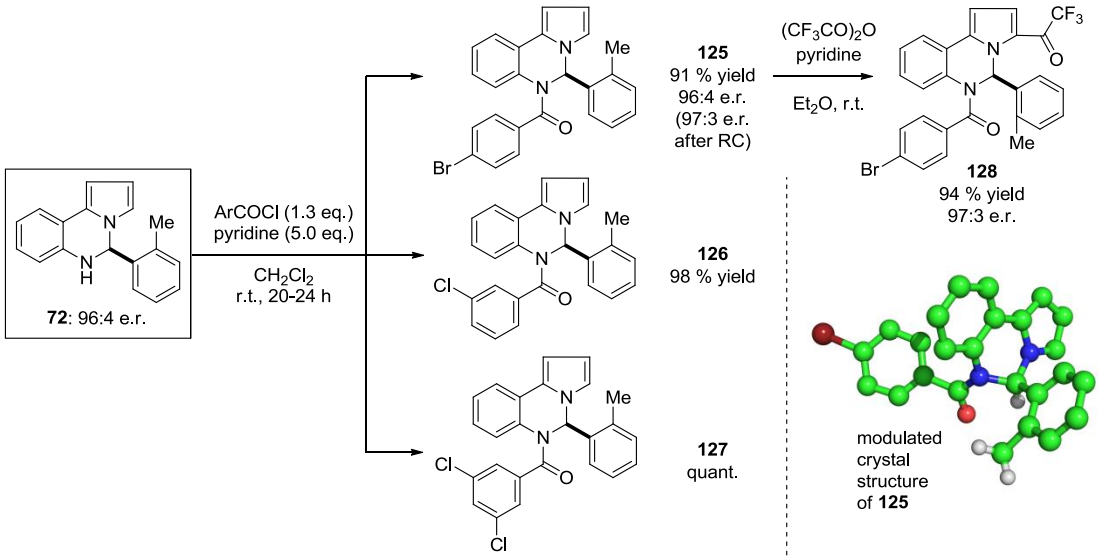
Scheme 2.27. Benzylic oxidation to form **124**

2.11. Determination of absolute stereochemistry

We hoped to determine the absolute stereochemistry of the cyclized products *via* single crystal X-ray diffraction. Unfortunately, although we had prepared several substrates containing a suitable heavy atom (Br or Cl), the enantioenrichment of these materials was not sufficiently high to rely upon crystallization of a single enantiomer. Therefore, we decided to functionalize **72** (96:4 e.r.) in order to obtain an enantioenriched derivative containing a heavy atom. Accordingly, we synthesised **125**, **126** and **127** by *N*-functionalization with halogenated benzoyl chloride derivatives, which led to the products in high yields (Scheme 2.28).[*] We then attempted to grow crystals of these compounds under a variety of conditions. Crystallization of **126** and **127** led to amorphous solids, but we were pleased to obtain analytical quality crystals of **125**. X-ray crystallography (performed by Dr Russell Driver) led to the structure for **125** shown below, but due to the modulated nature of the crystal the data was not of sufficiently high quality to reliably deduce absolute configuration. We hoped that modifying

[*] We confirmed that **125** and **128** were formed with no loss of enantiomeric purity by comparison with authentic racemic samples. It is assumed by analogy that **126** and **127** were also formed without loss of stereochemical integrity.

the pyrrole might lead to a more readily crystalline derivative. We began by recrystallizing **125** which led to a slight increase in enantioenrichment to 97:3 e.r. and then carried out Friedel-Crafts acylation of this material. This afforded **128** in high yield with no enantiomeric erosion, but several attempts at crystallization resulted in formation of modulated crystals.



Scheme 2.28. Attempts to ascertain absolute configuration by X-ray crystallography

2.12. Conclusion

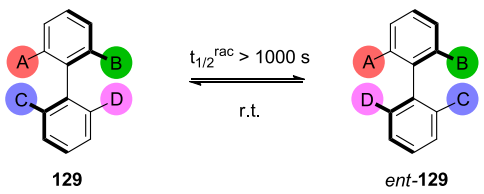
This chapter describes the development of a cation-directed asymmetric functionalization of pyrroles. This reaction proceeds with complete regioselectivity at the *N*1-position and we have synthesised 29 examples within this series. The enantioselectivity of the products shows a strong dependence upon the substitution pattern of the imine, although in some cases high selectivity was observed. We have successfully extended this approach to the cyclization of trifluoromethyl ketimines, enabling the synthesis of compounds containing quaternary stereogenic centres in excellent enantioselectivity. We have also applied this methodology to the synthesis of chiral heterocycles containing indole and pyrazole cores.

3. A Cation-Directed Desymmetrizing S_NAr Reaction

3.1. Asymmetric synthesis of axially chiral biaryls

Over the last two centuries, a great deal of effort has been devoted to identifying methods for the asymmetric synthesis of molecules containing stereogenic centres. In contrast, synthetic approaches for the enantioselective construction of axially chiral compounds have been much less extensively studied.[48] More recently, the emergence of new and powerful catalysts based on axially chiral architectures,[49] along with a greater awareness of the importance of axial chirality in Nature[50] have led to an increased demand for enantioselective synthetic methods targeting such materials. Atropisomeric biaryls represent the archetypal class of axially chiral molecule, and the remainder of this introduction describes methods for their asymmetric preparation.[51]

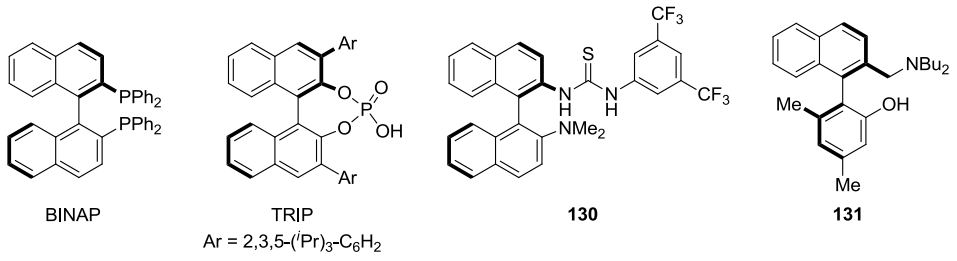
For a generic biaryl, such as **129**, provided that neither ring is symmetrical (i.e. A≠B and C≠D), and that there is a sufficiently large steric interaction between the four highlighted substituents the compound will be atropisomeric (Scheme 3.1).[48,52] That is to say, there exist two axially chiral enantiomeric conformers **129** and *ent*-**129** with an energetic barrier to interconversion which is large enough for the conformers to be isolable. Oki has arbitrarily defined a compound to be atropisomeric if racemization takes place with a half-life* of at least 1000 s at room temperature.[53]



Scheme 3.1. Interconversion of two enantiomeric forms of a generic axially chiral biaryl

* The half-life of racemization ($t_{1/2}^{rac}$) is defined as the time taken for an enantiopure sample to reach 75:25 e.r. (50 % e.e.). The rate of racemization is twice the rate of enantiomerization, i.e. $k_{rac} = 2k_{ent}$.

Although axially chiral biaryls are found in Nature, the most important role of this class of compounds lies within the field of asymmetric catalysis. Several examples of axially chiral biaryl ligands and auxiliaries are depicted in Figure 3.1. Perhaps the most well-known example is BINAP, which has proved to be an extremely effective ligand for the ruthenium catalysed asymmetric hydrogenation of π-bonds.[54] The chiral Brønsted acid TRIP has been employed as a catalyst in several important transformations including asymmetric transfer hydrogenation,[55] Diels-Alder[56] and Pictet-Spengler[57] reactions amongst others.[58] It is not necessary for the biaryl to be symmetrically substituted; for example bifunctional catalyst **130** has been developed which exploits simultaneous Lewis base and Lewis acid activation for an asymmetric Baylis-Hillman reaction.[59] Finally, auxiliaries based upon axially chiral biaryls are also extremely useful, such as aminophenol **131** which has been reported for the asymmetric addition of diethylzinc to aldehydes.[60]



BINAP | TRIP | **130** | **131**

Ar = 2,3,5-(^{i}Pr)$_3$-C$_6$H$_2$

Figure 3.1. Important examples of axially chiral biaryls as catalysts and auxiliaries

Methods for the catalytic asymmetric synthesis of atropisomeric biaryls can be broadly divided into four categories, which are represented schematically in Scheme 3.2.* They are as follows:

i. The union of two hindered fragments, which directly leads to a stereogenic axis.

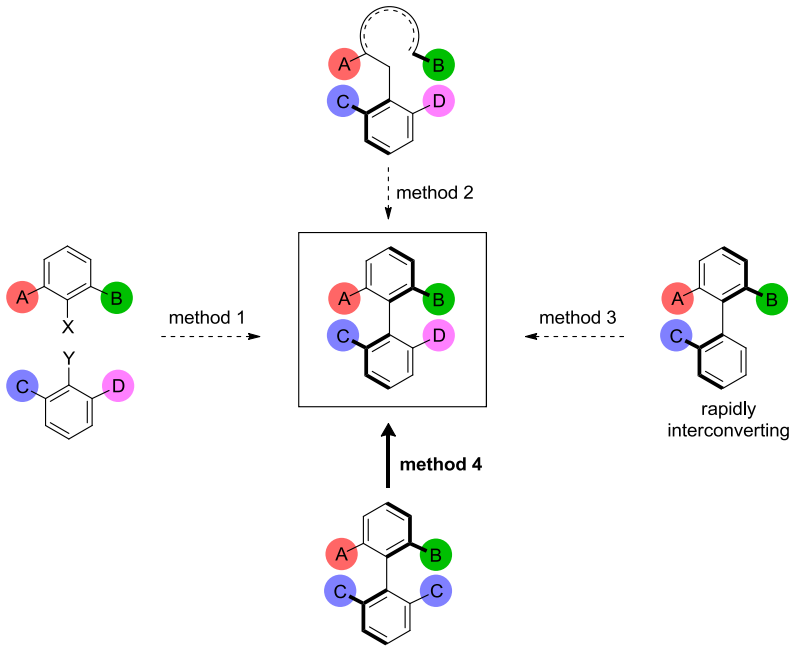
ii. Construction of one of the aromatic rings as the enantiodetermining step.

iii. Dynamic kinetic resolution of rapidly interconverting biaryls.

iv. Desymmetrization of configurationally stable, prochiral biaryls.

* The section which follows is restricted to discussion of catalytic asymmetric methods. Several diastereoselective methods for atropselective biaryl synthesis have also been established.[51]

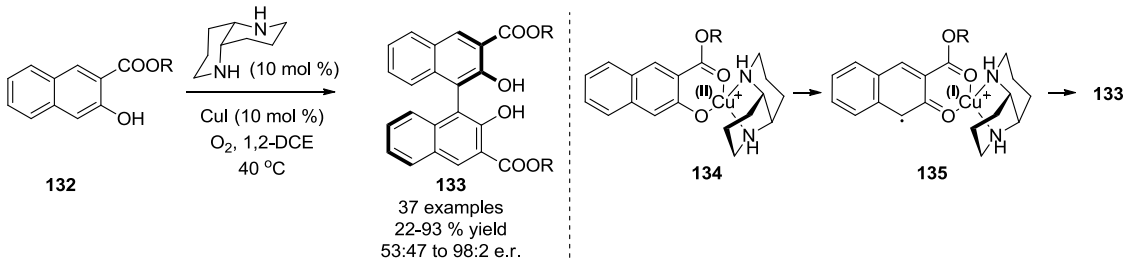
The first, second and third methods have already been comprehensively reviewed elsewhere, and only a brief description along with selected examples is provided here.[51]



Scheme 3.2. Methods for the catalytic asymmetric synthesis of axially chiral biaryls

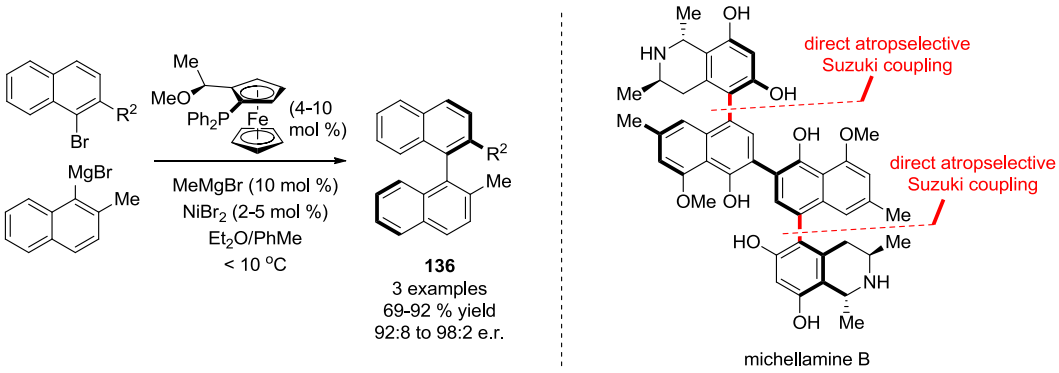
The first method - direct coupling represents a highly convergent method for the synthesis of axially chiral biaryls, but is inherently challenging since the asymmetric step involves construction of an extremely hindered biaryl bond. This approach has been most widely applied in oxidative coupling reactions and also in redox-neutral metal catalysed couplings. A representative example from each of these reaction manifolds is shown below.

The oxidative homo-coupling of hindered phenols has been carried out by Kozlowski *et al.* (Scheme 3.3).[61] In the presence of copper(I) and a chiral diamine ligand the coupled products **133** were formed in excellent enantioselectivity. Mechanistically, it is proposed that this reaction takes place *via* enantiodetermining dimerization of radical intermediate **135**, which is formed by copper(II) mediated single electron oxidation of the starting naphthol. Molecular oxygen acts as the terminal oxidant in this reaction, reforming the catalytically active copper(II) species.



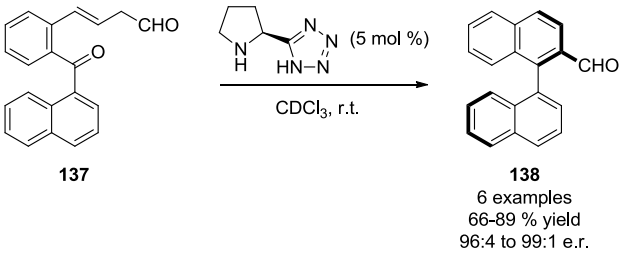
Scheme 3.3. Oxidative direct coupling - enantioselective copper catalysed dimerization of phenols

The area of redox-neutral atropselective coupling was pioneered by Kumada and Hayashi who demonstrated that hindered aryl Grignard reagents could be coupled with aryl bromides yielding axially chiral material in up to 97:3 e.r. (Scheme 3.4).[62] Since these discoveries, this area has been extensively investigated and even applied to the asymmetric synthesis of axially chiral complex natural products. For example, Tang and co-workers have employed highly enantioselective Suzuki couplings to form both stereogenic axes present within the complex natural product Michellamine B.[63]



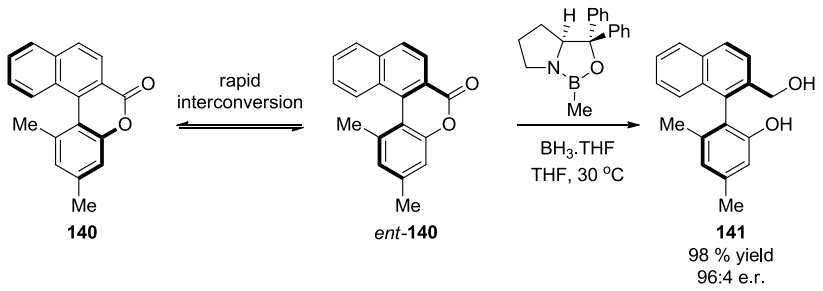
Scheme 3.4. Hayashi's redox-neutral direct coupling and a recent application within natural product synthesis

The second class of reactions, involving synthesis of an aryl ring is also an effective method for the construction of axially chiral biaryls. A representative example is a catalytic enantioselective annulation recently reported by Sparr *et al.* (Scheme 3.5). In this reaction a proline-derived catalyst controls the atropenantioselectivity of an aldol reaction, forming an aromatic ring which locks the compound into an axially chiral architecture.[64]



Scheme 3.5. Atropselective construction of an aromatic ring

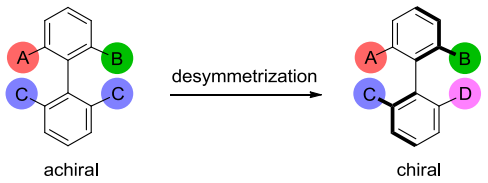
The third class of reactions involves dynamic kinetic resolution of configurationally unstable biaryls. Bringmann *et al.* have demonstrated that biaryl lactones such as **140** are configurationally labile at room temperature, but upon cleavage of the bridge (for example by asymmetric reduction), atropisomeric material can be obtained in high enantioselectivity (Scheme 3.6).[65] It is thought that the enantiodetermining step involves selective reaction of the CBS reagent with one enantiomer of the rapidly interconverting starting material.



Scheme 3.6. Dynamic kinetic resolution of a configurationally unstable bridged lactone

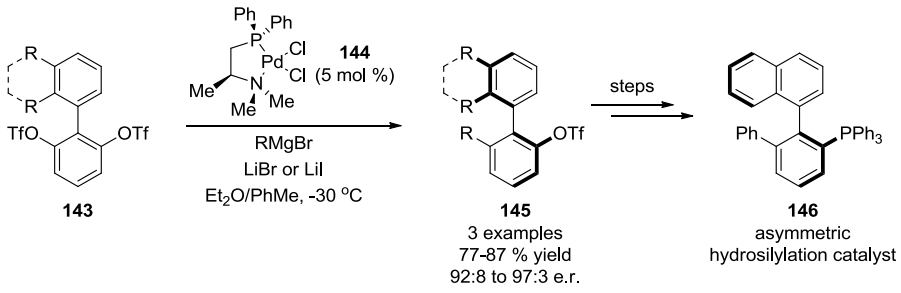
3.2. Desymmetrization of prochiral biaryls

We believed that the fourth class of reaction - desymmetrization of prochiral biaryls represents a particularly appealing atropselective method since it separates the formation of the hindered bond from the enantiodetermining step. The principle is to begin with a hindered starting material, rendered achiral by a plane of symmetry and then rely upon a catalytic asymmetric method to effect desymmetrization. This idea is represented schematically for desymmetrization of a generic prochiral biaryl (Scheme 3.7).



Scheme 3.7. A generic desymmetrization of prochiral biaryls

This area has been pioneered by Hayashi *et al.* who demonstrated that it is possible to desymmetrize prochiral substrates using a Kumada cross-coupling reaction (Scheme 3.8).[66*] Symmetrical ditriflates **143** were reacted with Grignard reagents in the presence of chiral complex **144**. This enabled the synthesis of the desymmetrized products in very high enantioselectivities, although the mechanism of stereoinduction was not discussed. This methodology was extended by cross-coupling the remaining aryl triflate in the enantioenriched products, culminating in the synthesis of **146**, which was demonstrated to be an effective chiral ligand for hydrosilylation.

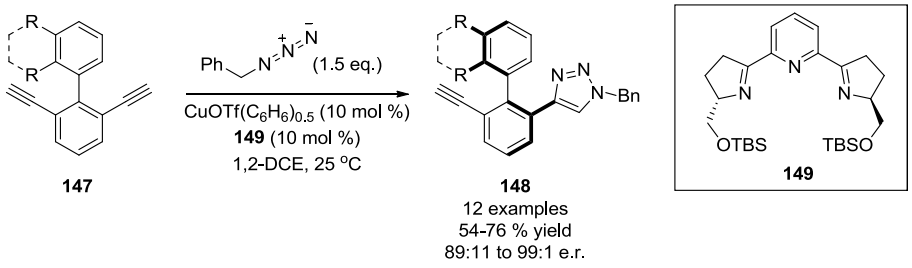


Scheme 3.8. Desymmetrizing Kumada coupling and elaboration to catalyst **146**

Uozumi *et al.* have recently disclosed a transition metal catalysed desymmetrization using click chemistry (Scheme 3.9).[67] In this reaction, a biaryl symmetrically substituted with two alkynes was desymmetrized by a Huisgen cycloaddition with benzyl azide. The enantioselectivity of this process was mediated by a chiral bis(oxazolinyl)pyridine (PyBox) ligand **149** along with copper(I). In all 12 examples investigated, desymmetrization took place in good to excellent

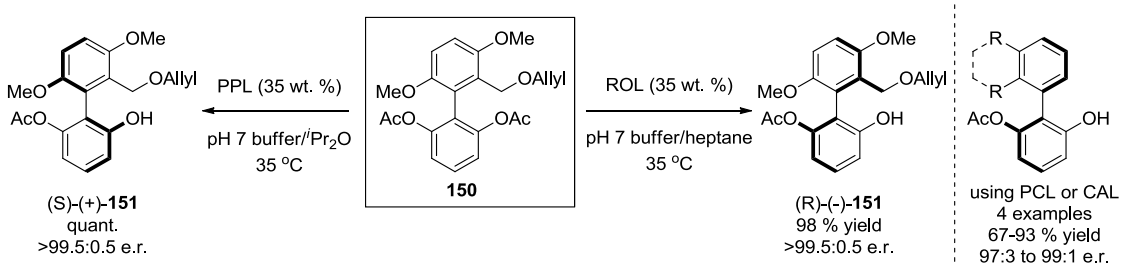
* Prior to this, Raston *et al.* had described one example of a chiral amine mediated asymmetric deprotonation of a prochiral biaryl. After quenching with carbon dioxide they obtained the product in 70:30 e.r.

yield with very high enantioselectivity, although the scope of the 1,3-dipole was limited to benzyl azide.



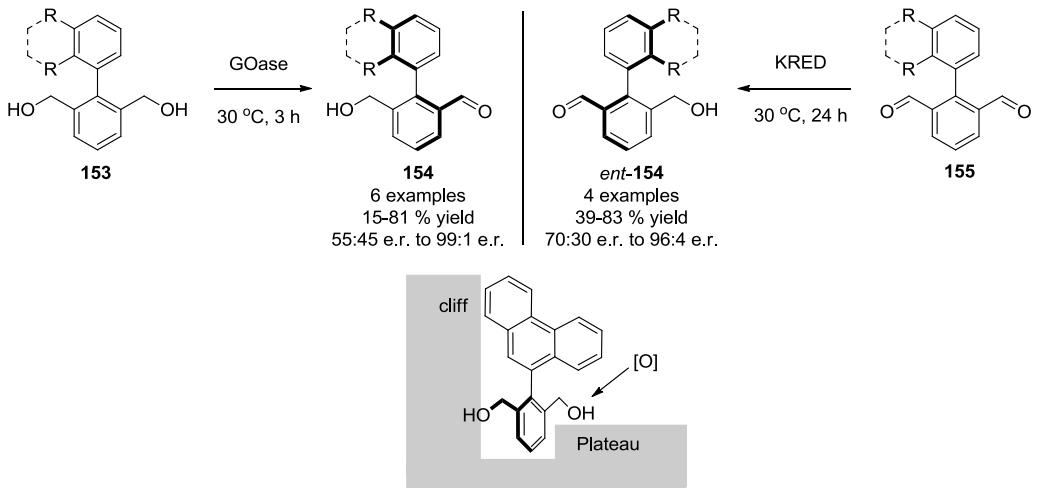
Scheme 3.9. Desymmetrization of **147** *via* an atropselective Huisgen cycloaddition

It has also been possible to carry out desymmetrization using enzymatic methods. Matsumoto and co-workers have described the deacylative desymmetrization of resorcinol derivatives (Scheme 3.10). The authors found that exposure of **150** to the enzyme PPL (porcine pancreatic lipase) resulted in highly enantioselective ester hydrolysis leading to (*S*)-(+)-**151** as a single enantiomer.[68] Conveniently, if the enzyme ROL (*rhizopus oryzae* lipase) was employed and the organic solvent was switched from diisopropyl ether to heptane, fully complementary selectivity was observed and (*R*)-(-)-**151** was the sole product detected. A series of trisubstituted biaryl compounds were also synthesised *via* an analogous method.[69] Depending on the substrate, either PCL (*pseudomonas cepacia* lipase) or CAL (*candida rugose* lipase) proved most effective, leading to desymmetrization with excellent levels of enantioselectivity in all four cases.



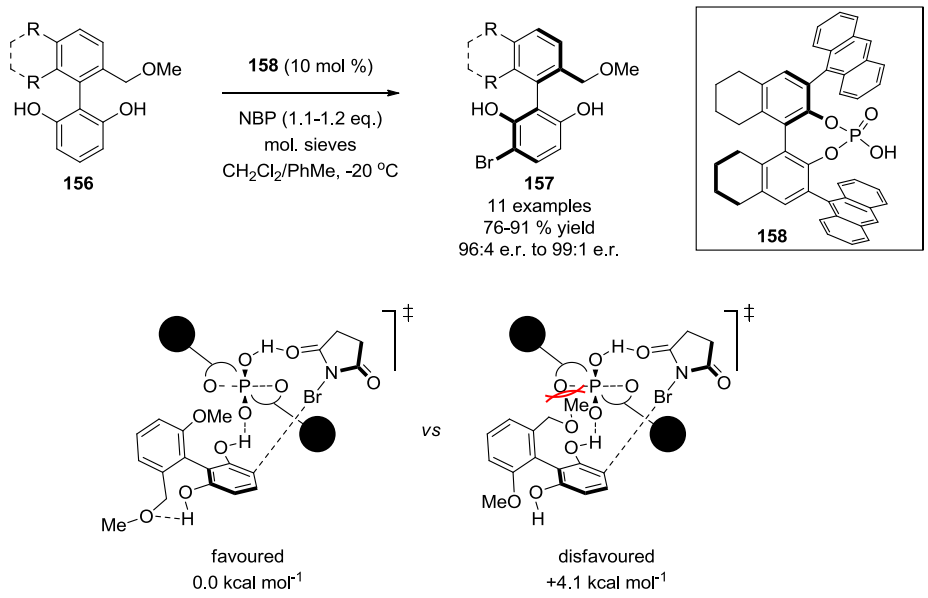
Scheme 3.10. Enzymatic desymmetrization of diacylresorcinol derivatives

Very recently, Clayden *et al.* have reported an enzymatic method for biaryl desymmetrization which involves manipulating the oxidation level of symmetrical dialdehydes or diols (Scheme 3.11).[70] The targets in this case were desymmetrized achiral biaryls **154** bearing benzyl alcohol and aldehyde substituents. These compounds could either be accessed by enzymatic oxidation of the symmetrical diols **153** or by reduction of the dialdehydes **155**. Conveniently, these methods proved to be complementary, leading to opposite enantiomers of **154**. The enantioselectivities observed within both reductive and oxidative manifolds were somewhat variable, although were very high in some cases. Based on the effect of different substitution patterns upon enantioselectivity along with a computational docking study performed on **153**, a model for the enantioselective oxidation was proposed. It was suggested that one border of the active site comprises an extremely bulky region (a cliff), but opposite to this, there exists a less bulky plateau which upon substrate binding can accommodate an *ortho*-substituent. A further bulky region of the enzyme (omitted for clarity) blocks the front face and oxidation is therefore forced to take place at the rear. The selectivity of the reductive process was not discussed.



Scheme 3.11. Enzymatic desymmetrization by redox manipulation along with a schematic model for oxidative desymmetrization

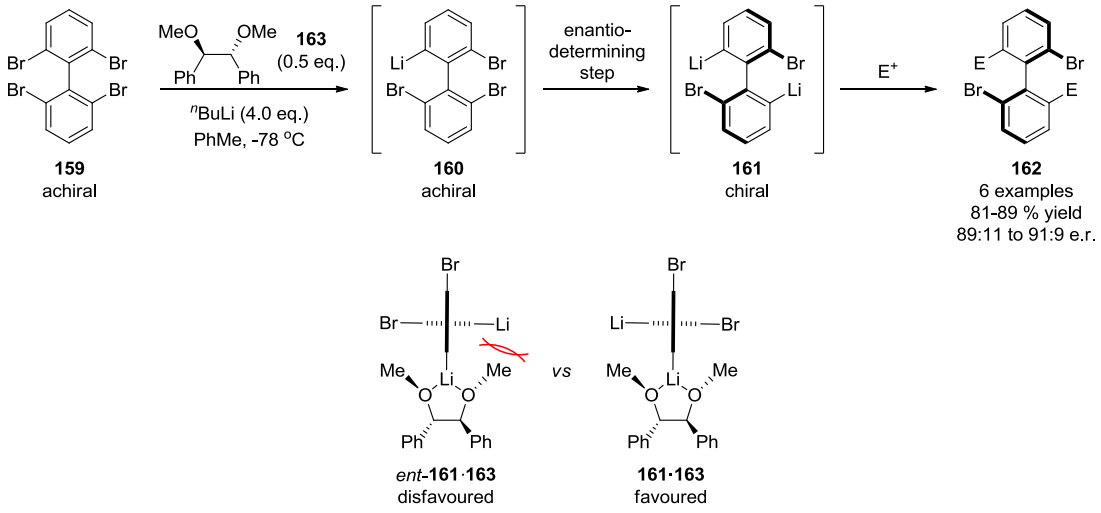
Akiyama *et al.* have described a rare organocatalytic biaryl desymmetrization involving a phosphoric acid catalysed bromination of prochiral resorcinol derivatives (Scheme 3.12).[71] A series of substrates containing an *ortho*-methoxymethyl substituent were brominated with *N*-bromophthalimide (NBP) in the presence of chiral phosphoric acid **158**. The resulting mono-brominated substrates were all obtained with very high levels of enantioenrichment and with excellent yields. This desymmetrization is unusual in that the selectivity does not originate from simple steric differentiation between the two *ortho*-substituents. Computational modelling suggests that the methoxymethyl group forms an intramolecular hydrogen-bond to one of the resorcinol O-H groups.* This rigidifies the substrate and leaves the remaining phenolic group free to hydrogen bond with the catalyst. The catalyst also forms an H-bond with the brominating agent, delivering it to the proximal *ortho*-position of the electron rich aromatic ring. The computational results suggest that the diastereomeric transition states depicted in Scheme 3.12 have an energy difference of 4.1 kcal mol^{-1}.



Scheme 3.12. Akiyama's phosphoric acid catalysed bromination along with proposed stereochemical model. The dark circles represent the 9-anthracenyl groups of catalyst **158**.

* The computation was simplified by modelling the reaction with NBS rather than NBP.

Alexakis *et al.* have extended the principle of biaryl desymmetrization to the asymmetric lithium halogen exchange of a substrate **159** containing a plane of symmetry in both aromatic rings (Scheme 3.13).[72*] In this case, the first lithium halogen exchange leads to intermediate **160** which is still achiral. The second lithiation is enantiodetermining, affording an axially chiral intermediate **161**, which could be quenched with a range of electrophiles including DMF, CO_2, methyl iodide, and iodine. The corresponding products were obtained in good yields and high enantioselectivities. It is noteworthy that this reaction was successfully carried out using sub-stoichiometric quantities of chiral ligand **163**. The authors tentatively rationalize the absolute stereochemistry of the products based on the stability of the key lithiated intermediate **161**. It is suggested that if **163** is present as a bidentate ligand during the enantiodetermining lithiation step, then *ent*-**161**·**163** would suffer a steric clash between the phenyl group of the ligand and the lithium (which is assumed to be extensively aggregated). Therefore it is preferred to form the alternative dilithiated species **161**·**163**.

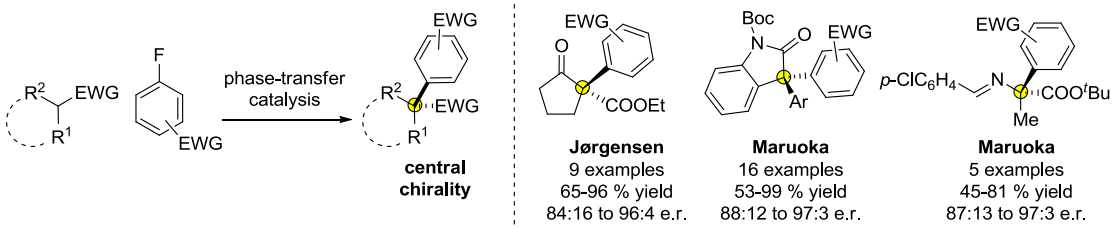


Scheme 3.13. Asymmetric lithium halogen exchange of tetrabromobiaryl **159** along with a stereochemical model

[*] This result built on the previous work of their own research group along with Kagan *et al.*, who independently described the lithium halogen exchange of dibrominated substrates.

3.3. Catalytic asymmetric S_NAr reactions

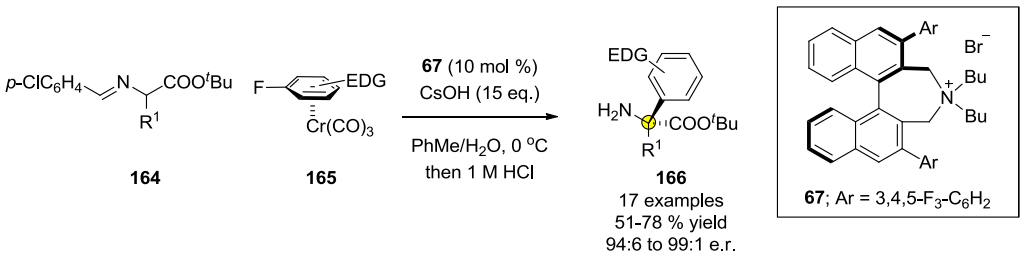
The nucleophilic aromatic substitution (S_NAr) reaction is a well-established method for the construction of functionalized aromatic systems. Despite this synthetic utility, few methods have been described which enable control over the absolute stereochemistry of this transformation. The asymmetric S_NAr reaction has been most extensively investigated within the context of the phase-transfer catalysed arylation of enolates with electron deficient aryl fluorides (Scheme 3.14). Jørgensen *et al.* have reported the arylation of cyclic β-ketoesters,[73] whilst the research group of Maruoka have employed both oxindoles[74] and glycine imine Schiff bases[75] as nucleophiles. In all three cases, these reactions proceeded with high enantioselectivity, although the scope of electrophile was limited to extremely reactive aryl halides such as Sanger's reagent (1-fluoro-2,4-dinitrobenzene).



Scheme 3.14. Formation of point chiral products in the asymmetric S_NAr reactions of trisubstituted enolates

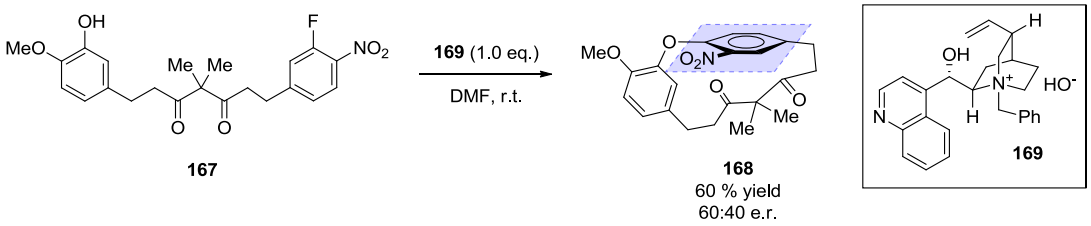
Very recently, Maruoka has described an asymmetric phase-transfer catalysed S_NAr reaction which takes place with electron rich aryl halide electrophiles.[76] This was achieved by taking advantage of the enhanced electrophilicity of η_6-chromium complexed arenes. In the presence of chiral phase-transfer catalyst **67**, a range of electron rich aryl fluoride η_6-$Cr(CO)_3$ complexes **165** underwent room temperature S_NAr reaction with α-amino acid derivatives **164** (Scheme 3.15). The quaternary stereogenic centre of the products **166** (following decomplexation with aqueous acid) was formed with very high enantioselectivity. Although this methodology involves the use of stoichiometric quantities of highly toxic chromium metal,

it represents a method to carry out a mild S_NAr reaction with aryl halides which would normally be completely unreactive.[77]



Scheme 3.15. Maruoka's catalytic asymmetric S_NAr reaction of enolates with chromium complexed arenes

Zhu *et al.* have developed an asymmetric S_NAr reaction for the synthesis of planar chiral biaryl ethers.[78] In this case, a stoichiometric quantity of chiral base **169** was able to promote an intramolecular S_NAr reaction between a phenol and a tethered nitrofluoroarene (Scheme 3.16). The product of this reaction, which is rendered chiral by virtue of restricted rotation of the tether about the plane of the hindered nitroarene, was formed in good yield and 60:40 e.r.



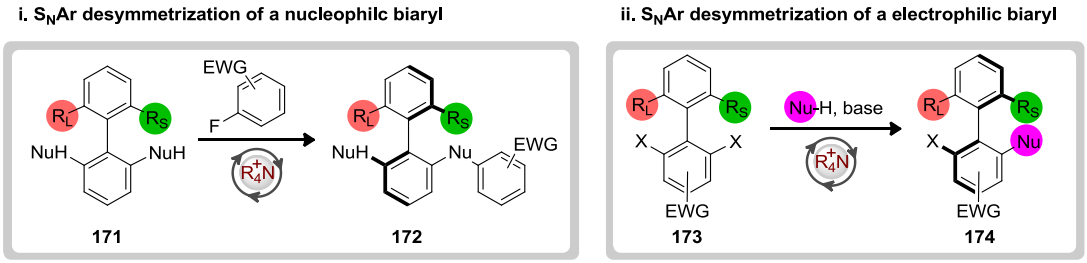
Scheme 3.16. Zhu's intramolecular S_NAr reaction for the synthesis of planar chiral ether **168**

3.4. Project aims

Our aim at the outset of this project was to combine two of the ideas discussed in this introduction and carry out desymmetrization of a prochiral biaryl *via* an asymmetric S_NAr reaction. We had in mind two possible approaches to achieve this goal (Scheme 3.17):

i. To begin with a prochiral biaryl **171**, symmetrically substituted with two nucleophilic functional groups. In the presence of a phase-transfer catalyst and an electron poor aryl halide we hoped to carry out a desymmetrizing S_NAr reaction.

ii. Essentially reversing this disconnection we hoped to synthesise a symmetrical electrophilic biaryl **173**, substituted with two prochiral leaving groups. We would then rely upon an appropriate combination of nucleophile and phase-transfer catalyst to carry out a desymmetrizing S_NAr reaction.

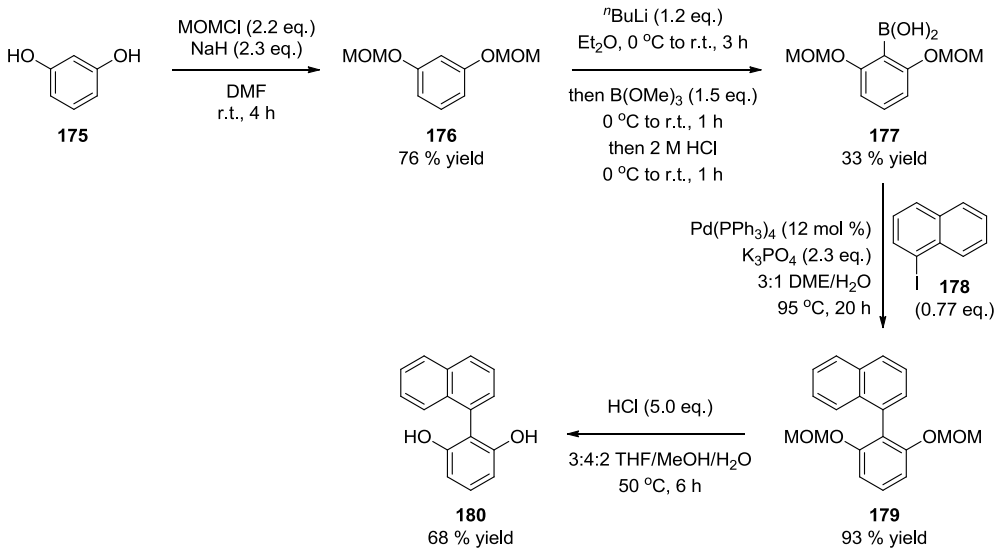


Scheme 3.17. Two proposed strategies for desymmetrizing S_NAr reaction

3.5. Desymmetrization of prochiral nucleophilic biaryls

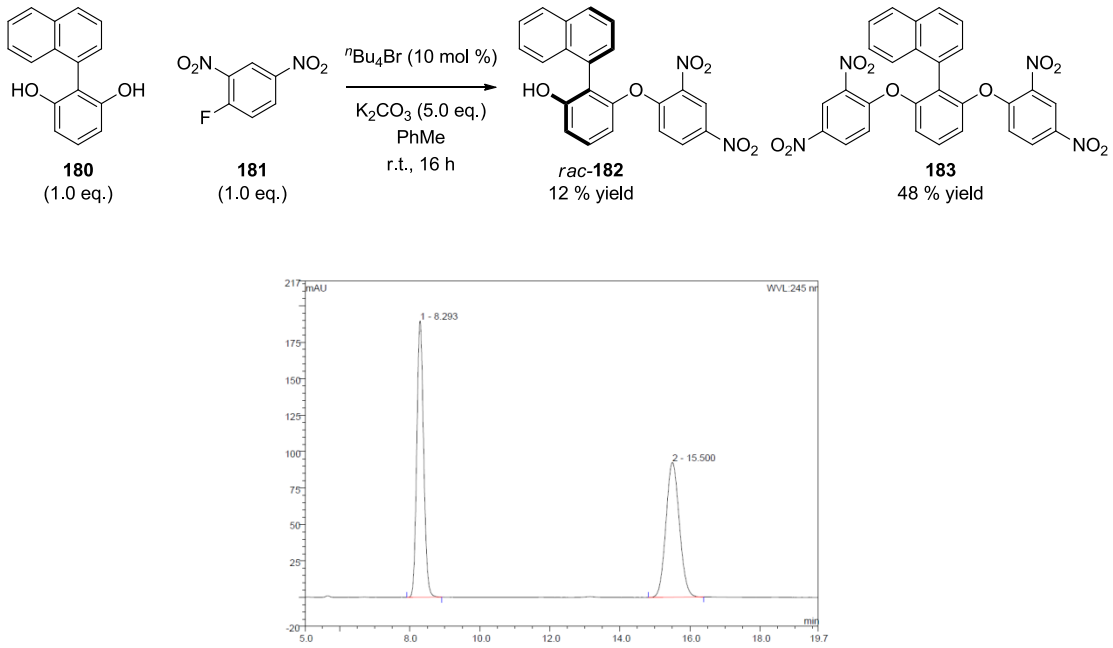
We began by investigating the cation-directed desymmetrization of a nucleophilic biaryl. We hoped that phenol would be able to serve as an effective phase-transfer nucleophile and therefore set out to investigate an extremely hindered resorcinol derivative **180**.[79] This starting material was synthesised in four steps according to the method described by Matsemotu *et al.*[69] This began with a double MOM protection of resorcinol, leading to **176** in 76 % yield. The two MOM groups acted as effective directing groups for an *ortho*-lithiation of the central position and the resulting aryl lithium was quenched with trimethylborate, which

after acidic hydrolysis led to boronic acid **177** in 33 % yield. Under standard conditions, this compound underwent Suzuki-Miyaura coupling with 1-iodonaphthalene affording biaryl **179** in excellent yield and this material was subsequently deprotected to give the desired free phenol **180** (Scheme 3.18).



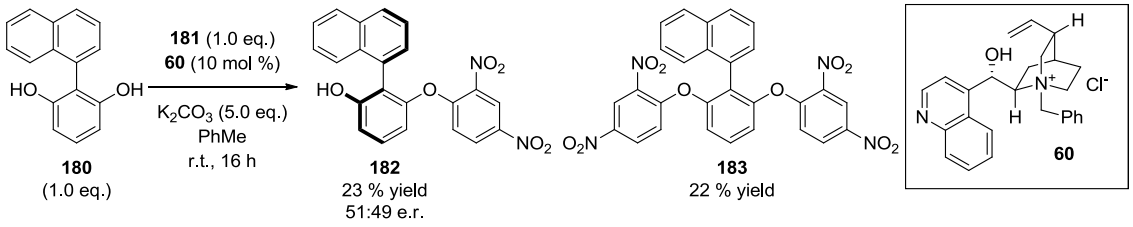
Scheme 3.18. Synthesis of a nucleophilic prochiral biaryl substrate **180**

We were then in a position to investigate the desymmetrization reaction of **180** and selected Sanger's reagent as a reactive electrophile. We initially attempted the key S_NAr reaction using potassium carbonate as a base along with an achiral phase-transfer catalyst. Under these conditions, we were surprised to observe predominantly achiral compound **183**, which results from diarylation. A small quantity of the desired monoarylated compound **182** was formed. We were pleased to see that **182** exhibited two clearly separated peaks by analytical chiral HPLC indicating it to be atropisomeric (Scheme 3.19).



Scheme 3.19. Racemic S_NAr reaction of **180** along with a chiral HPLC spectrum of *rac*-**182**

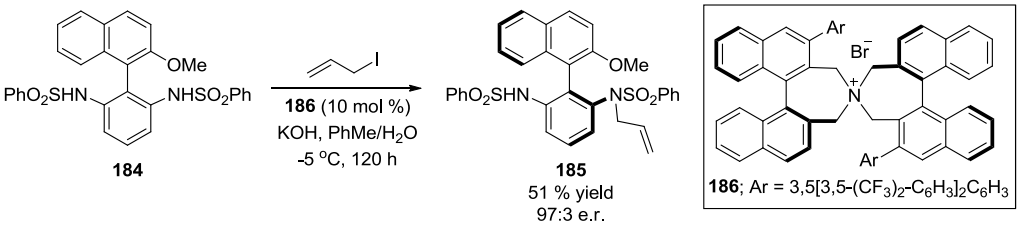
We next attempted the desymmetrization reaction under asymmetric conditions and accordingly **180** was treated with Sanger's reagent in the presence of solid potassium carbonate and a catalytic quantity of *N*-benzylcinchoninium chloride **60**. Under these conditions, the selectivity for single *vs* double addition was improved and the mono-arylated product was obtained in 23 % yield. However, this material was found to be essentially racemic (Scheme 3.20).



Scheme 3.20. Attempted asymmetric phase-transfer catalysed desymmetrization of **180**

It was at this point that Maruoka and co-workers published an elegant study describing the phase-transfer catalysed desymmetrization of prochiral anilines (Scheme 3.21).[80] In this work, a naphthyl substituted biaryl **184** was alkylated with allyl iodide leading to **185** in 97:3 e.r. We

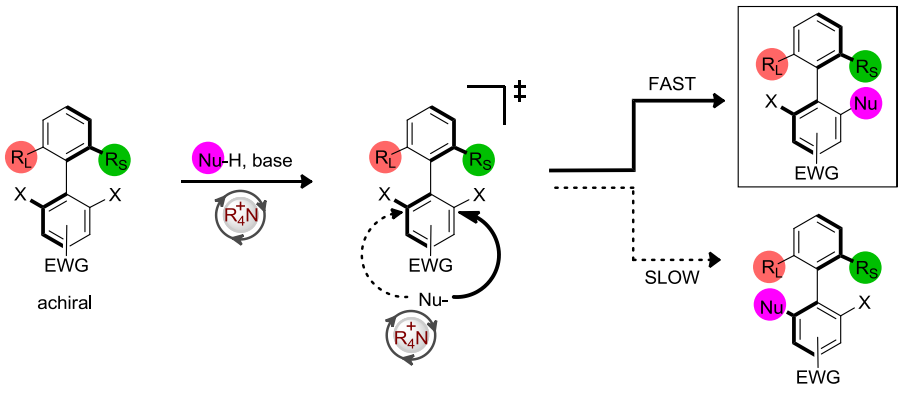
therefore felt it would be appropriate to refocus our efforts on the desymmetrization of prochiral electrophilic biaryls.



Scheme 3.21. Maruoka's desymmetrizing phase-transfer catalysed alkylation of a prochiral dianiline

3.6. Desymmetrization of prochiral electrophilic biaryls

Our aim was to synthesise a symmetrical, electrophilic biaryl. If such a compound could undergo a S_NAr reaction in which a nucleophile displaces one of two prochiral leaving groups, the symmetry within the starting material would be broken, and an axially chiral product would result (Scheme 3.22). We hoped that a phase-transfer catalyst might permit a nucleophile to selectively carry out such a reaction, allowing the nucleophile to differentiate between enantiotopic leaving groups.



Scheme 3.22. Our strategy - an atropselective desymmetrizing S_NAr reaction

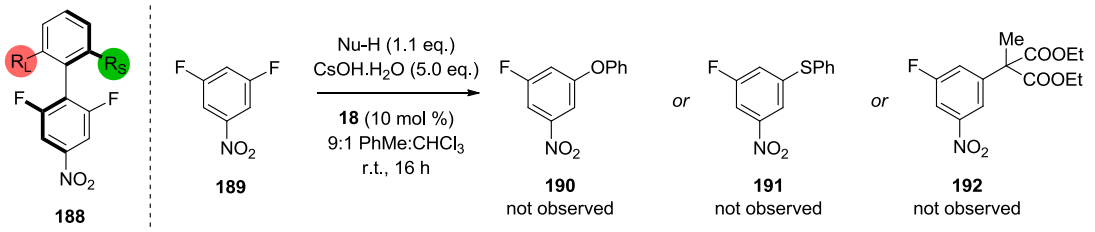
In order for a system to be amenable to such a transformation, there are several key requirements:

i. The starting material must possess of a plane of symmetry.

ii. The product must be sufficiently hindered to avoid racemization.

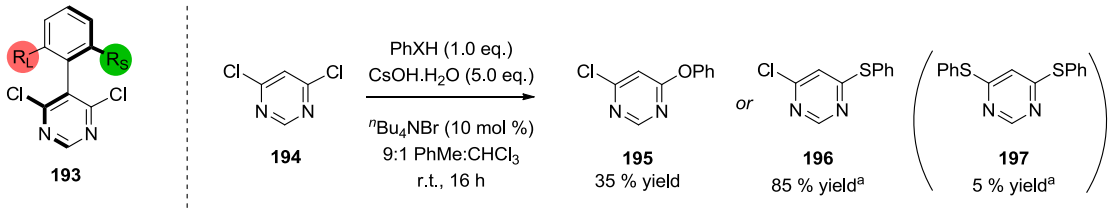
iii. The arene must be electrophilic enough to undergo facile S_NAr under mild conditions.

We believed that a difluoronitroarene such as **188** might satisfy these criteria, but were unsure about how much of an activating effect the *meta*-nitro group would provide. We therefore attempted some reactions to investigate S_NAr reactivity with a test substrate **189**. Under typical phase-transfer conditions, we observed no reactivity with phenol, thiol or malonate nucleophiles suggesting that this electrophile is not sufficiently activated (Scheme 3.23).



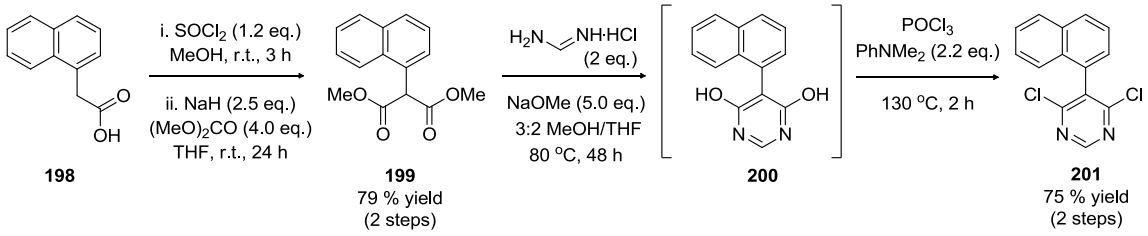
Scheme 3.23. Possible difluoronitroarene substrates and unsuccessful test reactions with **189**

We knew that incorporation of nitrogen atoms into an aromatic ring also leads to increased electrophilicity. This effect is particularly strong in the case of pyrimidines, which led us to consider symmetrical dichloropyrimidines as potential substrates (Scheme 3.24). We carried out a test reaction between an unsubstituted dichloropyrimidine **194** and phenol, and were pleased to isolate substituted product **195** in 35 % yield. With thiophenol, which has previously been demonstrated to be a particularly effective S_NAr nucleophile,[81] excellent reactivity was observed and the product **196** was isolated in 85 % yield along with a small quantity (5 %) of by-product **197**, originating from double addition of the thiol.



Scheme 3.24. Possible dichloropyrimidine substrates and successful test reactions with **194**. (a) $^{n}Bu_4NBr$ (10 mol %), KOH (5.0 eq.) in PhMe/H_2O at r.t. for 1 h.

Following this promising result, we decided to investigate an extremely hindered 1-naphthyl substituted dichloropyrimidine **201**. This compound was prepared *via* a four step route, which commenced with esterification and acylation of commercially available carboxylic acid **198** leading to the corresponding α-arylmalonate **199** in a good yield over two steps (Scheme 3.25). This malonate was then refluxed with formamidine hydrochloride in the presence of sodium methoxide, effecting cyclization to dihydroxypyrimidine **200** which was used without purification in the next step. Treatment of crude **200** with phosphorus (V) oxychloride and *N*,*N*-dimethylaniline gave the desired dichloropyrimidine **201** in 75 % yield from **199**.

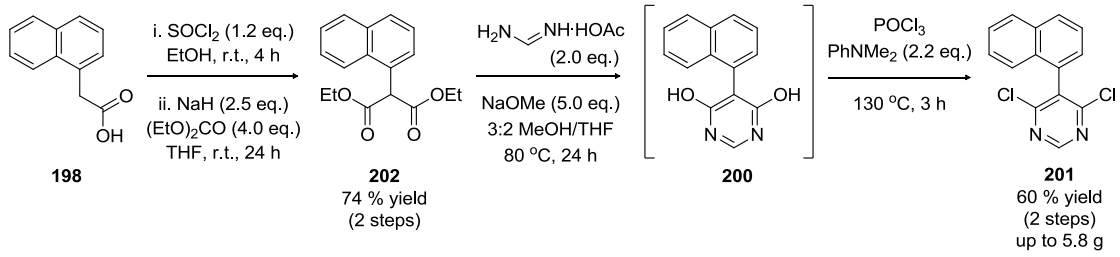


Scheme 3.25. First generation synthesis of dichloropyrimidine **201**

Subsequently, we found diethylmalonate **202** to be a preferable intermediate, since purification *via* column chromatography on a large scale proved more straightforward.[*] We were also able to carry out the cyclization step with the acetate salt of formamidine which is significantly less expensive than the corresponding hydrochloride salt. This second generation

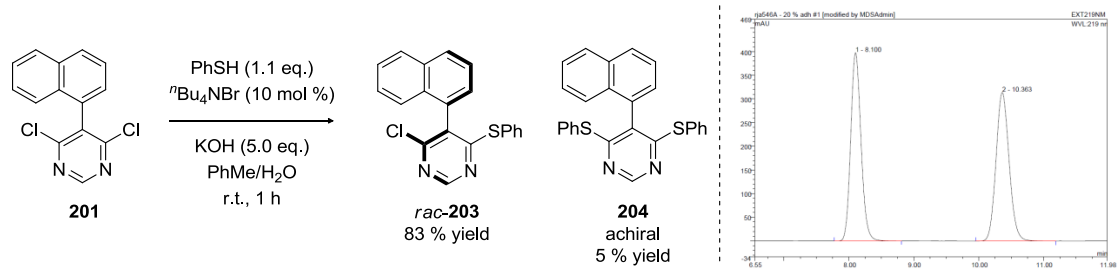
[*] **199** was somewhat unstable to chromatography and crystallization of the crude reaction mixture proved capricious.

synthesis proceeded in good yield and allowed us to synthesise multi-gram quantities of **201** (Scheme 3.26).



Scheme 3.26. Synthesis of dichloropyrimidine substrate **201**

With **201** in hand, we were in a position to attempt a desymmetrizing S_NAr reaction. Accordingly, **201** was treated with a slight excess of thiophenol along with catalytic tetra-*n*-butylammonium bromide in a biphasic mixture of toluene and 50 % aqueous potassium hydroxide. Pleasingly, the desired S_NAr reaction took place, forming **203** in 83 % yield after one hour. The reaction showed excellent selectivity for mono *vs* double substitution - achiral by-product **204** resulting from double addition was produced in only 5 % yield. When we subjected **203** to analytical chiral HPLC, we were pleased to see clear separation of the two enantiomers indicating this material to be atropisomeric (Scheme 3.27).

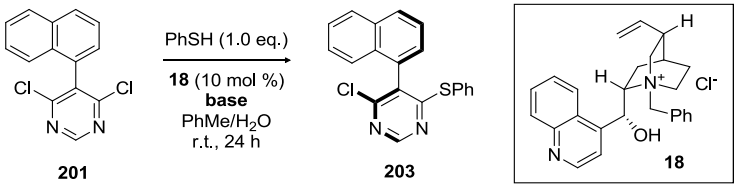


Scheme 3.27. S_NAr reaction of **201** and analytical chiral HPLC trace for *rac*-**203**

3.7. Optimization of asymmetric reaction conditions

Next, we set out to develop an asymmetric variant of this transformation. We began our investigation with chiral cinchonidine derived phase-transfer catalyst **18** and carried out a small screen of bases. Our initial results were disappointing – both aqueous and solid

potassium hydroxide led to **203** as a racemate (Table 3.1, entries 1-2) and similar results were obtained with cesium hydroxide (Table 3.1, entries 3-4). We were therefore delighted to find that using aqueous potassium carbonate, the product **203** was obtained in 58:42 e.r.* (Table 3.1, entry 5).



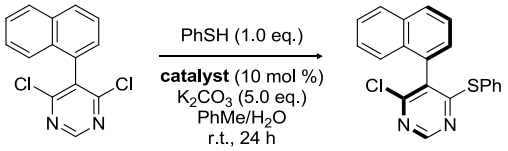
Entry	Base [eq.]	e.r.
1	KOH(aq.) [10]	50:50
2	KOH(s) [1.0]	51:49
3	CsOH(aq.) [10]	49:51
4	$CsOH.H_2O$(s) [1.0]	48:52
5	K_2CO_3(aq.) [10]	58:42

Table 3.1. The effect of base on the desymmetrizing S_NAr reaction

We then investigated the effect of different chiral phase-transfer catalysts on the reaction. We evaluated the performance of an extensive library of cinchona alkaloid-derived ammonium salts (for full details see Appendix E, key results are shown in Table 3.2). Protection of the *C*9-hydroxyl group of the catalyst had a detrimental effect upon enantioselectivity, and near racemic product was observed (Table 3.2, entry 2). The possible origins of this effect are discussed in detail in Chapter 4. Use of pseudoenantiomeric catalysts derived from cinchonine or quinidine **60** and **206** led to comparable levels of enantioselectivity (Table 3.2, entries 3-4), but when we evaluated quinine derived catalyst **53**, we observed significantly higher selectivity, obtaining the product in 87:13 e.r. (Table 3.2, entry 5). It is noteworthy that despite the pseudoenantiomeric nature of these catalysts, in all four cases the major enantiomer of the product was formed with the same absolute configuration. Substitution of the benzyl

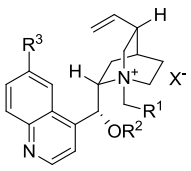
* Using 1.0 equivalents of solid potassium carbonate, low conversion to **203** was observed.

group of the catalyst was extensively evaluated, but in all cases led to reduced enantioselectivity along with an inversion of absolute configuration (Table 3.2, entries 6-11). Interestingly, chiral phase-transfer catalysts containing biaryl backbones **66** and **67** were unable to catalyse this reaction (Table 3.2, entries 12-13).[41]

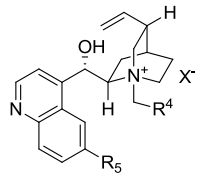


201 **203**

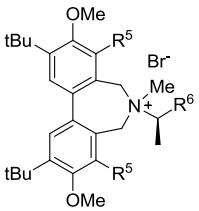
Entry	Catalyst	e.r.
1	**18**	58:42
2	**53**	48:52
3	**60**	61:39
4	**206**	55:45
5	**55**	87:13
6	**207**	39:61
7	**208**	46:54
8	**209**	43:57
9	**210**	43:57
10	**211**	45:55
11	**212**	43:57
12[a]	**66**	n.d.
13[a]	**67**	n.d.



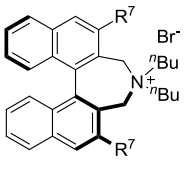
18: R^1 = Ph; R^2 = H; R^3 = H; X = Cl
53: R^1 = Ph; R^2 = Allyl; R^3 = H; X = Br
55: R^1 = Ph; R^2 = H; R^3 = OMe; X = Cl
207: R^1 = 4-NO_2-C_6H_4; R^2 = H; R^3 = OMe; X = Br
208: R^1 = 3,5-$(CF_3)_2$-C_6H_3; R^2 = H; R^3 = OMe; X = Br
209: R^1 = 2,3,4-F_3-C_6H_2; R^2 = H; R^3 = OMe; X = Br
210: R^1 = 3-Me-C_6H_4; R^2 = H; R^3 = OMe; X = Br
211: R^1 = 2-Me-C_6H_4; R^2 = H; R^3 = OMe; X = Br
212: R^1 = 2-naphthyl; R^2 = H; R^3 = OMe; X = Br



60: R^4 = Ph; R^5 = H; X = Cl
206: R^4 = Ph; R^5 = OMe; X = Cl



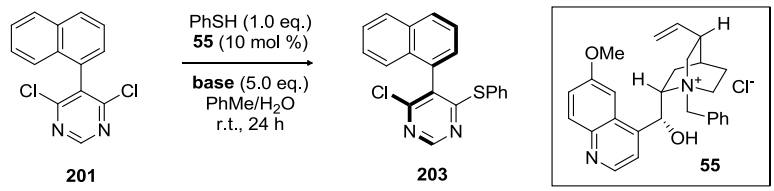
66
R^5 = 3,5-$(CF_3)_2$-C_6H_3
R^6 = 2-naphthyl



67
R^7 = 3,4,5-F_3-Ph

Table 3.2. Catalyst optimization for an atropselective S_NAr reaction. (a) Only trace conversion to **203** was observed.

These results identified *N*-benzylquininium chloride **55** to be the optimal phase-transfer catalyst for this reaction. We then expanded our optimization to other aqueous carbonate bases and different reaction solvents. A range of alkali metal carbonate bases were equally effective at promoting the reaction (Table 3.3, entries 1-3), although alkali-earth metal carbonate bases led to reduced selectivity (Table 3.3, entries 4-5). We also looked at silver carbonate, believing that formation of silver chloride might act as a driving force for S_NAr reaction, but we observed no reactivity (Table 3.3, entry 6). This may be a consequence of the low water solubility of Ag_2CO_3. Employing carbon tetrachloride, a solvent previously demonstrated to be effective for phase-transfer catalysed reactions of thiols, led improved enantioselectivity (Table 3.3, entry 7).[82] Finally, employing a slight excess of thiophenol led to a further increase in enantioselectivity and we obtained **203** in 97:3 e.r. (Table 3.3, entry 8). The origin of the effect of thiol stoichiometry on enantioselectivity is discussed in detail in Chapter 4.

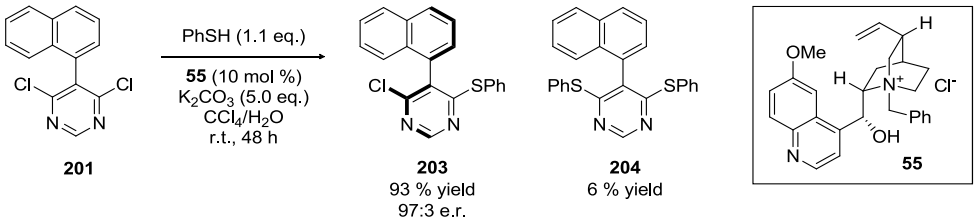


201 **203** **55**

Entry	Base [eq.]	Solvent	e.r.
1	K_2CO_3(aq.) [5]	PhMe	87:13
2	Li_2CO_3(aq.) [5]	PhMe	85:15
3	Cs_2CO_3(aq.) [5]	PhMe	86:14
4[a]	$CaCO_3$(aq.) [5]	PhMe	58:42
5[a]	$BaCO_3$(aq.) [5]	PhMe	64:36
6[b]	Ag_2CO_3(aq.) [5]	PhMe	n.d.
7	K_2CO_3(aq.) [5]	CCl_4	95:5
8[c]	K_2CO_3(aq.) [5]	CCl_4	97:3

Table 3.3. The effect of different carbonate bases. (a) poor conversion. (b) starting material only. (c) Using 1.1 equivalents of PhSH for 48 hours.

Carrying out this reaction on a 50 mg scale, we were able to isolate **203** in 93 % yield in 97:3 e.r. along with by-product **204** resulting from double addition in 6 % yield (Scheme 3.28).*



Scheme 3.28. Optimised conditions for phase-transfer catalysed desymmetrizing S_NAr reaction

The configurational stability of **203** proved to be remarkably high. Indeed, even when we heated an enantioenriched sample of this material (97:3 e.r.) to 100 °C in DMSO for 20 h, we detected no thermal racemization (Scheme 3.29).

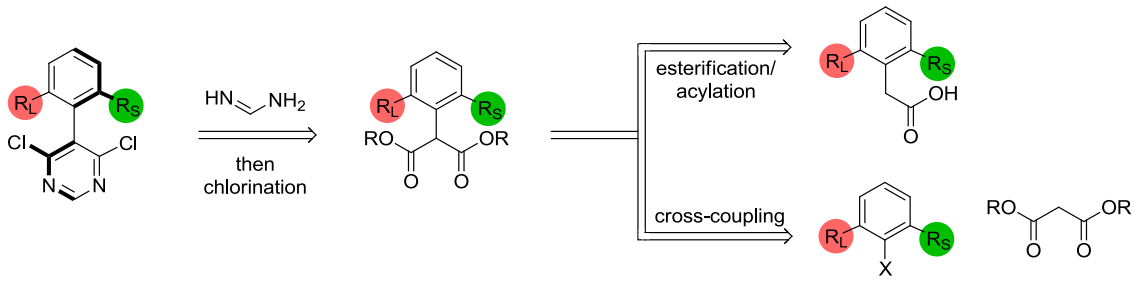


Scheme 3.29. Experiment to determine the barrier to thermal racemization of **203**

3.8. Substrate synthesis

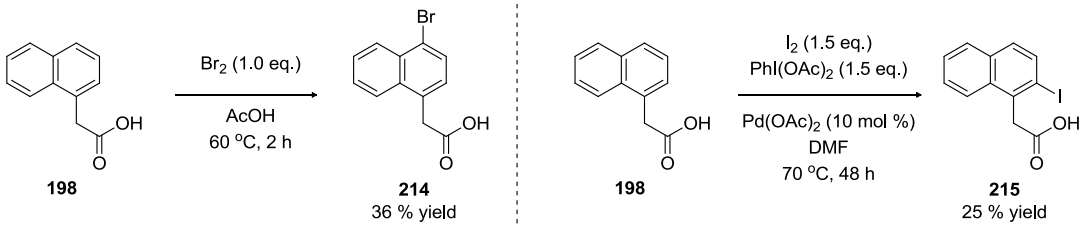
We set out to synthesise substrates containing functionalised naphthyl groups or hindered *ortho*- substituted aromatics. We envisaged that these compounds could also be synthesised from malonates by cyclization with formamidine followed by chlorination (Scheme 3.30). These malonates could then be prepared either by esterification and acylation of a carboxylic acid or *via* a cross coupling reaction between a malonate and an aryl halide.

* This reaction was carried out in a sealed vial under an atmosphere of nitrogen. In the absence of an inert atmosphere we detected small quantities of diphenyldisulfide, which presumably arises *via* aerobic oxidation of thiophenol.



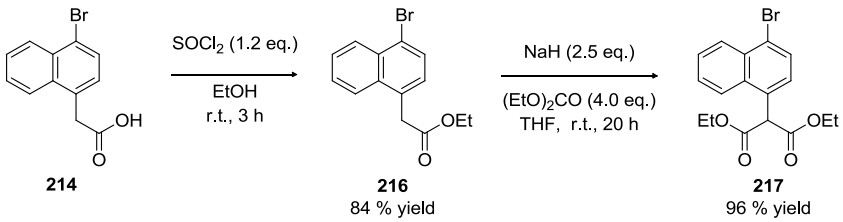
Scheme 3.30. Retrosynthetic analysis for different dichloropyrimidine electrophiles

We synthesised two malonates using the esterification/acylation route, and these were both derivatives of 1-naphthylacetic acid **198**. Bromination of 1-naphthylacetic acid was carried out according to a procedure described by Schubert-Zsilavecz *et al.*[83] The yield of this reaction was poor, but the reaction was carried out on a large scale enabling access to multi-gram quantities of **214**. Iodination of **198** was carried out using C-H activation methodology described by Yu *et al.*, leading to **215** in 25 % yield (Scheme 3.31).[84]



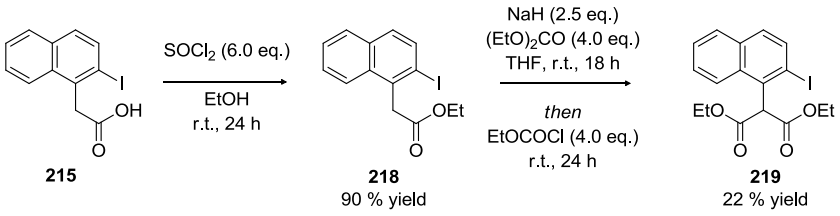
Scheme 3.31. Synthesis of substituted acids **214** and **215**

Brominated carboxylic acid **214** underwent esterification with thionyl chloride in ethanol leading to ester **216** in 84 % yield. The corresponding malonate **217** was formed under standard conditions in 96 % yield (Scheme 3.32).



Scheme 3.32. Esterification and acylation of brominated carboxylic acid **214**

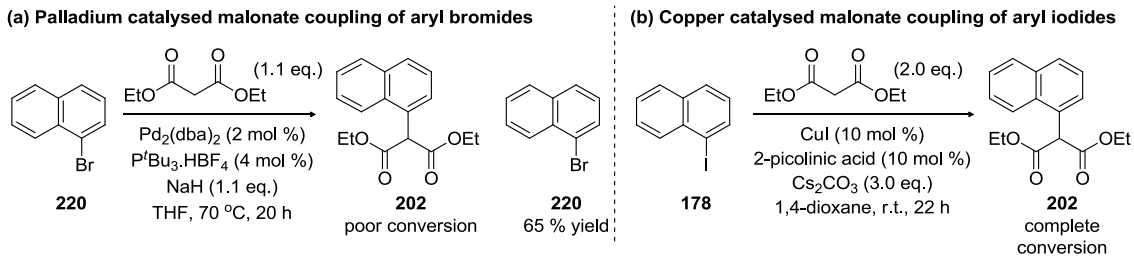
The hindered iodinated acid **215** proved considerably less reactive - esterification required an excess of thionyl chloride and took place slowly. Nevertheless, **218** was obtained in 90 % yield (Scheme 3.33). We were unable to acylate **218** with diethyl carbonate, but following addition of ethyl chloroformate as a more reactive acylating agent, we obtained a moderate yield of malonate **219**.



Scheme 3.33. Esterification and acylation of iodinated carboxylic acid **215**

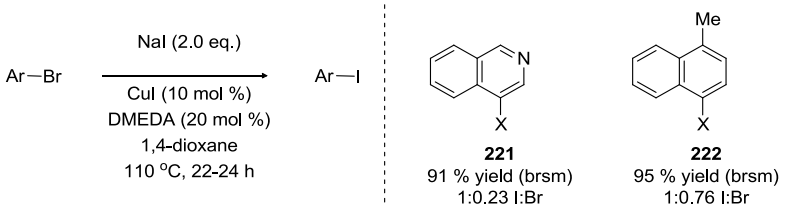
As described in Scheme 3.30, we planned to make the remainder of our α-arylmalonates *via* a metal catalysed cross-coupling reaction. Two approaches have been described in the literature for cross-couplings between malonates and hindered aryl halides. The first method reported by Hartwig *et al.* involved palladium catalysed coupling between malonates and aryl bromides;[85] whereas the second approach described by Kwong *et al.* described a copper catalysed coupling between malonates and aryl iodides.[86] In order to determine which of these methods would be most effective for the preparation of our substrates, we applied both conditions to the synthesis of α-naphtyhlmalonate **202** (Scheme 3.34). We found that under the palladium catalysed conditions low conversion to the desired arylmalonate was observed and the unreacted aryl bromide **220** was re-isolated in 65 % yield.[*] We believe this result may be partly due to the high air sensitivity of these reaction conditions. We found the copper catalysed conditions promoted coupling more efficiently, leading to complete conversion to **202** after 22 hours. We therefore decided to employ this method to synthesise the remainder of our malonates.

[*] The product could not be separated from diethyl malonate.



Scheme 3.34. Evaluation of methods for metal catalysed cross-coupling of malonates with aryl halides

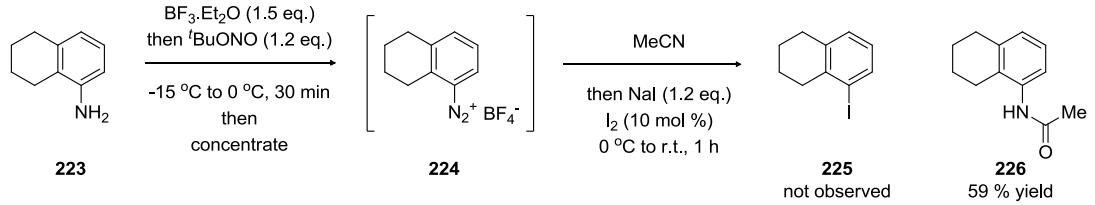
In order to use these copper catalysed conditions it was necessary to utilize aryl iodides as the halogenated coupling partner. However, in some cases only the corresponding aryl bromides were commercially available. Fortunately, we were able to make use of a copper catalysed Finkelstein reaction reported by Buchwald *et al.* to convert these bromides into iodides.[87] Using sodium iodide along with catalytic copper(I) iodide and a diamine ligand, we were able to synthesise iodide coupling partners **221** and **222** in good yields (Scheme 3.35). In both cases, we obtained incomplete conversion to the iodide, but we believed that subjection of the mixture to cross-coupling conditions would not be problematic.



Scheme 3.35. Synthesis of aryl iodides *via* a copper catalysed Finkelstein reaction

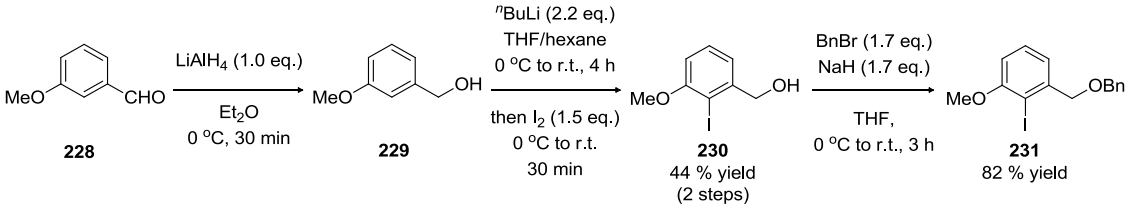
We also aimed to synthesise a tetrahydronaphthalene substrate. The only commercially available building block which appeared suitable was aniline **223**, which we hoped might be converted to the corresponding iodide through a Sandmeyer reaction. In practice, we carried out diazotization of **223** at -15 °C in dichloromethane and then removed the solvent under reduced pressure to afford the crude diazonium salt **224**. We then dissolved **224** in acetonitrile, but before sodium iodide could be added, a rapid and highly exothermic reaction took place leading to amide **226** in 59 % yield (Scheme 3.36). Related processes have been

described previously in the literature and are believed to arise from a Ritter-like reaction between the diazonium salt and the acetonitrile solvent.[88]



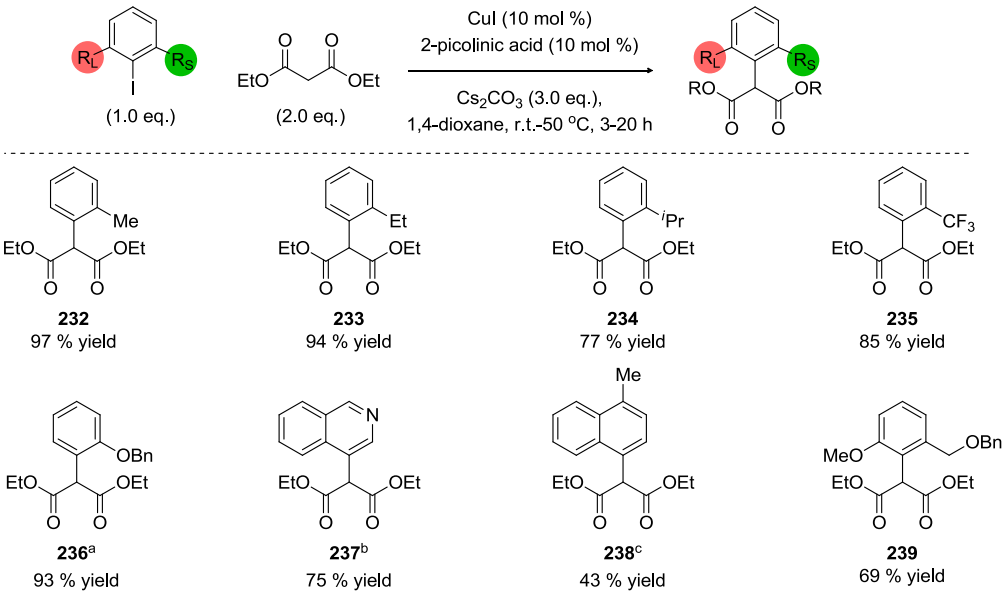
Scheme 3.36. Attempted Sandmeyer reaction leading to unexpected product **226**

We also wanted to investigate the effect of a 2,6-disubstituted arene. In order to obtain an appropriate aryl iodide, we began by reducing *meta*-anisaldehyde **228** with lithium aluminium hydride to afford **229**. According to a literature procedure, **229** then underwent *ortho*-lithiation with two equivalents of *n*-BuLi, and the resulting aryl lithium was trapped with iodine affording **230** in 44 % yield over 2 steps.[71] The free alcohol was then protected as the corresponding benzyl ether under standard conditions, leading to **231** in good yield (Scheme 3.37).



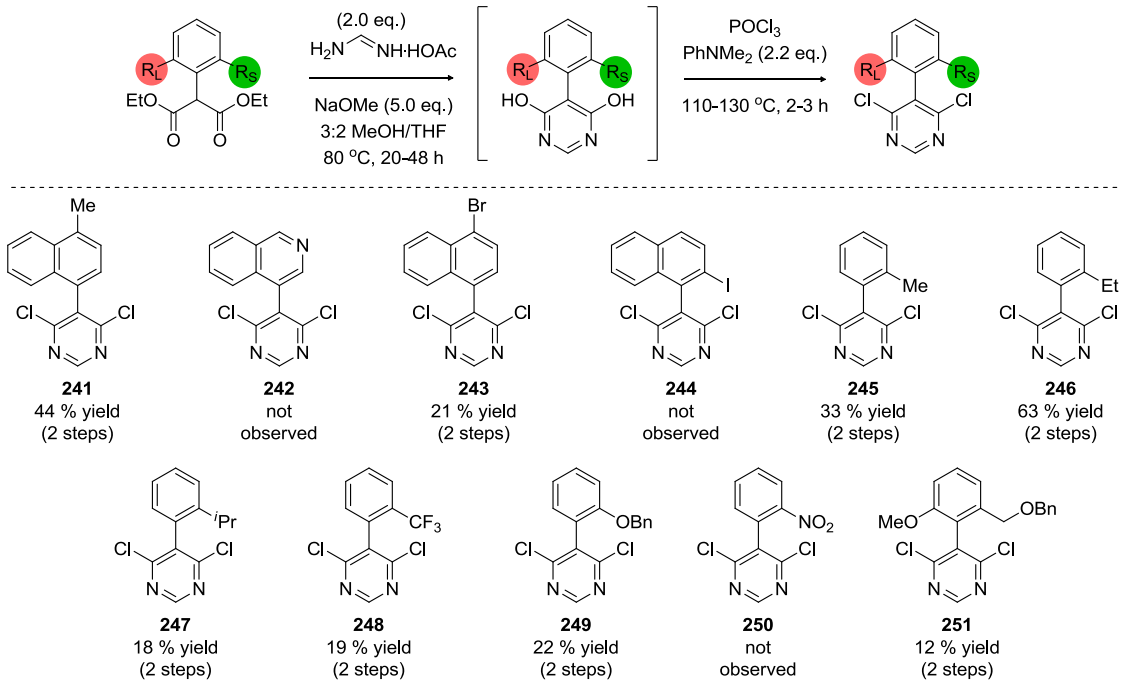
Scheme 3.37. Synthesis of doubly substituted aryl iodide **231**

This collection of aryl iodides, along with several commercially available iodoarenes were subjected to copper catalysed cross-coupling with diethylmalonate. This reaction proved very reliable, and we were pleased to obtain all of the desired malonates in good yields. Even in the case of extremely hindered malonates such as **239**, which bears two *ortho*-substituents, we observed the coupled product in 69 % yield (Scheme 3.38).



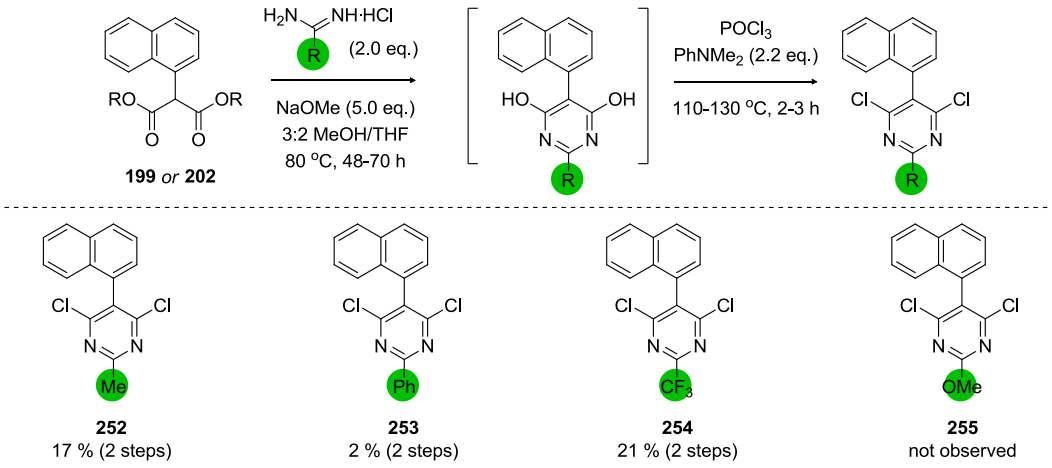
Scheme 3.38. Synthesis of α-arylmalonates *via* copper catalysed cross coupling. (a) The starting iodide was synthesised by benzylation of 2-iodophenol in 94 % yield. (b) Starting from a 1:0.23 of aryl iodide:bromide. (c) Starting from a 1:0.76 mixture of aryl iodide:bromide.

We then took this library of malonates along with those obtained earlier from the esterification/acylation route and subjected them the two step procedure involving cyclization with formamidine followed by dehydroxychlorination (Scheme 3.39). The yields for the individual substrates were not optimized, but the reactions were all carried out on a sufficiently large scale to obtain significant quantities (0.1-1.2 g) of the dichloropyrimidines. Using this method, we successfully synthesised eight substrates including naphthyl substituted dichloropyrimidines **241** and **243** along with several starting materials containing singly *ortho*-substituted aryl rings **245**-**249**. When we attempted to synthesise isoquinoline substrate **242**, we were unable to isolate any dihydroxypyrimidine after reaction with formamidine. In this case, the basic isoquinoline nitrogen meant we could not find a pH window in which the dihydroxypyrimidine would precipitate from water. In the case of **244** and **250**, the malonates underwent decomposition under the conditions employed for heterocycle formation.



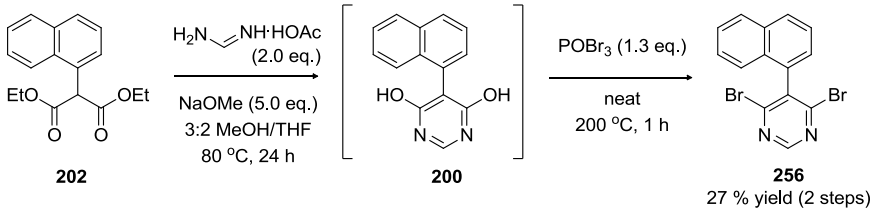
Scheme 3.39. Synthesis of dichloropyrimidines from malonates

We hoped that analogues substituted at the 2-position would be straightforward to synthesise, since the same malonate **199** could potentially be reacted with several different derivatives of formamidine and undergo dehydroxychlorination. The commercial availability of substituted formamidine reagents is quite limited, but we were able to access methyl, phenyl and trifluoromethyl substituted starting materials **252**, **253** and **254** (Scheme 3.40). We believe that reaction of **199** with *O*-methylisourea hydrochloride took place successfully, but we were unable to detect any of the desired product **255** after dehydroxychlorination.



Scheme 3.40. Synthesis of *C*2 substituted dichloropyrimidines

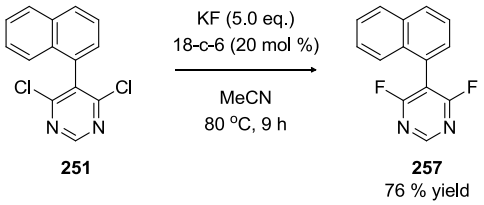
We next turned our attention to the synthesis of starting materials with different leaving groups. An analogous procedure was used to synthesise a dibromopyrimidine substrate **256** by heating **200** to 200 °C in the presence of $POBr_3$.* Using this procedure, we were able to obtain **256** in 27 % yield over 2 steps (Scheme 3.41).



Scheme 3.41. Synthesis of dibromopyrimidine **256**

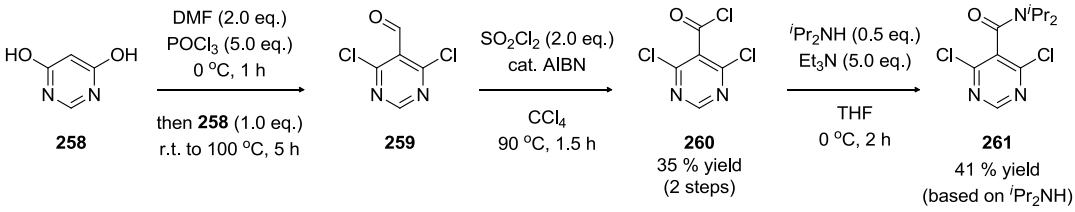
Synthesis of an analogous difluoropyrimidine substrate **257** was achieved from the corresponding dichloride **201**. This was accomplished by refluxing **201** in acetonitrile with excess potassium fluoride in the presence of catalytic crown ether, leading to **257** in good yield (Scheme 3.42).

* Reactions carried out in the presence of *N*,*N*-dimethylaniline led to inseparable by-products.



Scheme 3.42. Synthesis of difluoropyrimidine **257**

The final substrate we prepared was **261**, a dichloropyrimidine substituted with a sterically hindered amide. This compound was synthesised by a Master's student Benjamin Rahemtulla *via* a three step route (Scheme 3.43). According to a literature procedure, treatment of commercially available 4,6-dihydroxypyrimidine **258** with two equivalents of dimethylformamide and excess $POCl_3$ accomplished both Vilsmeier-Haak formylation and dehydroxychlorination leading to aldehyde **259**.[89] Subsequent radical chlorination of **259** with sulfuryl chloride afforded the corresponding acid chloride **260**, which was coupled with a sub-stoichiometric quantity of diisopropylamine leading to hindered amide **261**.



Scheme 3.43. Synthesis of a dichloropyrimidine substituted with a hindered amide (work by Benjamin Rahemtulla)

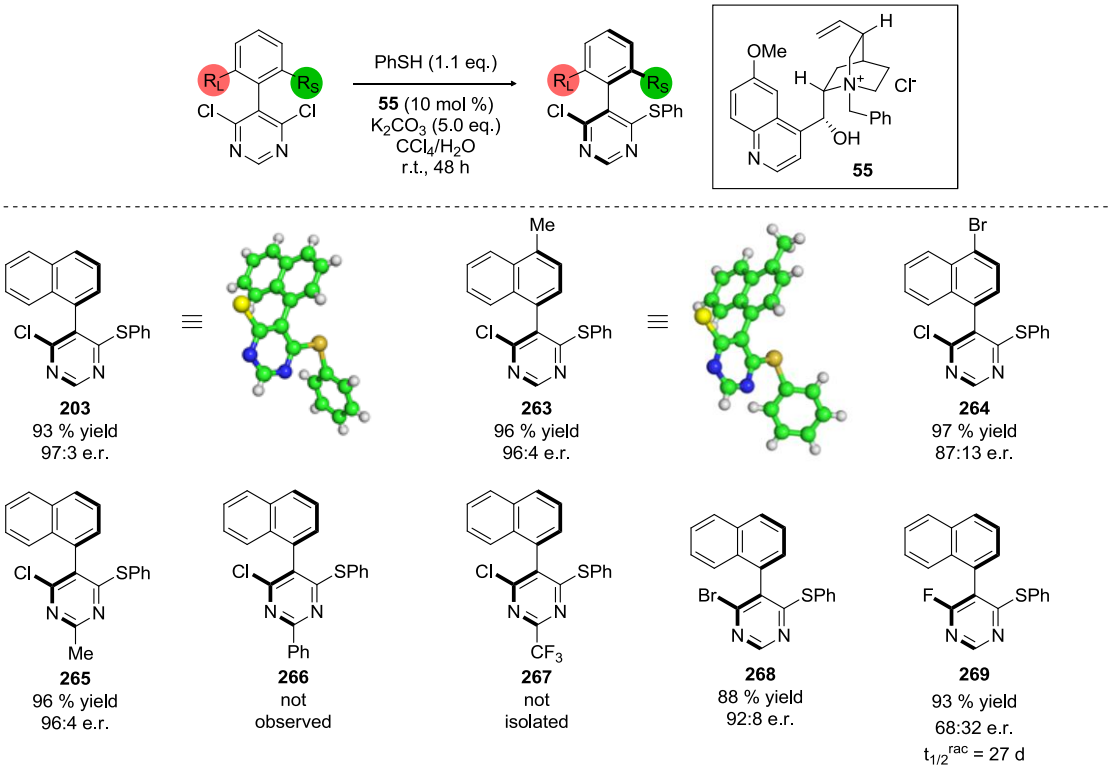
3.9. Electrophile scope

With these substrates in hand, we were now in a position to investigate the generality of the asymmetric S_NAr reaction. We began by investigating the effect of varying the electrophile (Scheme 3.44). Introduction of a methyl substituent to the 4-position of the naphthyl ring was well tolerated, and the product **263** was obtained in 96:4 e.r. and 96 % yield. With the help of Dr Russell Driver and Dr Peter Knipe, we were able to obtain X-ray crystal structures of both

203 and **263**, which enabled us to determine the major enantiomer to be (*R*)-configured.[*] When a more bulky bromine substituent was incorporated at the 4-position we obtained the substituted product **264** with slightly diminished enantioselectivity, although still in excellent yield. Substitution of the pyrimidine ring was also tolerated and a 2-methyl derivative was obtained with high enantioselectivity. When we evaluated a substrate with a phenyl group in the 2-position, we observed only unreacted starting material after 48 h. This is likely a consequence of the significant delocalization of the dichloropyrimidine stating material which must be broken in order to form a Meisenheimer adduct. Introduction of an electron withdrawing trifluoromethyl substituent to this position was problematic due to purification and analysis of the extremely non-polar products of the reaction.[†] Difluoropyrimidine **257** also underwent efficient S_NAr reaction, affording **269** in 93 % yield, but a modest 68:32 e.r. Desymmetrization of the analogous dibromopyrimidine took place, leading to the product **268** in excellent yield and 92:8 e.r. We hoped that the aryl bromide of this compound might serve as a useful synthetic handle for further manipulations.

[*] By analogy, we assume that the other compounds synthesised possess the same absolute configuration.

[†] Following S_NAr reaction ^{19}F NMR indicated that a mixture of starting material and two other products were present which we tentatively assign to be **267** and a by-product resulting from double addition of PhSH. Due to the non-polar nature of this mixture, we were unable to separate the components either by column chromatography or analytical chiral HPLC.

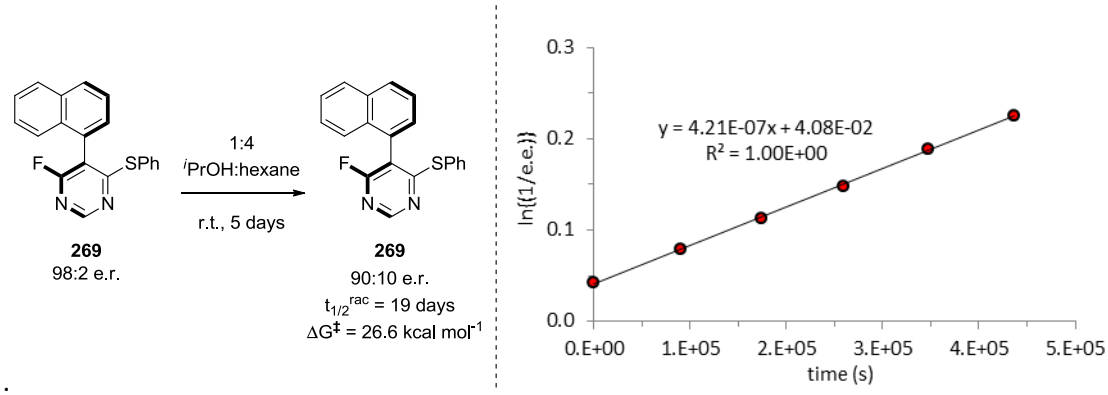


Scheme 3.44. Asymmetric S_NAr of substituted naphthyl dichloropyrimidines

Since **269** is substituted with a small aryl fluoride, we were interested to establish whether the lower enantioselectivity observed in this case could be a consequence of thermal racemization of the product. To test this theory, we used semi-preparative chiral HPLC to obtain a highly enantioenriched sample of **269** (98:2 e.r.). We then allowed this solution to stand at room temperature, removing aliquots every 24 hours and analysing their enantioenrichment. Over the course of four days we observed a decrease in enantioenrichment to 90:10 e.r. A plot of ln(1/e.e.) *vs* time for such data, should result in a straight line with a gradient of $2k_{ent} = k_{rac}$ (where k_{ent} is the rate constant for enantiomerization and k_{rac} is the rate constant for racemization).* When our data was plotted in this manner were able to determine that $k_{rac} = 4.21 \times 10^{-7}\ s^{-1}$, corresponding to a half-life of racemization $t_{1/2}^{rac}$ = 19 days. Using the Eyring equation, we calculated that the energetic barrier for this process is 26.6 kcal mol^{-1} (Scheme 3.45). From this result, we concluded that the low enantioselectivity was a result of

* It can be shown that $\ln(1/e.e.) = 2k_{ent}$ + constant. For a derivation of this equation, see Appendix F.

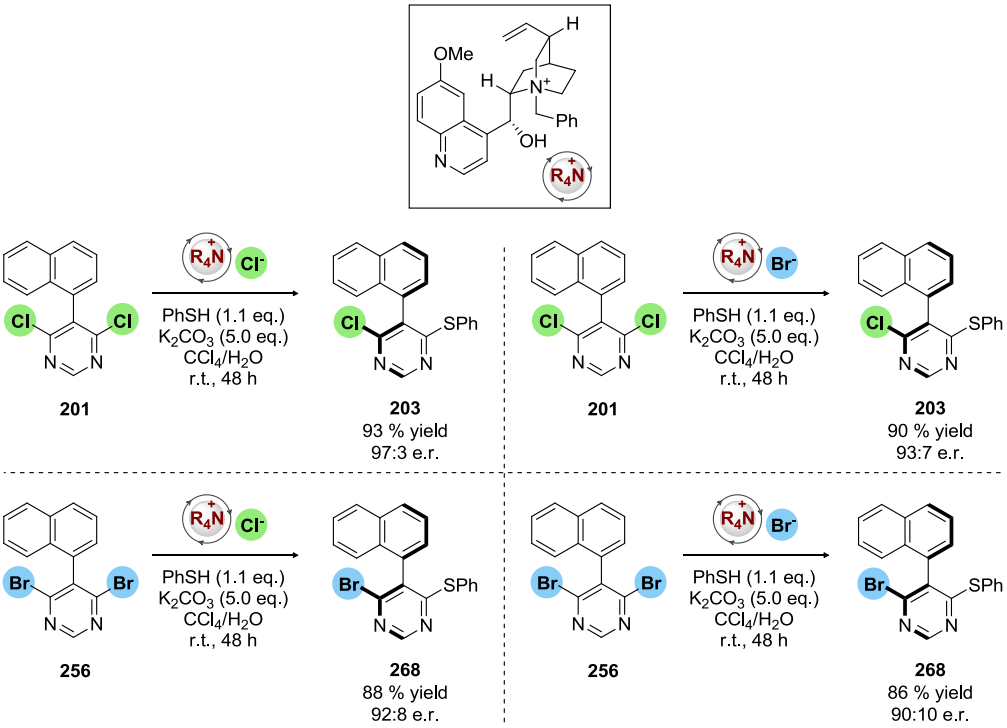
poor enantioinduction in the asymmetric S_NAr reaction rather than thermal racemization of the product.



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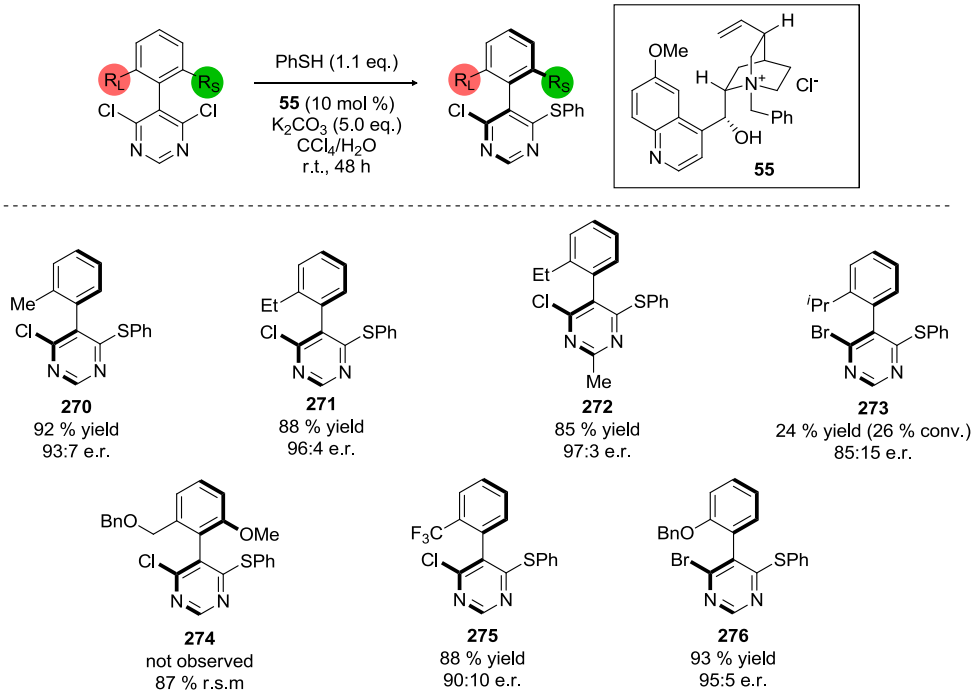
Scheme 3.45. Experiment to determine the rate of racemization of **269**

As an aside, during optimization we had been unable to clearly determine the effect the counter-ion has upon the reaction, since even in the presence of quaternary ammonium bromide catalysts the S_NAr reaction would generate an equivalent of potassium chloride. With dibromopyrimidine substrate **256**, we were in a position to be able to fully investigate this effect, and accordingly, we carried out the reaction with the four possible combinations of chloride/bromide catalyst along with dichloride/dibromide substrate (Scheme 3.46). The results clearly demonstrate the presence of bromide either within the catalyst or substrate has a detrimental effect upon enantioselectivity. One possible explanation is that bromide is more lipophilic than chloride and therefore sequesters the chiral cation in the organic phase enabling more extensive racemic background reactivity to occur.[90]



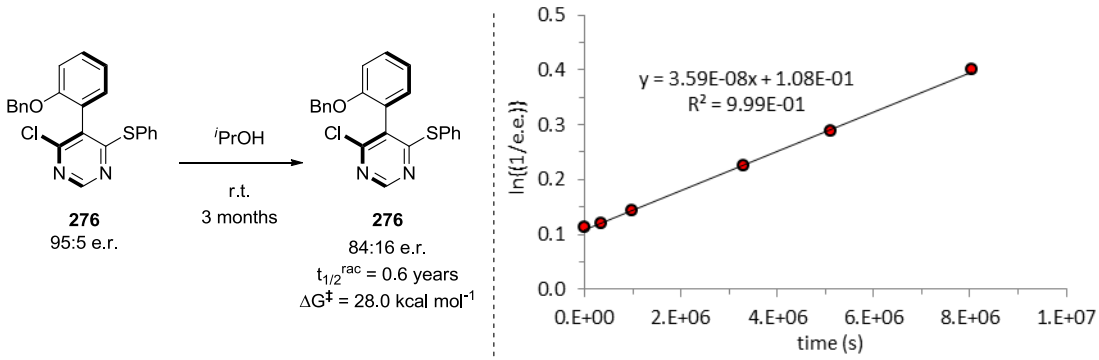
Scheme 3.46. The effect of chloride *vs* bromide on the asymmetric S_NAr reaction

Returning to electrophile scope we next carried out the desymmetrizing S_NAr reaction with a series of electrophiles containing a single *ortho*-substituent (Scheme 3.47). With a substrate containing an *ortho*-methyl group, we were delighted to obtain the product **270** in 92 % yield and 93:7 e.r. Moreover, we found that **270** had a high barrier to thermal racemization - no erosion of stereochemical integrity was observed after several months at room temperature. Increasing the steric bulk of this *ortho*-substituent by incorporation of an ethyl group led to the corresponding product **271** in 96:4 e.r. With an extremely bulky *ortho*-isopropyl substituted dichloropyrimidine, we observed low conversion to the substituted product **273**, although good enantioselectivity was still obtained. This trend was continued with hindered 2,6-disubstituted electrophiles, exemplified by **251**, which did not undergo any reaction after 48 h. Substrates containing both electron withdrawing and donating substituents were effectively desymmetrized, leading to products **275** and **276** with good levels of enantioselectivity.



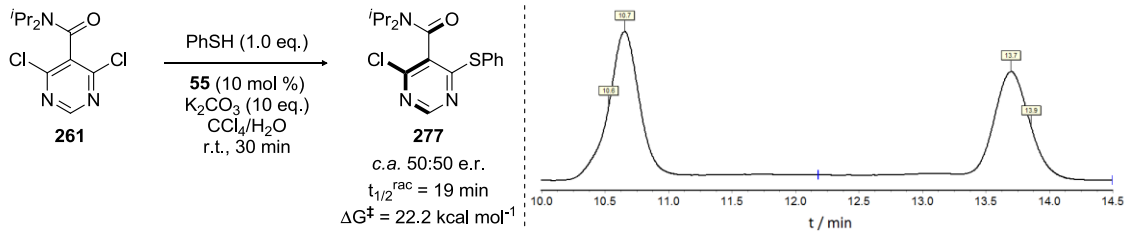
Scheme 3.47. Desymmetrizing S_NAr reactions of dichloropyrimidines bearing a single ortho-substituent

These products **270**-**276** all exhibited remarkably high conformational stability. We set out to determine the rotational barrier for the smallest compound in the series (benzyl ether substituted **276**). Aliquots from an enantioenriched solution of this material (95:5 e.r.) were monitored over time as described previously (Scheme 3.48). Over the course of three months, a small decrease in enantioenrichment was observed to 84:16 e.r. By plotting a graph of ln(1/e.e.) *vs* time as discussed previously, we were able to calculate the half-life of racemization for **276** to be around 0.6 years ($\Delta G^{\ddagger}$ = 28.0 kcal mol^{-1}). Moreover, a solid sample of this material underwent no detectable racemization after the same period of time. We assume by extension that the remainder of the compounds shown in Scheme 3.47 have a very high barrier to thermal racemization.



Scheme 3.48. Experiment to determine the rate of racemization of **276**

Desymmetrization of the analogous amide substrate was carried out by Benjamin Rahemtulla. Rapid and quantitative conversion was observed to **277**, but this product was essentially racemic (Scheme 3.49). The chiral HPLC spectrum obtained for **277** consisted of a pair of peaks separated by a region of raised baseline. This feature, which we term 'the Batman effect',[*91] has been described previously and results from enantiomers which interconvert on the HPLC timescale.[92] The rate of the exchange process can be determined based on the line shape of the spectrum, but the calculation involved is extremely tedious. Fortunately, Trapp *et al.* have disclosed a highly convenient online tool, enabling quantitative analysis of such HPLC data.[93] Using this method, we were able to calculate the energetic barrier for enantiomerization of **277** to be 22.2 kcal mol^{-1}, corresponding to a racemization half-life of 19 minutes. Perhaps the poor enantioselectivity observed in this case is therefore a reflection of rapid racemization of the product rather than poor enantioinduction in the desymmetrization.

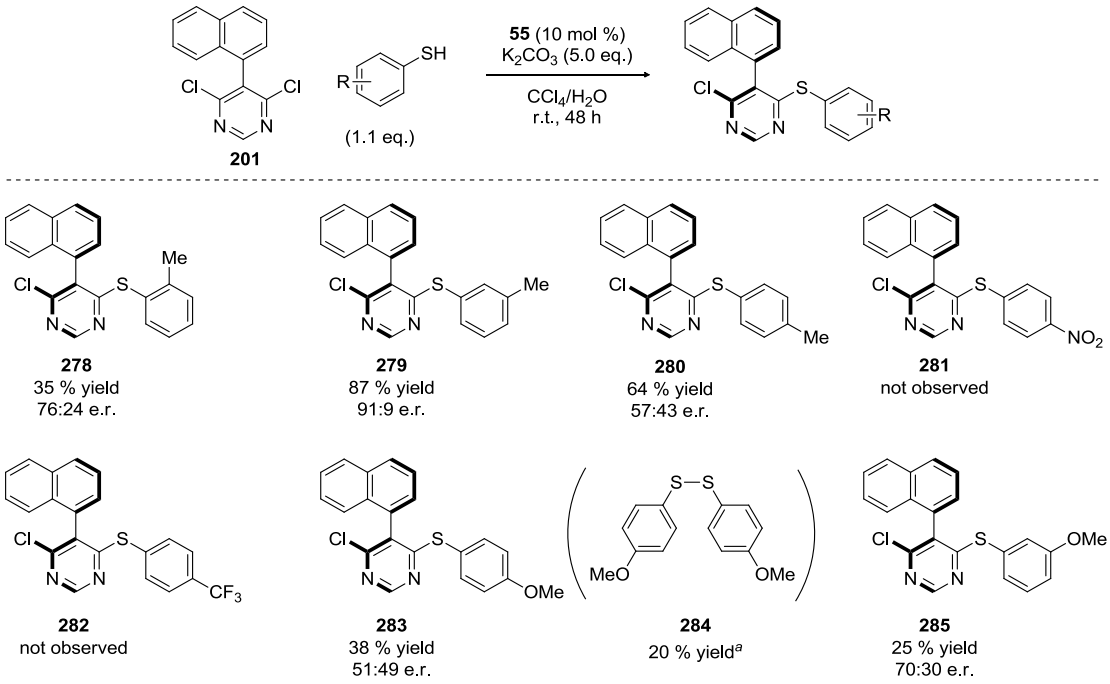


Scheme 3.49. S_NAr reaction of hindered amide **261** and chiral HPLC spectrum of **277** exhibiting a 'Batman effect' (reaction carried out by Benjamin Rahemtulla)

[*] This term refers to the similarity of related HPLC chromatograms to the Dark Knight in profile.

3.10. Thiol scope

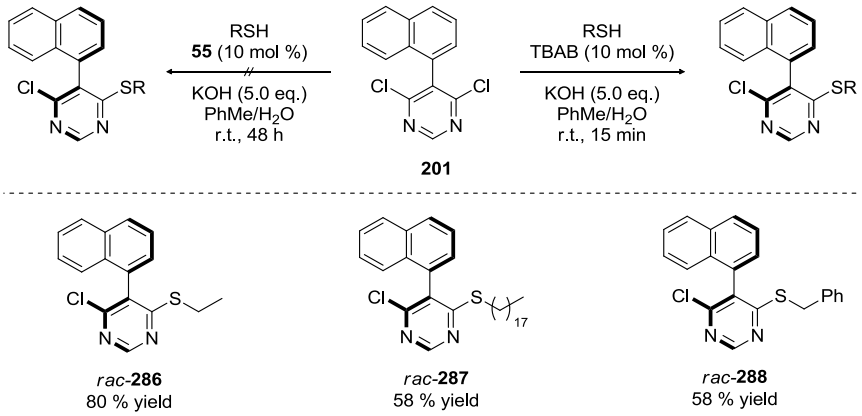
Using **201** as an electrophile, we carried out the asymmetric S_NAr reaction with a range of commercially available substituted thiophenols (Scheme 3.50). Introduction of an *ortho*-methyl substituent had a detrimental effect upon both reaction rate and enantioselectivity, affording **278** in 35 % yield and 76:24 e.r. When the methyl substituent was located in the *meta*- position, both selectivity and yield were restored and **279** was obtained good yield and 91:9 e.r. This does not appear to be a simple steric effect, since use of *para*-thiocresol led to reduced selectivity and yield. Introduction of an electron withdrawing group to the *para*- position completely shut down reactivity - products **281** and **282** were not observed. We assume that this low reactivity is a consequence of the increased stability of electron poor thiophenolates. It therefore came as a surprise that electron rich thiophenols were also less reactive than the unsubstituted case. Introduction of a *para*-methoxy substituent led to completely racemic **283** in low conversion (we also observed disulfide **284**, presumably originating from oxidation of the electron rich thiol by adventitious oxygen). When the methoxy substituent was moved to the *meta*- position, we again saw improved enantioselectivity and **285** was obtained in 70:30 e.r. in 25 % yield. The sluggish reactivity observed with *ortho*-alkyl substituted thiophenols in S_NAr reactions is precedented and has been attributed to the steric hindrance of these nucleophiles.[94] However, we do not currently understand the origins of the low reactivity observed with *meta*- and *para*- substituted electron rich thiols. It is clear that the phase-transfer catalyst is able to form a highly specific ion-pair with thiophenol and is therefore perhaps not so surprising that introduction of any substituent could have a significant impact on enantioselectivity.



Scheme 3.50. Asymmetric S_NAr reaction of **201** with substituted aromatic thiols. (a) This material could not be fully separated from unreacted starting dichloropyrimidine **201**.

Benjamin Rahemtulla investigated an analogous substitution reaction with aliphatic thiols (Scheme 3.51). The racemic reactions, catalysed by tetra-*n*-butylammonium bromide were all somewhat sluggish, although afforded the substituted products **286**, **287** and **288** in good yields. Unfortunately, with optimised asymmetric catalyst **55**, he observed no conversion to the desired products after 48 hours.* We believe that this reduced reactivity may be a consequence of the lower acidity of alkyl thiols compared with thiophenols.[95]

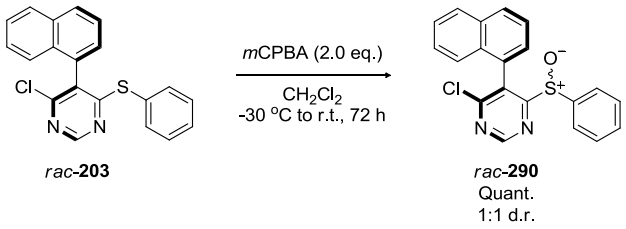
* Ben also investigated analogous conditions several other nucleophiles including peroxides, hydroxylamines, nitroalkanes, malonates and amides. Unfortunately, in all cases no reactivity was observed with **201**.



Scheme 3.51. Reaction with aliphatic thiols (work by Benjamin Rahemtulla)

3.11. Derivatization of substituted products

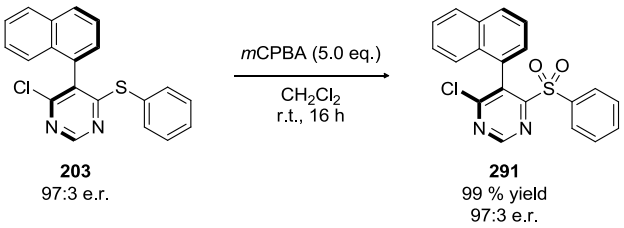
In order to demonstrate the synthetic utility of the desymmetrized reaction products, we hoped to carry out a series of derivatization reactions. We selected **203** as a representative example and began by investigating whether it was possible to oxidise the thioether. We treated **203** with 2.0 equivalents of *m*CPBA in dichloromethane and observed quantitative formation of sulfoxide **290**, which was formed as a 1:1 mixture of diastereomers (Scheme 3.52).*



Scheme 3.52. Oxidation of **203** to a diastereoisomeric mixture of sulfoxides

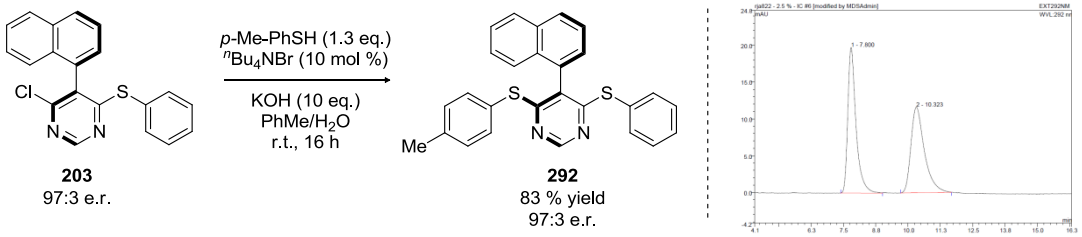
Employing five equivalents of *m*CPBA at room temperature, we were able to synthesise sulfone **291** in near quantitative yield. When enantioenriched starting material was employed (97:3 e.r.) we obtained the product with no loss of enantiomeric enrichment (Scheme 3.53).

* The diastereomers could be separated by column chromatography.



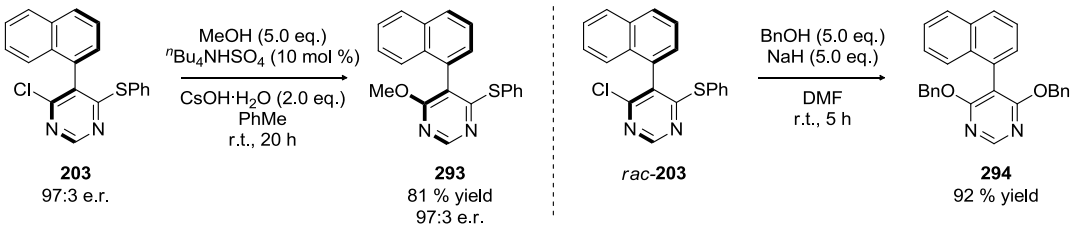
Scheme 3.53. Oxidation of sulfide **203** to sulfone **291**

All of the products of the desymmetrization reaction contain a second reactive aryl halide and we hoped that this might serve as a useful handle for further functionalization either through substitution reactions or cross-coupling. We began by treating an enantioenriched sample of **203** (97:3 e.r.) with *para*-thiocresol under phase-transfer catalysed conditions. This led to substituted product **292** in 83 % yield with no loss of stereochemical integrity (Scheme 3.54). Since the symmetry in **292** is only broken by the presence of a methyl group on one of the phenyl rings, we were pleasantly surprised to observe baseline separation of the two enantiomers with chiral HPLC.



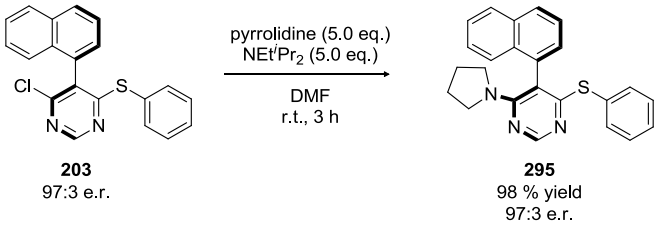
Scheme 3.54. S_NAr reaction with a substituted thiol and chiral HPLC trace of *rac*-**292**

We next investigated oxygen based nucleophiles. Using an excess of methanol under phase-transfer conditions it was possible to carry out the desired substitution reaction in 81 % yield leading to **293** without loss of stereochemical purity. Interestingly, with benzyl alcohol under more forcing conditions we observed displacement of both chloride and thiophenolate and achiral product **294** was isolated in 92 % yield (Scheme 3.55). This raises the interesting possibility that the thiol might be employed as a traceless handle – setting the absolute stereochemistry before undergoing displacement.



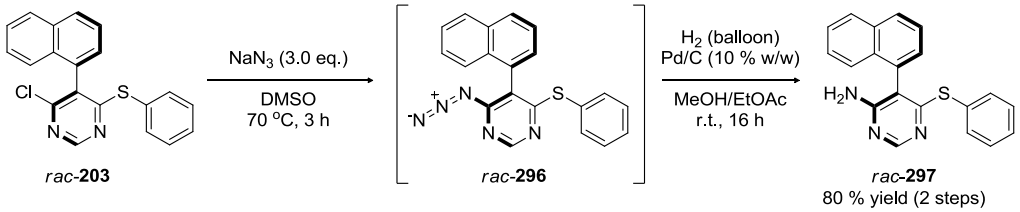
Scheme 3.55. S_NAr reaction with alcohol nucleophiles

We also investigated nitrogen nucleophiles and were pleased to find that secondary amines as exemplified by pyrrolidine effectively underwent S_NAr reaction in the presence of Hunig's base (Scheme 3.56). The substituted product **295** was obtained in near quantitative yield, with no erosion of enantiomeric purity.



Scheme 3.56. S_NAr reaction with a secondary amine nucleophile

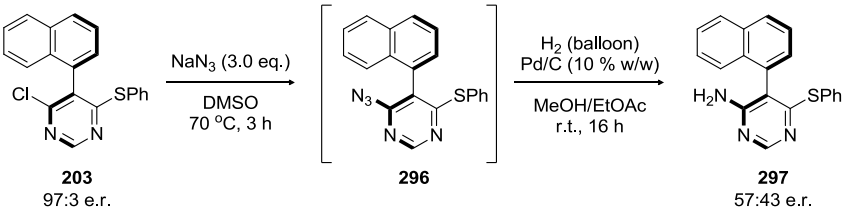
The corresponding unsubstituted aniline was also of interest to us since we hoped it would prove a useful precursor for the synthesis of axially chiral catalysts. We began by carrying out a S_NAr reaction of *rac*-**203** with three equivalents of sodium azide. The resulting crude aryl azide *rac*-**296** was then subjected to catalytic hydrogenation, effecting reduction to *rac*-**297** in 80 % yield over two steps (Scheme 3.57).*



Scheme 3.57. Azide substitution/reduction route to racemic aniline **297**

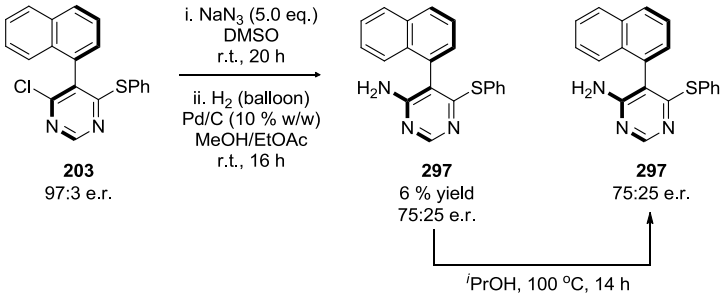
* We also isolated the azide, but found that this resulted in a lower yield over two steps and was less preferable from a safety perspective.

We then repeated this sequence on a small scale with enantioenriched starting material **203** (97:3 e.r.). Unfortunately, we found that **297** was obtained in 57:43 e.r., a dramatically lower level of enantioenrichment than that of the starting material (Scheme 3.58).



Scheme 3.58. Loss of enantiomeric purity following azide S_NAr and reduction

We suspected that the S_NAr reaction lay at the root of this problem and therefore carried out the substitution at room temperature with a large excess of sodium azide.* Following reduction, **297** was obtained in an improved 75:25 e.r., although the conversion was poor. This loss of stereochemical integrity cannot be explained by racemization of aniline **297**, which underwent no decrease in enantioenrichment upon heating to 100 °C for 14 hours (Scheme 3.59).

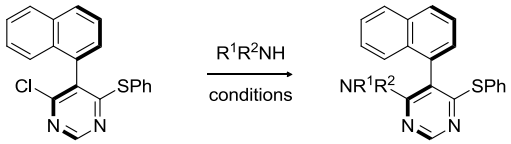


Scheme 3.59. Attempted azide S_NAr at room temperature

These results led us to seek alternative methods to prepare **297**. We attempted S_NAr reactions with *n*-propylamide and dibenzylamine and also evaluated a copper catalysed cross-coupling recently reported by Ma *et al.* (Table 3.4, entries 1-3).[96] Unfortunately, these reactions all failed to generate **297** and only starting material was observed. Pleasingly, we found that

* Racemization could occur if either azide **296** and/or the Meisenheimer complex involved in its formation were configurationally unstable. We were not able to investigate this effect further because we were unable to identify chiral HPLC conditions that separated the enantiomers of **296**.

simply heating **203** to 100 °C with excess ammonia in a mixture of DMSO and water led to the desired aniline **297** in 82 % yield (Table 3.4, entry 4).

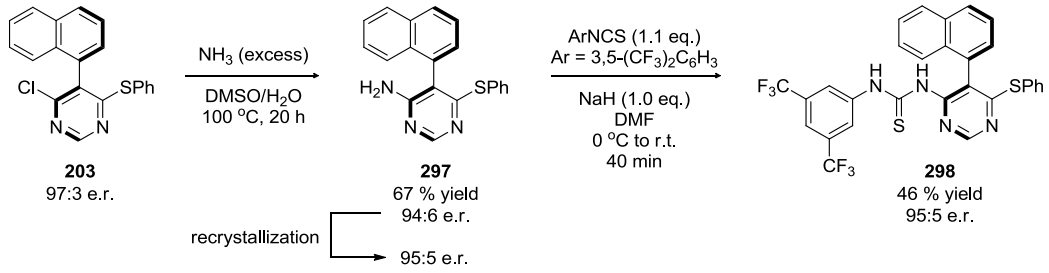


rac-**203**

Entry	NR_1R_2H [eq.]	conditions	result
1	EtO_2CNH_2 [1.2]	KO^{t}Bu (1.2 eq.), THF, r.t., 15 h	no reaction
2	Bn_2NH [2.0]	NEt^{i}Pr$_2$ (3.0 eq.), DMF, r.t., 24 h	no reaction
3	aq. NH_3 [xs]	CuI (0.2 eq.), trans-4-hydroxyproline (0.4 eq.), K_2CO_3 (3 eq.), DMSO, 50 °C, 24 h	no reaction
4	aq. NH_3 [xs]	DMSO, 100 °C, 20 h	82 % yield (17 % rsm)

Table 3.4. Conditions evaluated to synthesise aniline **297**

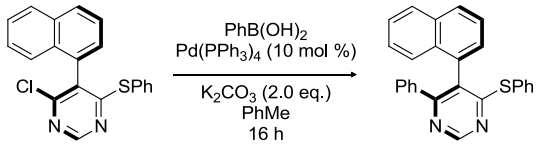
Upon repeating this reaction with enantioenriched starting material **203** (97:3 e.r.) we isolated the product **297** in 67 % yield and 94:6 e.r. [*] This loss of enantioenrichment is surprisingly small given the forcing nature of the conditions employed. Recrystallization of **297** led to a small recovery in enantioenrichment to 95:5 e.r. This aniline was converted to the corresponding half-Schreiner thiourea in 46 % yield without loss of stereochemical integrity (Scheme 3.60). Future work will probe the efficacy of this compound as an asymmetric hydrogen bonding catalyst.



Scheme 3.60. Synthesis of thiourea **298**, a potential asymmetric hydrogen bonding catalyst

[*] The starting material was recovered in 38 % yield and 97:3 e.r.

We were also interested in using the aryl chloride of the product to carry out Suzuki-Miyaura cross-coupling reactions. We found that exposure of **203** to a slight excess of phenylboronic acid along with potassium carbonate and catalytic tetrakis(triphenylphosphine)palladium(0) at 100 °C led to **299** in 98 % yield but with some loss of enantiomeric purity (85:5 e.r.) (Table 3.5, entry 1). Racemization in the cross coupling of atropisomeric aryl halides has been investigated in some detail by Stoltz *et al.* and is thought to occur *via* formation of a cationic aryl-palladium (II) intermediate.[97*] We attempted to circumvent this problem by carrying out the reaction at lower temperatures. At room temperature and 60 °C, we observed low conversion to **299**, but 75 °C proved to be a sweet-spot, enabling us to obtain the coupled product in 89 % yield without any enantiomeric erosion (Table 3.5, entries 2-4).



203
97:3 e.r.

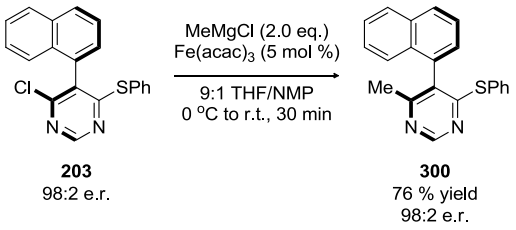
299

entry	eq. $PhB(OH)_2$	temperature	yield **299**	e.r. **299**
1	1.3	100 °C	98 %	85:15
2	1.5	r.t.	no reaction	-
3	1.5	60 °C	trace	-
4	1.5	75 °C	89 %	97:3

Table 3.5. Optimization of Suzuki-Miyaura cross-coupling of **203**

We were also able to substitute the chlorine with an alkyl substituent *via* a Kumada cross-coupling reaction. This was achieved with methylmagnesium chloride in the presence of a catalytic quantity of iron (III) acetoacetate, leading to substituted product **300** in 76 % yield without loss of optical purity (Scheme 3.61).[98]

[*] In our case, this is supported by the observation that we observed no racemization of either starting material **203** or product **299** upon heating to 100 °C for 20 hours.

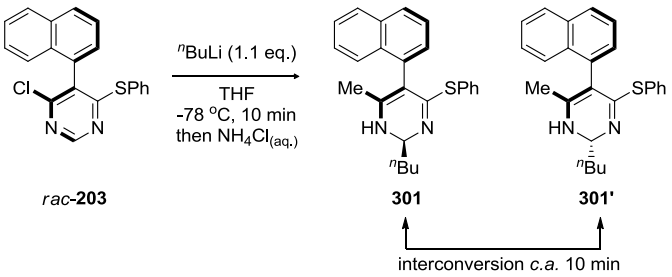


203
98:2 e.r.

300
76 % yield
98:2 e.r.

Scheme 3.61. Kumada coupling of **203**

Finally, we hoped to be able to carry out lithium-halogen exchange of **203** and then trap the resulting organolithium intermediate with electrophiles. Upon treatment of **203** with *n*-butyl lithium at -78 °C, we instead observed nucleophilic addition of the butyl group to the pyrimidine forming a mixture of diastereoisomeric products **301** and **301'**. These compounds could be partially separated chromatographically, but underwent interconversion before they could be fully characterized (Scheme 3.62).*



rac-**203**

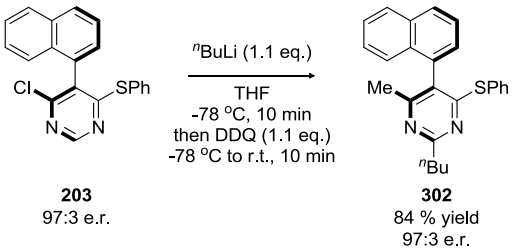
301

301'

Scheme 3.62. Nucleophilic addition of *n*-butyllithium to the pyrimidine

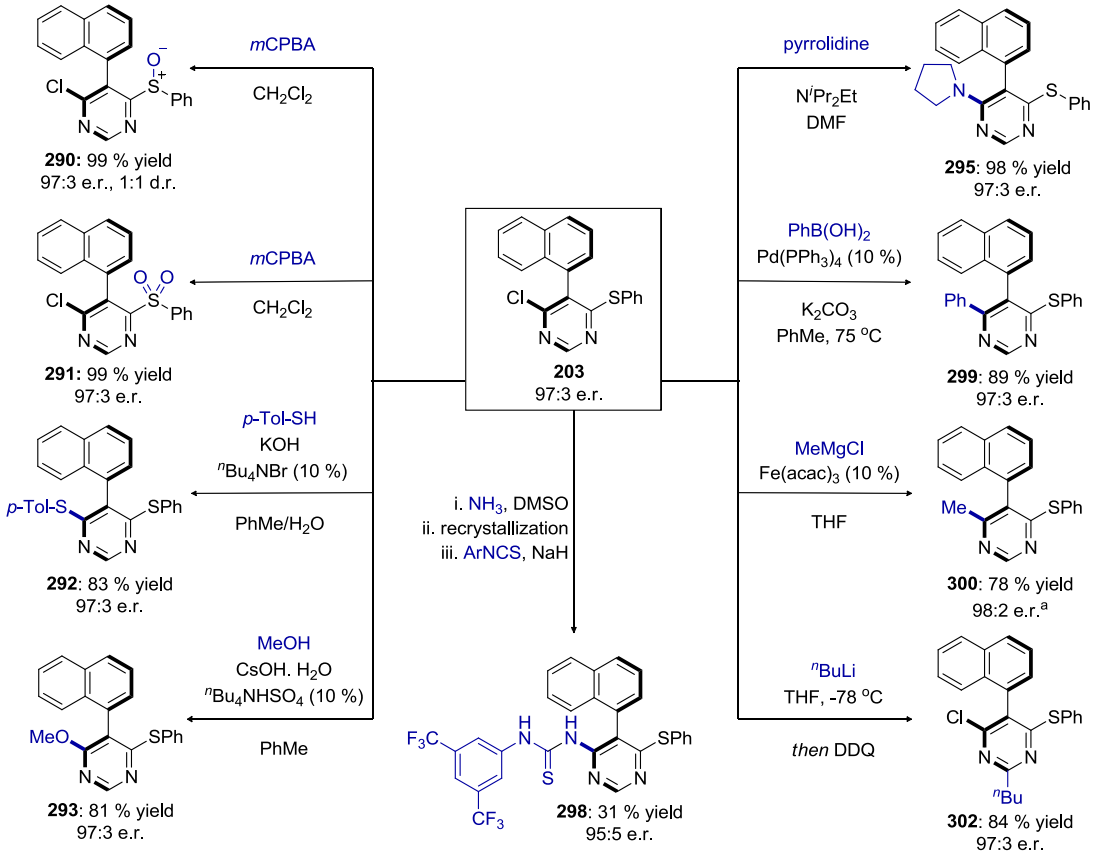
Although unexpected, we found that we could capitalize on this process by carrying out nucleophillic addition of an alkyl lithium reagent to the 2-position of the pyrimidine and then quench the intermediate with DDQ. This effected re-oxidation, and the corresponding pyrimidine product was isolated in 84 % yield without loss of enantiomeric purity (Scheme 3.63).†

* We tentatively characterised **301** and **301'** by ^{1}H NMR and low resolution mass spectroscopy.
† This reaction was also successful with dichloropyrimidines (see experimental section for details).



Scheme 3.63. Functionalization of the 2-position of the pyrimidine

For clarity, a complete summary of these derivatization reactions is presented in Scheme 3.64.



Scheme 3.64. Summary of product derivatization reactions carried out. (a) Starting material **203** was 98:2 e.r.

3.12. Conclusion

Following reaction optimization, a highly enantioselective method for desymmetrization of dihalopyrimidines has been developed. This reaction shows broad scope with respect to the electrophilic component although the nucleophile is restricted to a limited set of aromatic thiols. We have probed the configurational stability of the products using a variety of methods

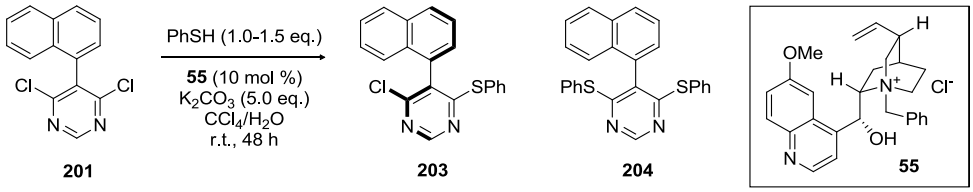
and have generally found these compounds to be remarkably robust with respect to thermal racemization. The synthetic utility of the desymmetrized products has been explored by carrying out a range of different derivatizations. The remaining aryl chloride of the products was found to be a particularly effective handle for further functionalization and a range of substitutions and metal catalysed cross-couplings were carried out at this position.

The chapter which follows describes our work towards understanding the mechanism of this reaction.

4. Mechanistic Studies

4.1 Tandem desymmetrization/kinetic resolution

During optimization of the asymmetric desymmetrization reaction, we made the observation that a slight excess of thiophenol led to the product **203** in increased enantioselectivity (Chapter 3). In order to probe the origin of this effect, we investigated the use of higher loadings of thiophenol (Table 4.1). A clear trend was observed – an increased loading of thiophenol resulted in more double addition to form **204**. This led to a slightly diminished yield of single addition product **203**, accompanied by higher levels of enantioenrichment (up to 98:2 e.r.).



Entry	Eq. PhSH	yield **203**	e.r. **203**	Yield **204**
1	1.0	98[a]	95:5	-
2	1.1	93	97:3	6
3	1.3	90	98:2	8
4	1.5	93	98:2	7

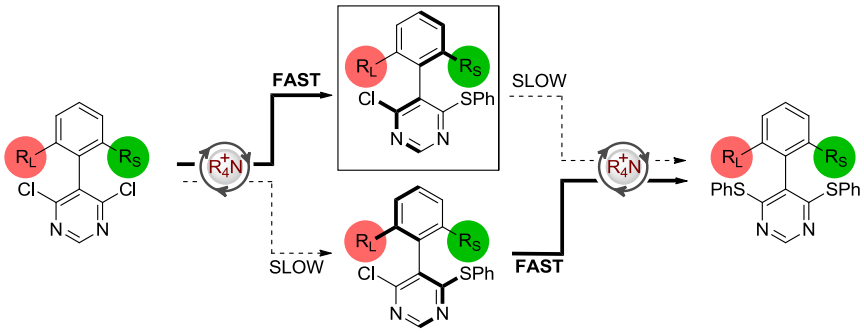
Table 4.1. Investigating the effect of increased loading of thiophenol. (a) brsm (94 % conversion).

We speculated that one possible explanation of this observation is that the catalyst is carrying out a kinetic resolution at the second addition step (Scheme 4.1). This would imply that the catalyst serves two functions:

i. Initially, desymmetrization of **201** occurs, leading to an excess of one enantiomer of the product **203**.

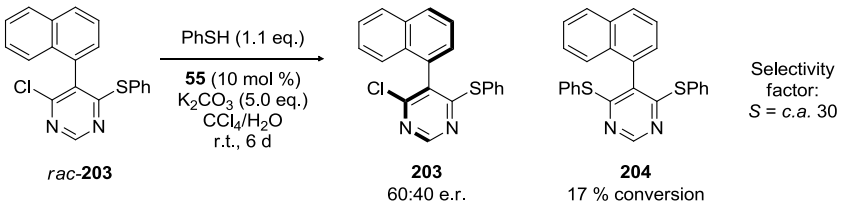
ii. Subsequently, a kinetic resolution of **203** takes place in which the minor enantiomer of **203** is scavenged more rapidly than the major. This serves as a proof-reading event, enhancing the enantioselectivity of the process as a whole.

This proposal is consistent with the seminal work of Hayashi *et al.* who observed a similar phenomenon in the metal catalysed desymmetrization of prochiral biaryls.[66]



Scheme 4.1. Tandem desymmetrization/kinetic resolution mechanism

To test this hypothesis, we synthesised racemic **203** and subjected it to asymmetric conditions. After six days we observed 17 % conversion to **204**. The recovered starting material **203** was found to be enantioenriched to 60:40 e.r., with the major enantiomer being the same as that observed in the desymmetrization reaction (Scheme 4.2).



Scheme 4.2. Kinetic resolution of *rac*-**203**

This result provides strong experimental support for the tandem desymmetrization/kinetic resolution mechanism proposed above. This data also allowed us to quantify* the efficiency of the kinetic resolution by calculating an *S* factor using the equation given below. By this

* This result must be interpreted with caution, since at low conversion the calculation for S factor is very sensitive to both e.e. and conversion. For example, with 19 % e.e., at 17 % conversion S = 32, but at 18 % conversion S = 17 and at 16 % conversion S = 962.

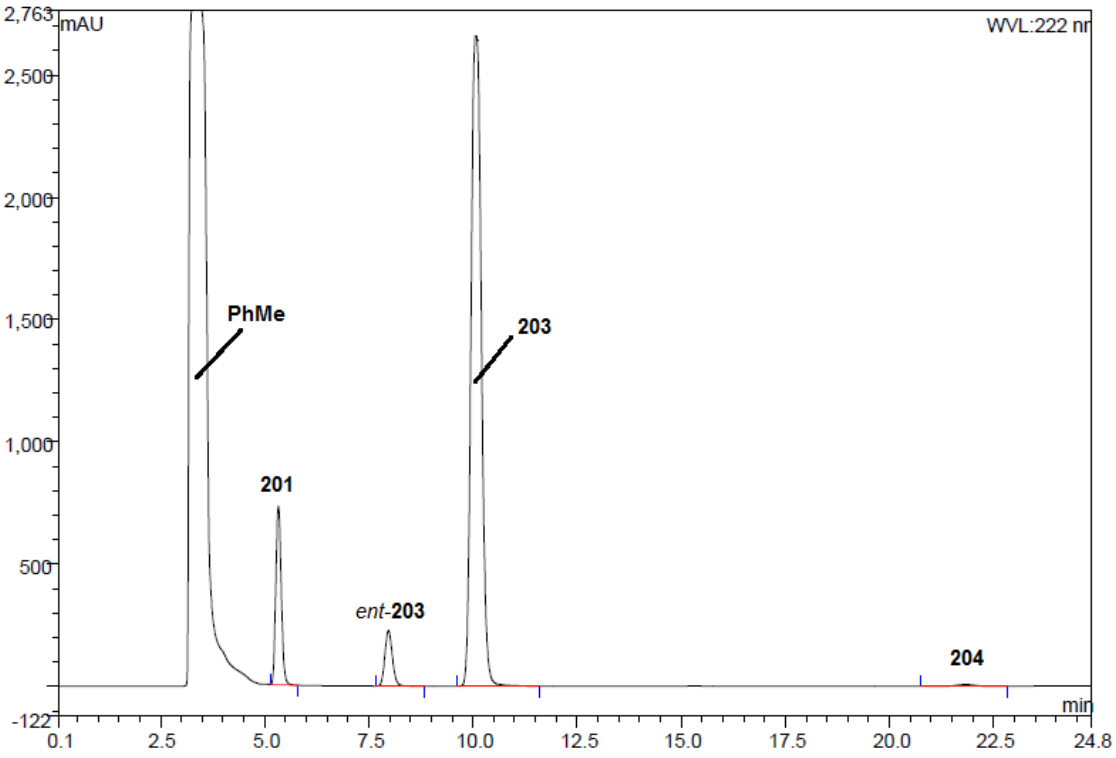
method, we calculated that the reaction in Scheme 4.2 takes place with an *S* factor of approximately 30. This high selectivity explains why the kinetic resolution is so effective at removing the minor enantiomer.

$$S = \frac{k_{\mathrm{ent-}\mathbf{203}}}{k_{\mathbf{203}}} = \frac{\ln(1 - conversion)(1 - e.e.)}{\ln(1 - conversion)(1 + e.e.)}$$

4.2 Kinetic studies

To aid our understanding of this phase-transfer catalysed process, we decided to investigate the kinetic profile of the reaction. In order to perform kinetic analysis, it was necessary to identify a method which would enable us to monitor the concentrations of the starting material and products over the course of the reaction. We found that small aliquots from the reaction mixture (filtered through a plug of silica gel) could be effectively analysed by analytical chiral HPLC. A representative HPLC trace from the desymmetrization of **201** is shown below and it can be seen that the starting material **201**, both enantiomers of the product (**203** and *ent*-**203**) and by-product **204** are all well resolved from each other. To simplify the HPLC analysis, we made the assumption that the reaction mixture contained only a mixture of these four compounds.[*]

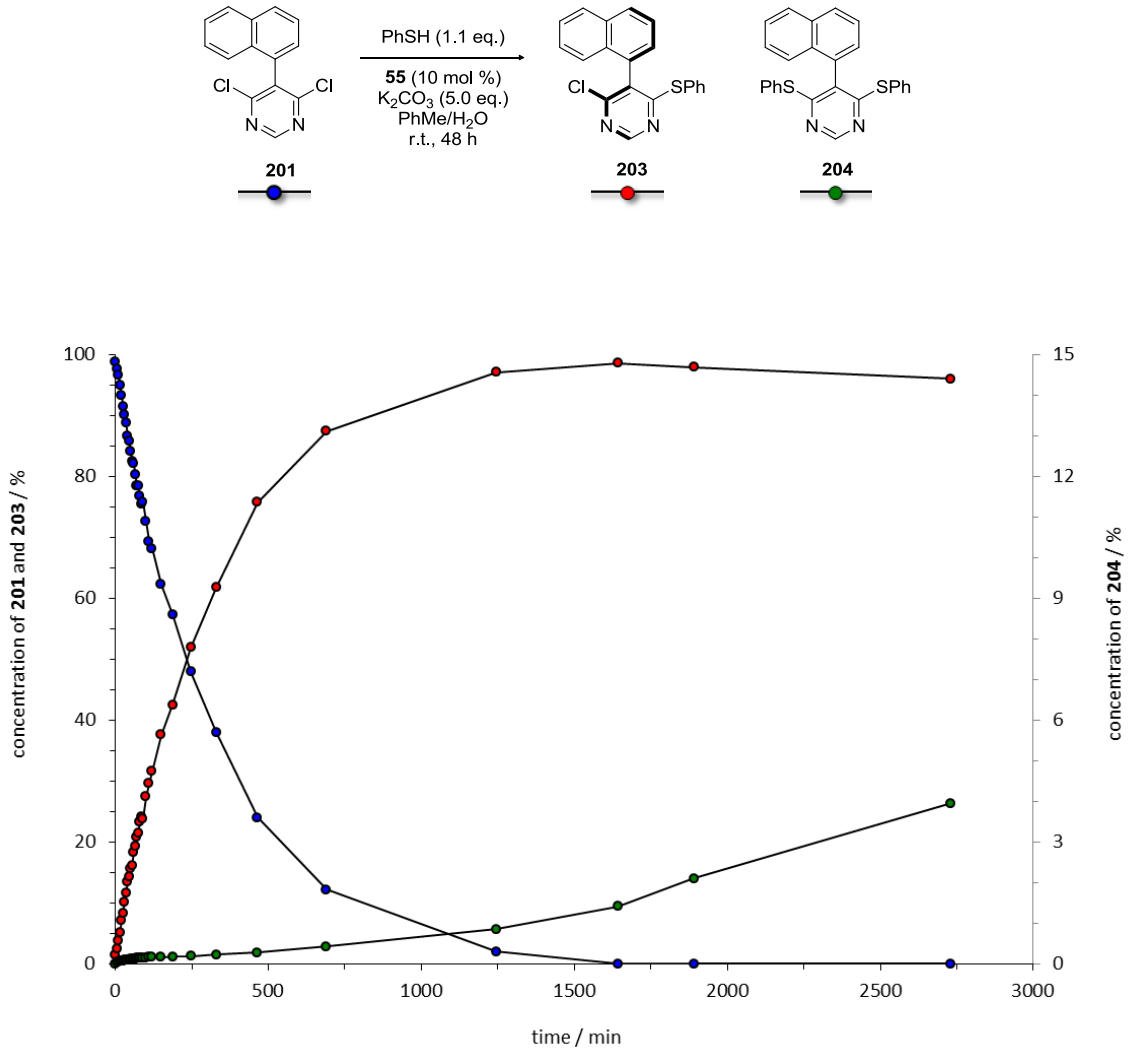
[*] Since essentially quantitative mass balance is observed, the relative concentrations of these four species were compared without reference to an internal standard. Calibration was achieved *via* HPLC analysis of known mixtures of **201**, *rac*-**203** and **204** (see experimental section for details).



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	5.33	n.a.	729.737	111.834	12.17	n.a.	BMB*
2	7.97	n.a.	226.407	47.128	5.13	n.a.	BMB
3	10.07	n.a.	2671.228	756.460	82.29	n.a.	BMB
4	21.83	n.a.	6.842	3.870	0.42	n.a.	BMB*
Total:			3634.214	919.292	100.00	0.000	

Figure 4.1. Representative HPLC trace from asymmetric desymmetrization reaction

Using this method, we set about monitoring the desymmetrization reaction under our previously optimized conditions. The resulting data is shown below in Scheme 4.3. In the early stages of the reaction the rate of consumption of starting material **201** (and build-up of the product **203**) was approximately linear. As the reaction progressed, the rate began to decrease suggesting a kinetic dependence upon one or both of the starting materials. The reaction was complete after approximately 30 hours. After this time, the product was slowly consumed along with concomitant formation of by-product **204** (shown in green on an expanded axis). This observation can be explained by the kinetic resolution described previously.



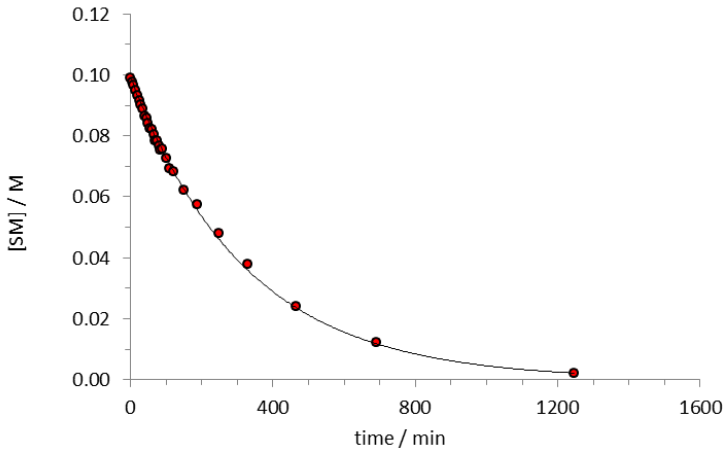
Scheme 4.3. Monitoring the composition of the reaction mixture over time

We next investigated the overall kinetic order of the reaction. This was achieved by plotting the above data against integrated 0^{th}, 1^{st} and 2^{nd} order rate equations. The relevant three expressions and corresponding plots are shown below (Figure 4.2).* The data were an extremely good fit (R^2 = 0.999) for the integrated profile of a pseudo-first order process and from the gradient we estimated the rate constant to be 3.1 x 10^{-3} min^{-1}.

* Additionally, a second order plot of $\ln\{([PhSH][SM]_0)/([PhSH]_0[SM])\}$ *vs* time which allows for the small difference in initial concentration between PhSH and **101** also resulted in a curved line.

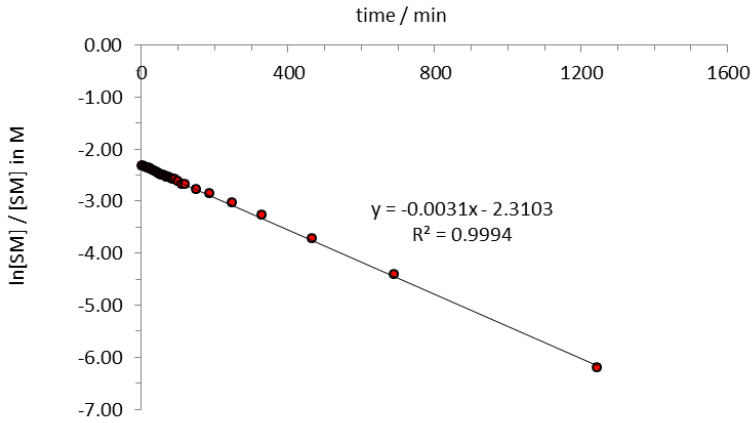
0th order:

$$[SM] = [SM]_0 - kt$$



1st order:

$$ln[SM] = ln[SM]_0 - kt$$



2nd order:

$$\frac{1}{[SM]} = \frac{1}{[SM]_0} + 2kt$$

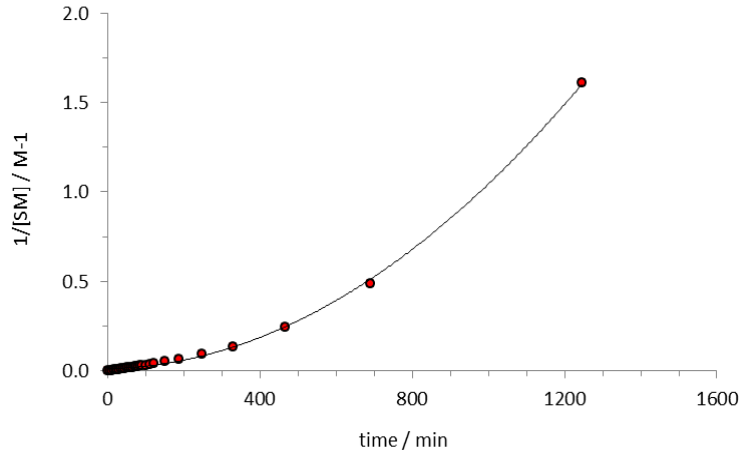


Figure 4.2. Integrated 0th, 1st and 2nd order plots for asymmetric desymmetrization of starting material (SM) **201**

However, since the substrate and thiol were present in near equimolar starting concentrations and react with 1:1 stoichiometry, at this point we could not identify which component was the origin of the first order dependence. We hoped to obtain this information using the method of initial rates. To test the viability of this approach, we repeated the asymmetric reaction,

sampling the reaction every five minutes over the first hour (Figure 4.3). The data within this region was fitted to a linear regression line and from the gradient we calculated the initial rate of reaction to be 3.0 (±0.2) x 10^{-4} M min^{-1}.* Given an initial concentration of substrate of 0.1 M, this corresponds to a pseudo-first order rate constant of around 3.0(±0.2) x 10^{-3} min^{-1}, which is in very good agreement with the value of 3.1 x 10^{-3} min^{-1} obtained from the integrated plot.

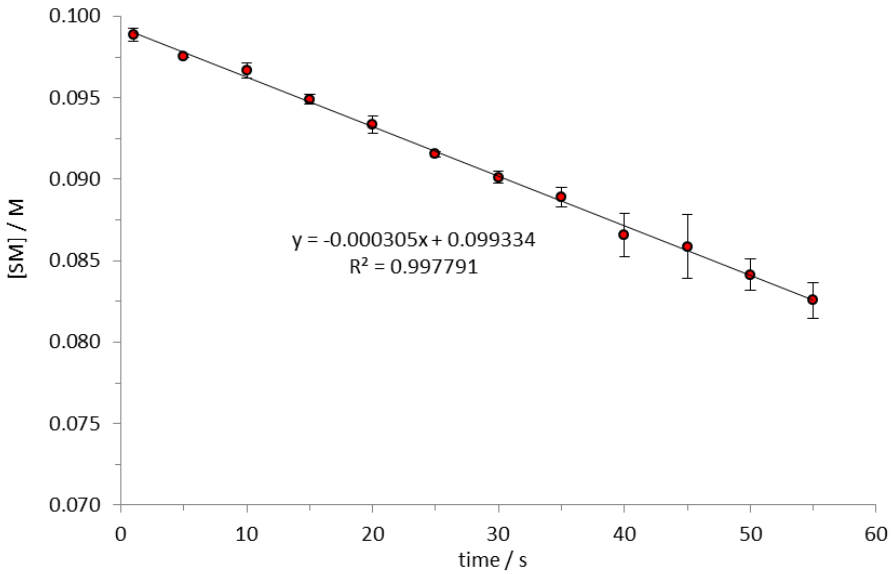


Figure 4.3. Monitoring the reaction using initial rates

Having demonstrated that the initial rates method was a viable means to measure the reaction rate, we set about determining the kinetic order with respect to substrate. A range of different initial concentrations of **201** between 0.01 and 0.2 M were employed and the initial rates in each case were determined. The kinetic order was then obtained by a bilogarithmic plot of initial rate versus initial substrate concentration. Using this method, we obtained the data shown in Figure 4.4 and determined the kinetic order with respect to substrate to be 0.98.

* This initial rate corresponds to an average over three identical runs. The error is the standard deviation of the three calculated gradients. The data plotted in Figure 4.3 shows averaged data over three runs along with standard deviation.

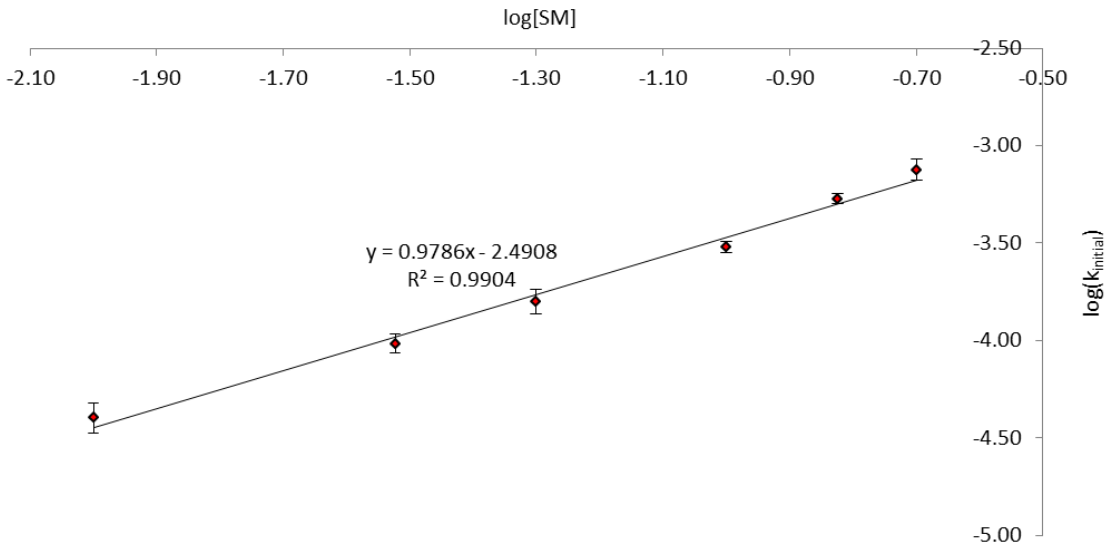


Figure 4.4. Bilogarithmic plot to determine kinetic order with respect to substrate

We now kept the concentration of substrate constant and varied the loading of thiophenol from 0.0055 to 0.44 M. The data from this plot exhibited saturation behaviour – at high concentrations of thiol (> 0.55 M) the concentration of thiol has little impact on the rate of reaction. However, at low concentration (< 0.55 M) the concentration of thiol exerts a strong influence upon the rate of reaction.

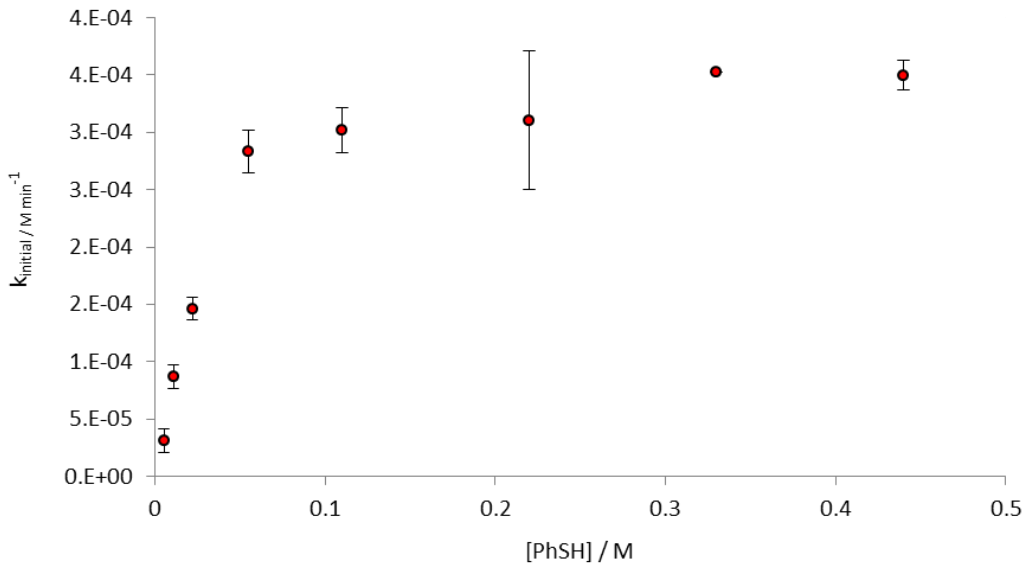


Figure 4.5. Bilogarithmic plot to determine kinetic order with respect to thiophenol

We then performed the reaction with various concentrations of phase-transfer catalyst **55** and again monitored the initial reaction rate (Figure 4.6). We found that with a low loading of catalyst (less than 20 mol %) the order in catalyst was close to 0.5. Surprisingly, if the catalyst loading was increased further a reduction in initial rate of reaction was observed. The latter effect may be indicative of a change in mechanism, but we do not currently have a detailed explanation for this phenomenon. Moreover, since all of our asymmetric reactions operate with 10 mol % of catalyst, we concluded that in the relevant concentration range the kinetic order with respect to catalyst is close to 0.5.

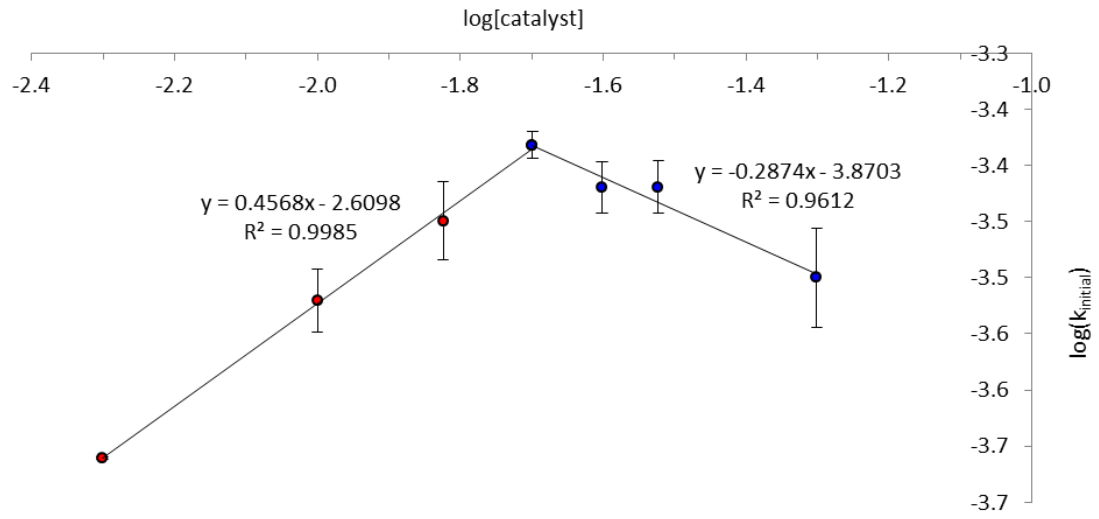


Figure 4.6. Bilogarithmic plot to determine kinetic order with respect to catalyst

We also found that the concentration of aqueous potassium carbonate has a strong effect upon the rate of the substitution reaction. At higher concentrations (approaching saturation), this effect was particularly strong, with a large increase in rate observed between 40 and 50 % aqueous hydroxide. We believe that one possible explanation for this effect may be the lack of hydration possible in more concentrated aqueous solution.[10]

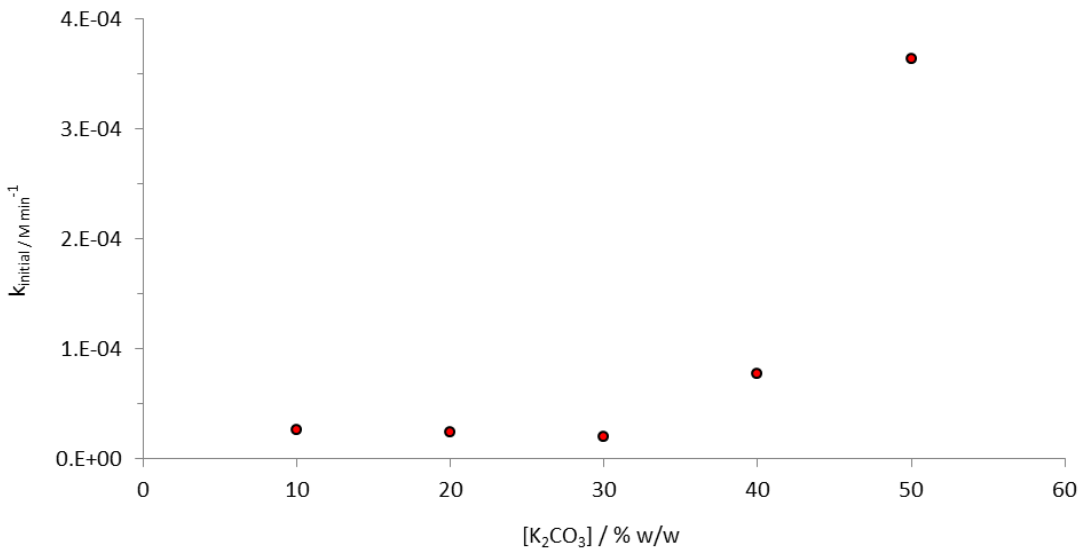


Figure 4.7. Variation of concentration of aqueous K_2CO_3

We next varied the stirring speed from 250-1400 r.p.m. and examined the effect upon initial rate of reaction. We found that the reaction exhibits a strong dependence upon stirring speed and that with very low rates of stirring the rate of reaction was close to zero.

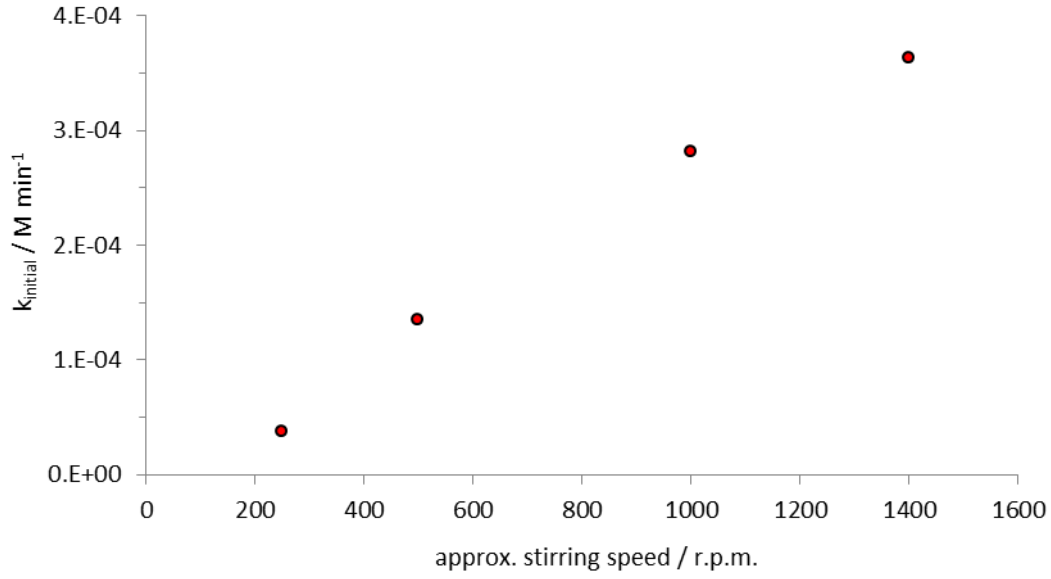


Figure 4.8. Variation of the stirring rate

As discussed previously, two scenarios have been set out in the literature:

i. An interfacial process, which displays strong dependence upon stirring speed

ii. An extractive process, which displays no dependence upon stirring speed *above a certain key threshold critical for mass transfer*

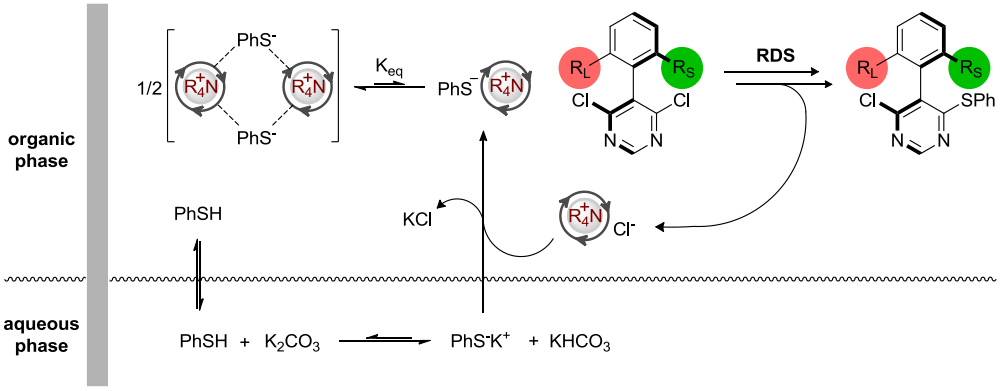
However, our stirring speed plot must be interpreted with some caution, since the previously reported systems all employ aqueous hydroxide with aromatic hydrocarbon solvents. In the asymmetric S_NAr reaction, the solvent is carbon tetrachloride, which is more dense that the aqueous base. At lower stirring speeds it was clearly the case that the reaction mixture was composed of two phases which were not fully mixed. It is therefore unclear what the key threshold critical for mass transfer is in such a system would be.

Our kinetic studies allowed us to conclude that the asymmetric desymmetrization reaction takes place with the following rate law:

$$\frac{d[product]}{dt} = k[substrate][thiophenol]^{sat}[catalyst]^{0.5}$$

The simple first order dependence of the reaction rate upon substrate suggests that this process takes place *via* an extractive mechanism in which rate determining arylation takes place in the organic phase. We speculate that the complex kinetic behaviour in thiol may be explained by saturation of the catalyst with thiophenolate – i.e. the rate determining S_NAr reaction has a simple first order dependence upon $PhS^-{\bullet}NR_4^+$, but with excess thiophenol the concentration of this species becomes limited by the quantity of phase-transfer catalyst available. Accordingly, we might expect to observe a simple first order kinetic dependence upon the phase-transfer catalyst. However, the observed order in catalyst is actually close to 0.5, a result which is consistent with the resting state of the catalyst being dimeric. If the active reagent were formed by reversible dissociation of a dimer, then provided that dissociation is rapid and the equilibrium lies greatly in favour of the dimer (such that only a very small concentration of monomer is present at any time) a catalyst order of 0.5 would be expected.[12]

Overall, we therefore tentatively propose a mechanism which is initiated by potassium carbonate mediated deprotonation of thiophenol in the aqueous phase (Scheme 4.4). The resulting potassium thiophenolate undergoes counter-ion metathesis with the catalyst leading to a lipophilic ion-pair which is extracted into the organic phase. This ion-pair undergoes an equilibrium aggregation process, forming an off-cycle dimer which represents the resting state of the catalyst. Only a small amount of active monomer is present at any one time, and it is this dissociated species which undergoes rate determining S_NAr reaction with the substrate, forming the product and regenerating the catalyst.

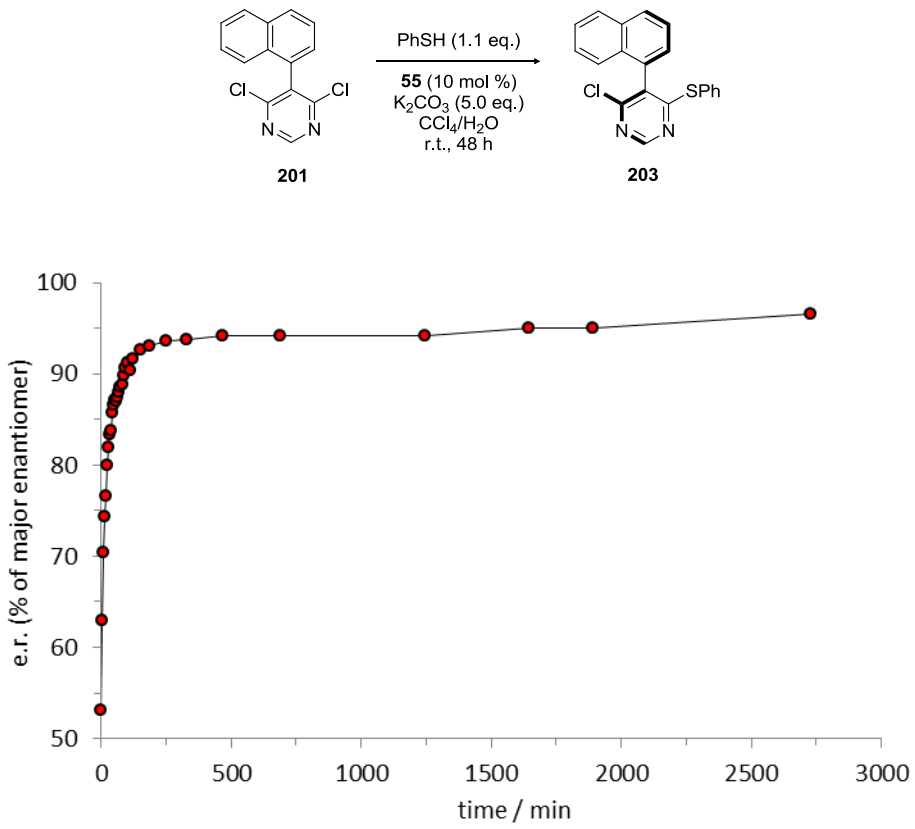


Scheme 4.4. Proposed modified extractive mechanism for phase-transfer catalysed desymmetrizing S_NAr reaction

4.3 Enantioselectivity as a function of time

Throughout our kinetic studies, we had used HPLC in order to determine the concentrations of the various species. Since the data was gathered using a chiral column, an unanticipated consequence of the method was that we were also able to determine the enantioselectivity of **103**. This allowed us to make a very surprising observation: the initial product formed was essentially racemic. Since the enantioenrichment at the end of the reaction is 97:3 e.r., this seems to imply that the asymmetric reaction is becoming more enantioselective as the reaction takes place. We plotted enantioenrichment as a function of time and found that initially the e.r. rose rapidly and within 90 minutes had reached 90:10 e.r. After this, the rate of increase slowed, and appeared to level off after 500 min (*c.a.* 8 h) to approximately 94:6 e.r.

This was followed by a gradual rise in enantioenrichment between 1000 and 3000 min (17-48 h), which is a consequence of the kinetic resolution described previously (Scheme 4.5).

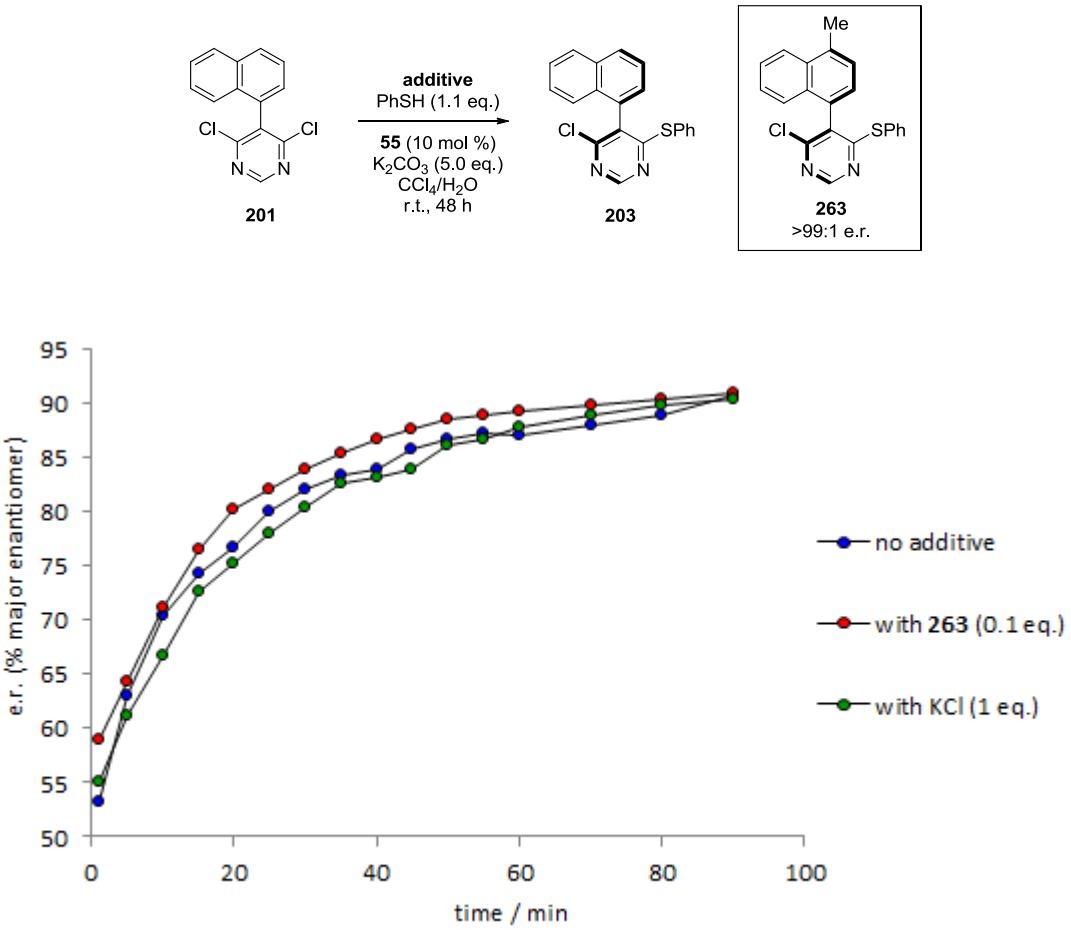


Scheme 4.5. Variation in enantioenrichment of **203** over the course of the reaction

We speculated that one possible explanation of such a result might be that the phase-transfer catalyst is modified under the reaction conditions. However, upon analysis of the crude reaction mixture by ^{1}H NMR spectroscopy, the peaks corresponding to the catalyst displayed identical chemical shifts and multiplicities to those of **55**.

We also wondered whether the non-linear enantioselectivity could be explained by asymmetric autocatalysis brought about by one of the reaction products. We set out to test this hypothesis by carrying out a substitution reaction in the presence of highly enantioenriched product. In order to distinguish the added enantioenriched material from the product formed in the reaction, we used a closely related compound **263**, tagged with an additional remote methyl substituent. The addition of a single enantiomer of this material

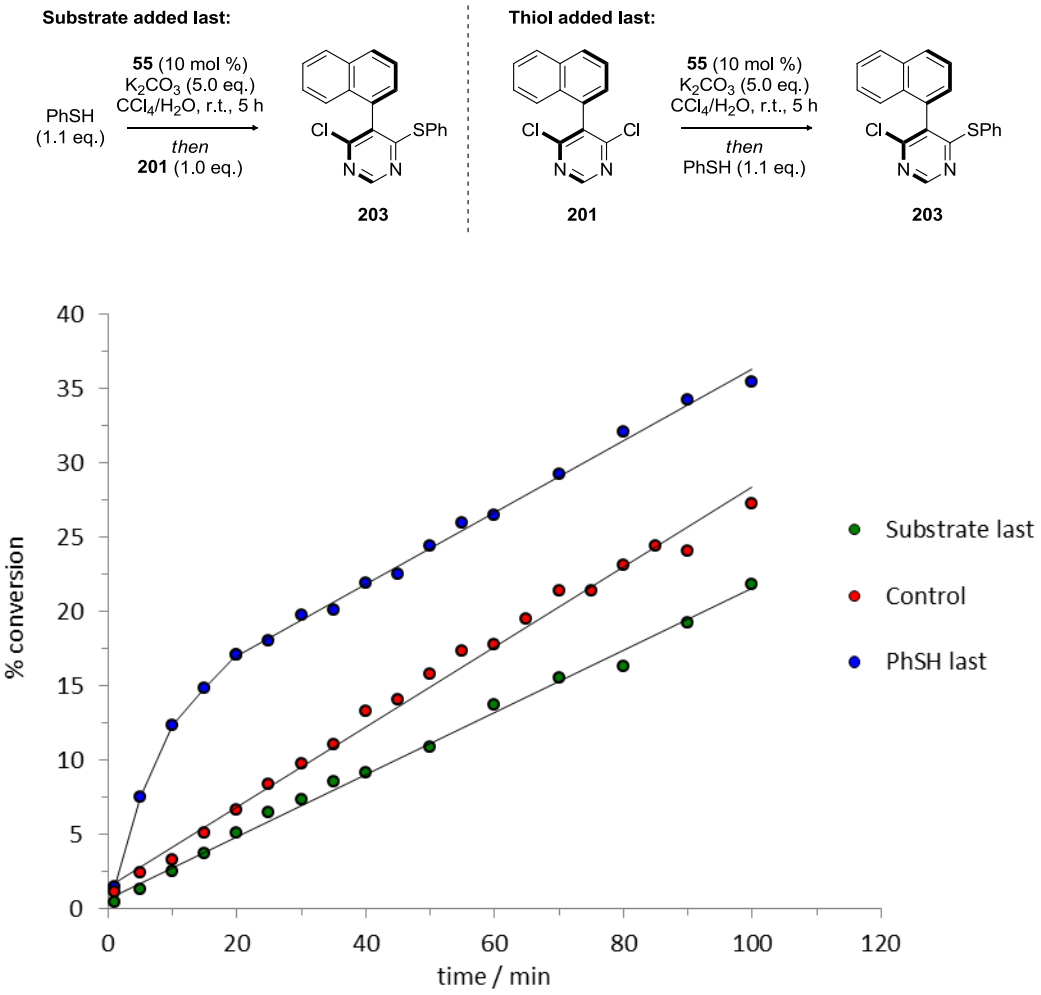
(obtained by semi-preparative chiral HPLC) did not appear to have a significant effect on the enantioselectivity of the product formed in the S_NAr reaction. Additionally, carrying out the asymmetric reaction in the presence of stoichiometric potassium chloride did not have any impact the enantioselectivity profile of the reaction. These results imply that autocatalysis is not responsible for this effect (Scheme 4.6).



Scheme 4.6. Product addition experiments with **263** and KCl

Our proposed mechanism (Scheme 4.4) requires a number of pre-equilibrium steps to take place before the reactive species $PhS^{-}\bullet NR_4^{+}$ is generated. We speculated that if one or more of these equilibria were not rapidly established, then it is possible that another competing process might initially be able to take place leading to the product in reduced enantioselectivity. We hoped that it might be possible to probe such an effect by investigating the consequences of premixing.

We carried out two separate experiments (Scheme 4.7) which were compared to the standard reaction as a control (red data points). In the first case (green data points), we stirred substrate, catalyst and base in carbon tetrachloride for five hours and then added thiophenol. In a second experiment (blue data points), we stirred thiophenol, catalyst and base in carbon tetrachloride for five hours and then added the substrate. In both experiments t=0 was taken to be the time at which the final reagent was added. When substrate was added last, we observed a comparable rate of reaction to the control. Interestingly, when the thiol was added last we observed rapid conversion to **203** over the first 10 minutes after which the reaction rate gradually slowed to a comparable level to the control reaction.



Scheme 4.7. Premixing experiments monitoring conversion over time

With the same data, we then plotted the enantioenrichment of **203** against time. We found that when the thiol was added last the enantioselectivity of the reaction was significantly lower, i.e. the rapid process leading to the formation of **203** within the first 10-20 minutes described above takes place in a non-selective manner. In contrast, when the substrate was added last, a much higher initial level of enantioinduction (81:19 e.r.) was observed.

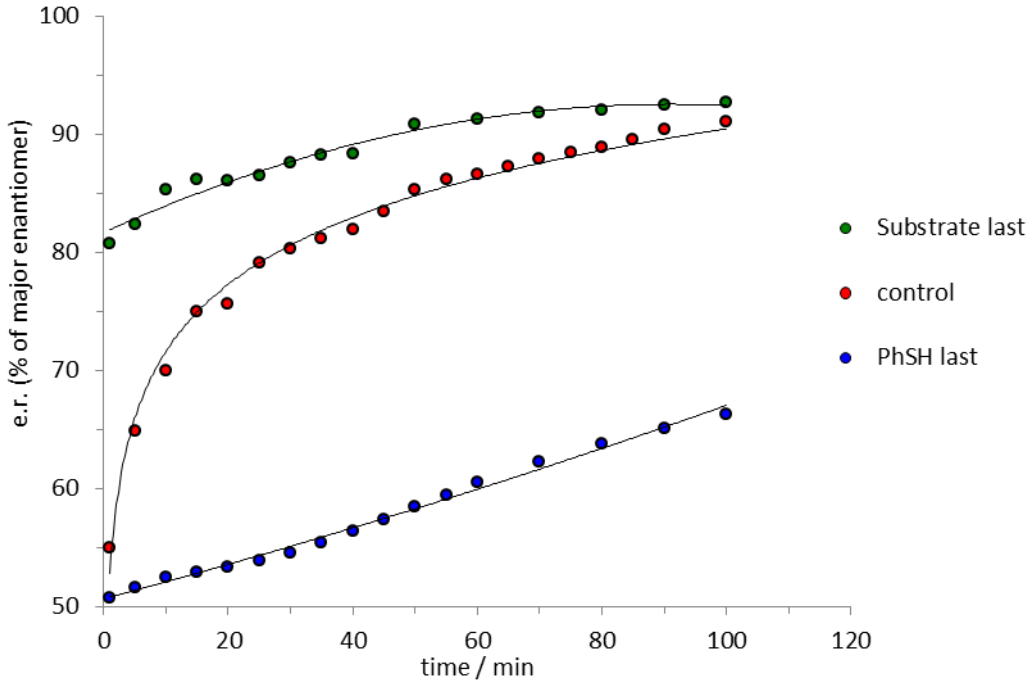


Figure 4.9. Premixing experiments monitoring enantioenrichment over time

These experiments suggest that at the outset of the reaction a slow process competes with the usual enantioselective substitution reaction. The observation that premixing catalyst, base and thiol results in higher initial selectivity, leads us to speculate that this slow process likely involves one or both of the following steps:

i. transport of thiol or thiophenolate to the aqueous phase

ii. exchange of thiophenolate with the catalyst

In order to understand the precise origins of this effect, further more detailed physicochemical experiments will be required.

4.4 Conclusion

We have investigated the mechanism of the desymmetrizing S_NAr reaction described in the previous chapter. By varying the loading of thiophenol, we have been able to identify that a kinetic resolution of the substituted products is partly responsible for the high selectivity observed in the desymmetrization. Carrying out the kinetic resolution of racemic mono-substituted product enabled us to determine that this resolution takes place with an *S* factor of approximately 30. Following a detailed initial rates kinetic study we were able to determine the substitution reaction obeys the following rate law:

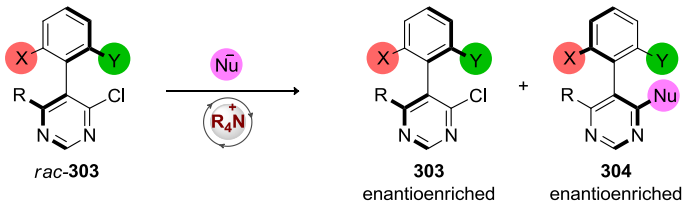
$$\frac{d[product]}{dt} = k[substrate][thiophenol]^{sat}[catalyst]^{0.5}$$

During the course of this work we made the surprising observation that the enantioselectivity of the reaction is initially very low and then increases. Although we do not fully understand the origins of this effect, we have shown that premixing the system before the dichloropyrimidine is added is able to significantly restore enantioselectivity from the outset of the reaction.

5. Kinetic Resolution of Axially Chiral Biaryls

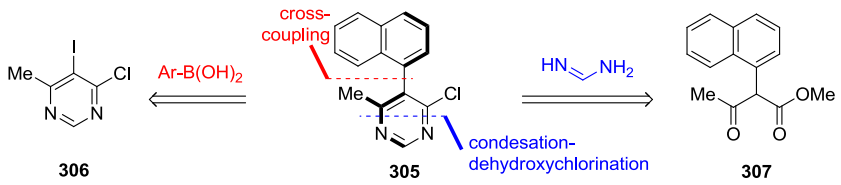
5.1 Kinetic resolution of configurationally stable biaryls

The logical extension of the asymmetric desymmetrization reaction was to carry out the kinetic resolution of a configurationally stable axially chiral biaryl. Following our success with dichloropyrimidine electrophiles, we envisaged a closely related chloropyrimidine scaffold **303**. If one enantiomer of *rac*-**303** reacted more rapidly than the other, a kinetic resolution could be achieved resulting in enantioenrichment of both the remaining starting material and the product **304** (Scheme 5.1).



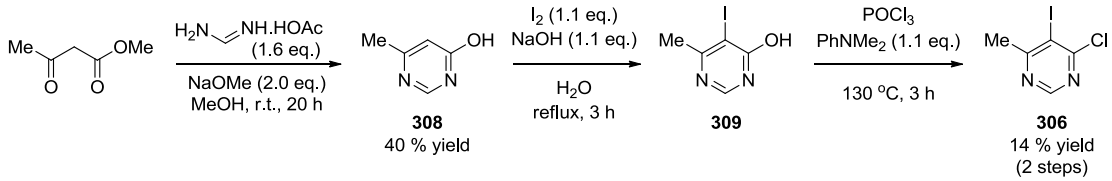
Scheme 5.1. Kinetic resolution of a configurationally stable chiral biaryl **303**

We decided to commence this investigation with an alkyl substituted starting material **305**. We hoped that it might be possible to assemble this compound by carrying out a chemoselective cross-coupling between known aryl iodide **306** and a hindered boronic acid. We were attracted to this method as we felt it represented a highly convergent method to synthesise analogues. However, we hoped that if this approach proved unsuccessful, we could fall back on a more familiar approach involving condensation of a β-ketoester **307** with formamidine followed by dehydroxychlorination (Scheme 5.2).



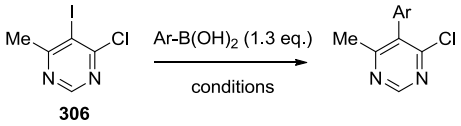
Scheme 5.2. Potential retrosynthetic strategies for kinetic resolution starting material **305**

We began by investigating the cross-coupling route. The requisite aryl iodide **306** was synthesised in three steps from methyl acetoacetate according to literature procedures.[99] This route involved initial condensation with formamidine, followed by a regioselective iodination under basic conditions leading to pyrimidone **309**. This material underwent dehydroxychlorination under our standard conditions to form **306** in 14 % yield over two steps (Scheme 5.3).



Scheme 5.3. Synthesis of iodinated coupling partner **306**

We then attempted a cross-coupling reaction between **306** and phenyl boronic acid. Unfortunately, under anhydrous conditions, the only material we could isolate was recovered starting material (Table 5.1, entry 1). Upon switching the base to aqueous potassium phosphate we were able to isolate a small quantity of the desired product, although more forcing conditions led to decomposition (Table 5.1, entry 2-3). We saw a significant improvement when we changed the ligand to dppf, and the product was isolated in 42 % yield, although this material was contaminated by c.a. 10 % of an unknown impurity (Table 5.1, entry 4).[100] When we switched to 1-naphthyl boronic acid we observed only recovered starting material (Table 5.1, entry 5).

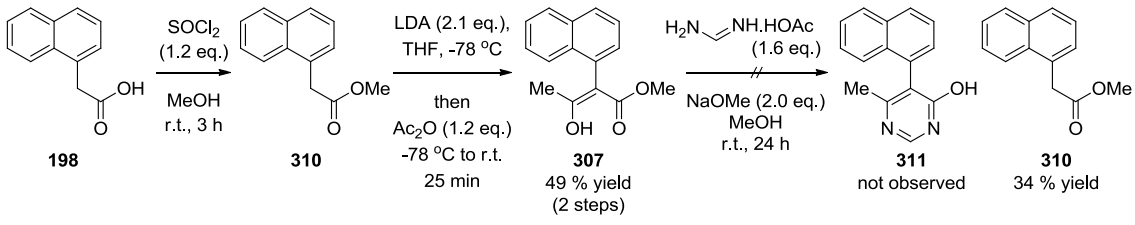


306

Entry	Ar	Conditions	Result
1	Ph	$Pd(PPh_3)_4$ (10 mol %), K_2CO_3 (2.0 eq.), PhMe, 90 °C	no reaction
2	Ph	$Pd(OAc)_2$ (10 mol %), SPhos (20 mol %), K_3PO_4 (2.0 eq.), dioxane, 60 °C	18 % yield (54 % RSM)
3	Ph	$Pd(OAc)_2$ (10 mol %), SPhos (20 mol %), K_3PO_4 (2.0 eq.), dioxane, μw 130 °C	decomposition
4	Ph	$PdCl_2(dppf)CH_2Cl_2$ (10 mol %), K_3PO_4 (3.0 eq.), dioxane, 70 °C	42 % yield
5	1-nap	$PdCl_2(dppf)CH_2Cl_2$ (10 mol %), K_3PO_4 (3.0 eq.), dioxane, 70 °C	no reaction

Table 5.1. Attempted synthesis of kinetic resolution substrates *via* palladium catalysed cross-coupling

At this point we decided to focus our attention on the alternative synthetic route discussed earlier, employing naphthyl substituted β-ketoester **307**. After some optimization, we found that this compound could be prepared by esterification of 1-naphthylacetic acid followed by base mediated acylation with acetic anhydride. This afforded **307** in 49 % yield over two steps. We now attempted to condense this compound with formamidine under our previously optimized conditions. To our disappointment, we did not observe any of the desired dihydroxypyrimidine, and only ester **310** was isolated (Scheme 5.4). This material likely arises from a retro-Claisen reaction of **307** under the relatively harsh reaction conditions.

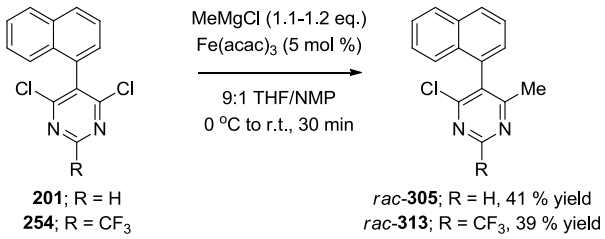


198 → **310** → **307** (49 % yield (2 steps)) → **311** (not observed) + **310** (34 % yield)

Scheme 5.4. Attempted synthesis of pyrimidone **311** *via* β-ketoester **307**

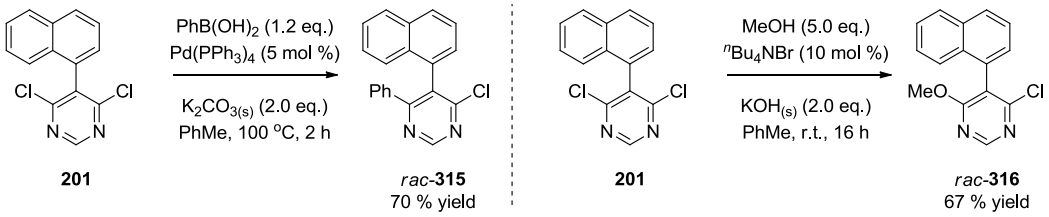
At this point, we attempted to prepare the desired substrate **305** *via* a Kumada cross-coupling of dichloropyrimidine **201**. This constituted a particularly appealing approach since we already had a significant amount of dichlorinated material in hand from the desymmetrization reaction. We found that methylmagnesium chloride underwent an effective Kumada cross-

coupling allowing us to obtain the desired chloropyrimidine **305** in 41 % yield.[98] We were also able to synthesise a trifluoromethyl substituted derivative *via* an analogous method in 39 % yield (Scheme 5.5).



Scheme 5.5. Preparation of kinetic resolution substrates by Kumada coupling

We took this opportunity to prepare some other starting materials by functionalizing **201**. A phenyl containing derivative **315** was prepared in 70 % yield by a Suzuki coupling with phenyl boronic acid under previously optimized conditions. We also synthesised an electron rich chloropyrimidine **316** *via* a S_NAr reaction between **201** and methanol in good yield (Scheme 5.6).

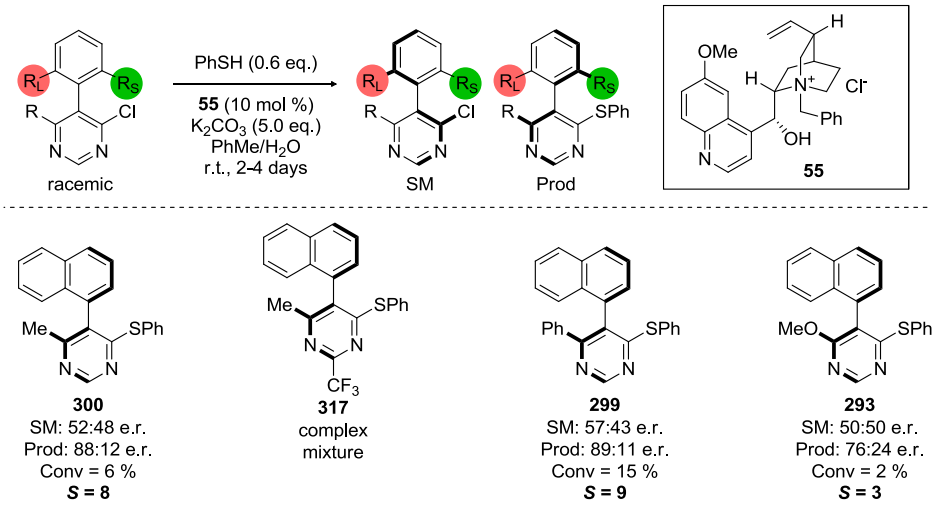


Scheme 5.6. Synthesis of additional substrates **315** and **316**

We were then in a position to attempt the kinetic resolution of these compounds. Since we had previously experienced some success with the kinetic resolution of *rac*-**203**, we chose to employ thiophenol as a nucleophile under analogous conditions to those developed for the desymmetrization reaction. Conveniently, for resolutions in which both the starting material and product are chiral the conversion can be determined using the following equation:[80]

$$conversion = \frac{e.e.(SM)}{e.e.(Prod) + e.e.(SM)}$$

For methyl substituted **305**, we found that after 48 hours 6 % conversion to the substituted product **300** had taken place, which was present in 88:12 e.r. Based on the enantioenrichment of the recovered starting material and product we calculated a selectivity factor of 8 for this kinetic resolution. The trifluoromethyl substrate **313** led to a mixture which we were unable to analyse.* With the phenyl substituted analogue **315**, we saw slightly improved conversion and we calculated a selectivity factor of 9. Unsurprisingly, the electron rich methoxy substituted chloropyrimidine underwent very slow substitution and we calculated a selectivity factor of 3 (Scheme 5.7).



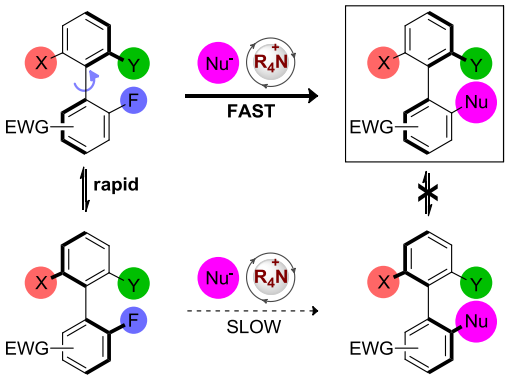
Scheme 5.7. Kinetic resolution of configurationally stable axially chiral biaryls

Despite the low conversions, the enantioselectivities obtained in these reactions were promising. Moreover, the major enantiomer of products **300**, **299** and **293** possessed the same absolute stereochemistry as the materials obtained previously from desymmetrization followed by derivatization. This implies that the absolute sense of enantioinduction observed in the desymmetrization and kinetic resolutions are analogous. However, we were concerned that the low reactivity observed in the latter case precludes this approach from being synthetically viable. Accordingly, we set out to find a more reactive system.

* Due to the non-polar nature of this mixture, we were unable to separate the components either by column chromatography or analytical chiral HPLC.

5.2 Dynamic kinetic resolution of configurationally unstable biaryls

It is often the case in S_NAr reactions that enhanced reactivity is observed with aryl fluorides over aryl chlorides. Indeed, all of the catalytic asymmetric S_NAr reactions reported in the literature employ aryl fluorides as reactive electrophiles.[73, 74] At first sight, this appears to be a limitation, but we wondered if we could take advantage of both the high reactivity and small size of aryl fluorides in the development of a dynamically kinetically resolved S_NAr reaction. We hoped to employ a starting material containing an electron poor aryl group with an *ortho*-fluoro substituent. We envisaged that the sterically small nature of the fluorine would allow rapid interconversion of the two enantiomers of this starting material.[101] Carrying out a S_NAr reaction with a bulky nucleophile would then lead to atropisomeric material with a high energy barrier to racemisation. If a chiral cation could enable a nucleophile to react preferentially with one enantiomer of the starting material, then a dynamic kinetic resolution would be achieved (Scheme 5.8).[102]

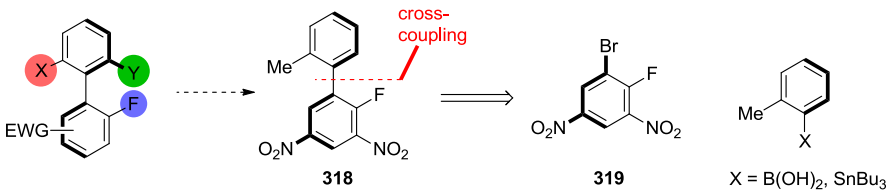


Scheme 5.8. Proposed cation-directed S_NAr reaction - dynamic kinetic resolution of aryl fluorides

5.3 Dynamic kinetic resolution of 2,4-dinitrofluoroarenes

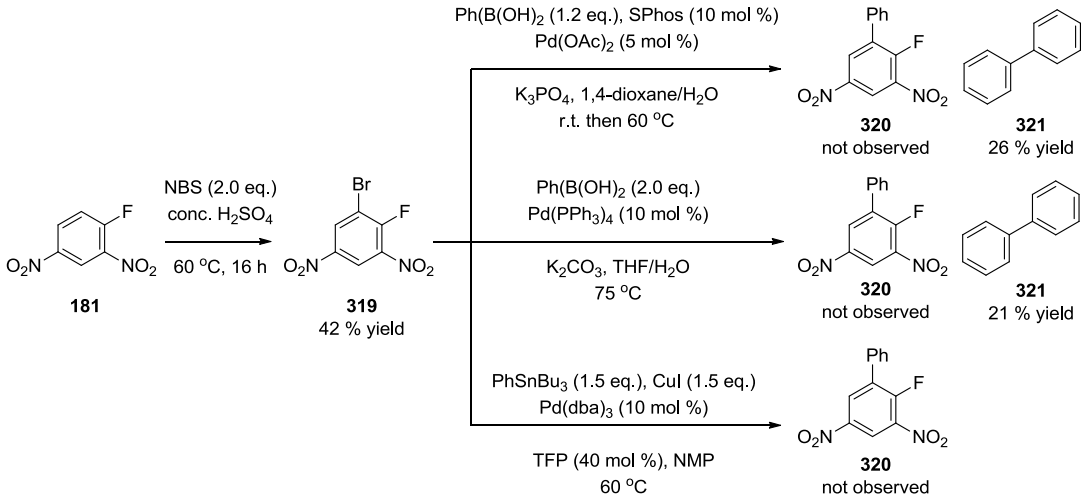
We felt that incorporation of two nitro groups located *ortho*- and *para*- to an aryl fluoride would result in a substrate poised to undergo efficient S_NAr reaction. We therefore envisaged substrate **318**, which contains this substitution pattern along with a hindered aryl group. We

hoped that the biaryl bond could be formed by a cross-coupling reaction between known aryl bromide **319** and an appropriate nucleophilic partner (Scheme 5.9).



Scheme 5.9. First generation substrate along with retrosynthetic analysis

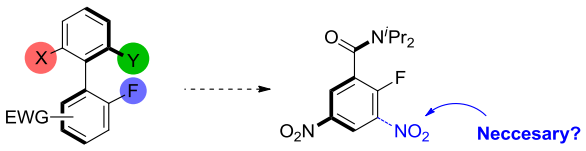
In the forward sense, **319** was obtained in 47 % yield by bromination of Sanger's reagent in concentrated sulfuric acid (Scheme 5.10).[103] To determine whether cross-coupling of this bromide was feasible, we investigated a Suzuki-Miyaura coupling with phenylboronic acid. We found that the only non-baseline material we were able to isolate was biphenyl in 26 % yield, presumably formed by the reduction of Pd(II) to Pd(0). Alternative conditions employing solid base along with tetrakis(triphenylphosphine)palladium(0) gave a similar result. Attempted Stille coupling led to only starting material. We felt that synthesis of **318** would likely prove even more challenging as a sterically demanding coupling partner would be required. We therefore decided to pursue alternative substrates.



Scheme 5.10. Synthesis of bromide **319** and attempted cross-coupling reactions

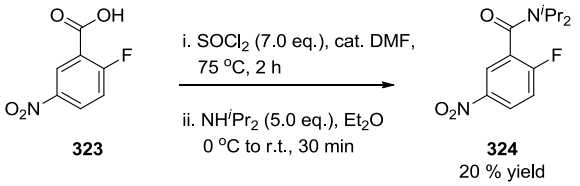
5.4 Dynamic kinetic resolution of hindered amides

We were attracted to amide substrates for two reasons: firstly, we believed that they would be much easier to synthesise; secondly we hoped that the amide itself might serve as an electron withdrawing group, removing the requirement for the second nitro substituent (Scheme 5.11).



Scheme 5.11. Development of a second generation substrate

Commercially available 2-fluoro-5-nitrobenzoic acid **323** was activated as the acid chloride and then reacted with diisopropylamine, leading to the desired amide substrate **324** in 20 % yield (Scheme 5.12).

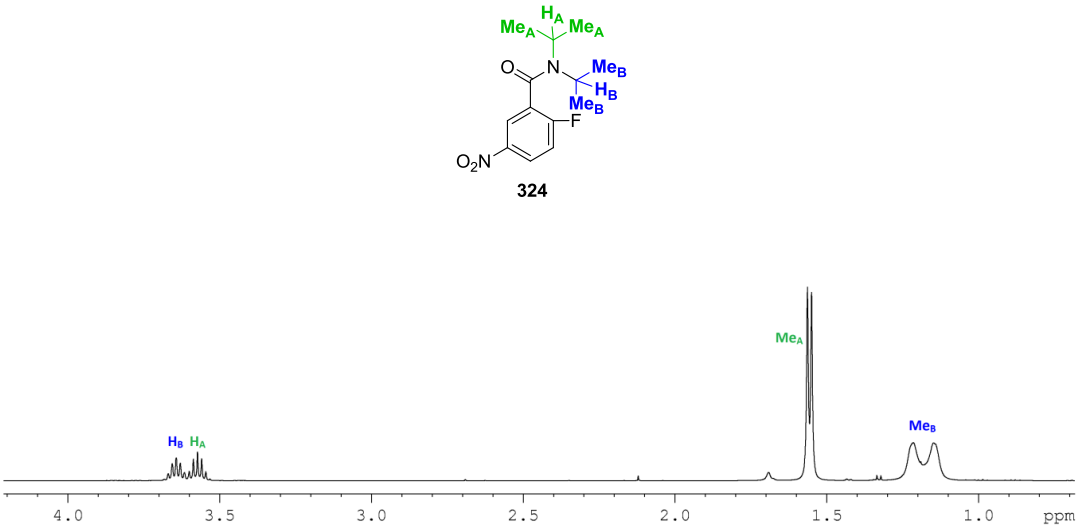


Scheme 5.12. Synthesis of 2nd generation starting material **324**

We were intrigued by the ^{1}H NMR spectrum of **324**, specifically the peaks resulting from the *N*,*N*-diisopropyl amide. The critical region of the spectrum is shown below in Figure 5.1. By following COSY correlations from the downfield septets corresponding to H_A and H_B we were able to deduce that the sharp doublet at 1.55 ppm (6H, Me_A) and the broad feature centred around 1.2 ppm (6H, Me_B) correspond to the *cis*- and *trans*- isopropyl groups of the amide respectively.* The signal for Me_B is complex, appearing to be partially resolved into two peaks on the verge of coalescence. This effect is most likely explained by restricted rotation about

* This assignment is somewhat tentative and is based on the expectation that the amide substituents *cis*- to oxygen appear downfield relative to those oriented *trans*- to oxygen.[104]

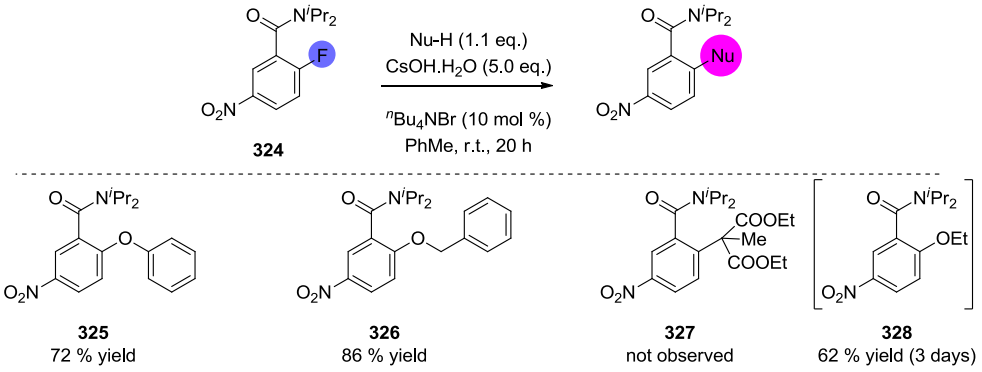
the Ar-CO axis which occurs on a timescale similar to that of the ^{1}H NMR experiment. This coalescence is unlikely to be explained by restricted rotation about the N-CO bond, since the signals from H_A and H_B, which are separated by a comparable chemical shift difference exhibit no signs of coalescence or line broadening. Presumably, the signal from Me_A has already undergone coalescence at this temperature, leading to the observed 6.9 Hz doublet which originates from coupling to H_A. Using this information, we can tentatively estimate the timescale of the enantiomerization process to be on the order of 10 ms, i.e. the enantiomers of **324** interconvert rapidly at room temperature.



324

Figure 5.1. An excerpt from the ^{1}H NMR spectrum of **324**

We investigated phase-transfer catalysed S_NAr reaction of **324** with several nucleophiles (Scheme 5.13). With phenol and benzyl alcohol, good reactivity was observed and the corresponding products **325** and **326** were obtained in high yields. Under analogous conditions, α-methyl diethylmalonate did not undergo S_NAr reactivity and after three days, the only product we were able to isolate was **328** in 62 % yield. This compound presumably arises from a S_NAr reaction with ethoxide, generated by ester hydrolysis of the malonate.



324

325
72 % yield

326
86 % yield

327
not observed

328
62 % yield (3 days)

Scheme 5.13. Phase-transfer catalysed S_NAr reactions with **324**

The region of the ^{1}H NMR spectra of **325** corresponding to the diisopropylamide is shown in Figure 5.2. The four methyl groups are clearly resolved as four separate doublets. A COSY spectrum allowed us to correlate each of the upfield septets with a pair of methyl resonances. This enabled us to assign the upfield and downfield pairs of methyl resonances separated by a large chemical shift to correspond to *E*/*Z* isomers of the amide. Comprehensive studies carried out by Clayden *et al.* and others and have concluded that hindered diisopropylamides adopt well-defined solution state conformations such as that shown for **325** below.[104] The isopropyl group *cis*- to oxygen straddles the amide carbonyl with its two methyl groups, pointing its hydrogen towards the *trans*-isopropyl group. This proton is then straddled by the two methyl groups of the *trans*-isopropyl group. nOe analysis carried out on **325** fitted well with this model. **325** is represented below in this conformation with the four key methyl groups labelled as **A**, **B**, **C** and **D** along with key nOe interactions.*

* The assignment of Me_A *vs* Me_B and Me_C *vs* Me_D is arbitrary.

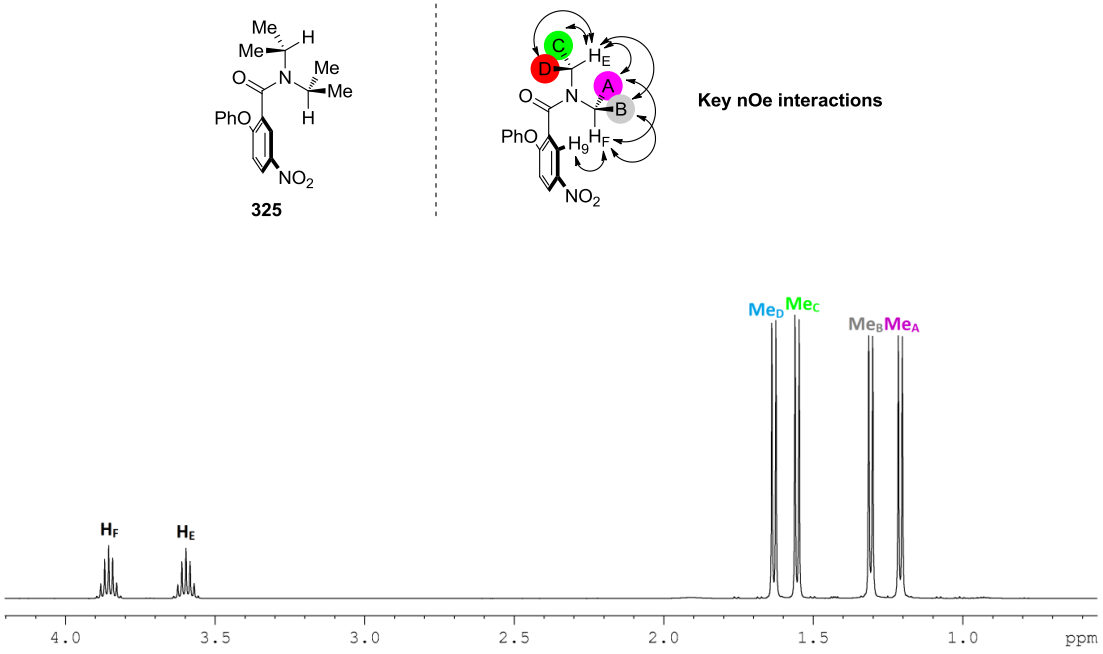


Figure 5.2. ^{1}H NMR of **325** and nOe correlations demonstrating preferred conformation

From the anisochronicity of this ^{1}H NMR spectrum we concluded that introduction of a bulkier substituent *via* S_NAr had increased the barrier for the enantiomerization process. However, since **325** eluted as a single peak from all of six of our analytical chiral HPLC columns we were unsure what the rate of enantiomerization of this compound was. With the help of Professor Tim Claridge, we carried out EXSY experiments to investigate exchange processes taking place over longer timescales (D_8 = 200 ms). EXSY is essentially a 1D nOe experiment where selected resonances can be irradiated. nOe correlations to other protons close in space appear as positive signals, but if the irradiated proton is able to undergo a chemical or conformational exchange with another proton environment on a timescale comparable with the mixing time, a negative signal will be detected. We began by irradiating H_E and H_F (Figure 5.3). Each of these environments showed an EXSY correlation to the other indicating that a process is taking place which interconverts the double bond isomers of the amide. The positive signals to the methyl groups are nOe correlations.*

* Upon irradiation of H_F, a small nOe correlation can also be seen to the singlet at 8.25 ppm corresponding to H_9 (the *ortho* position of the nitroarene).

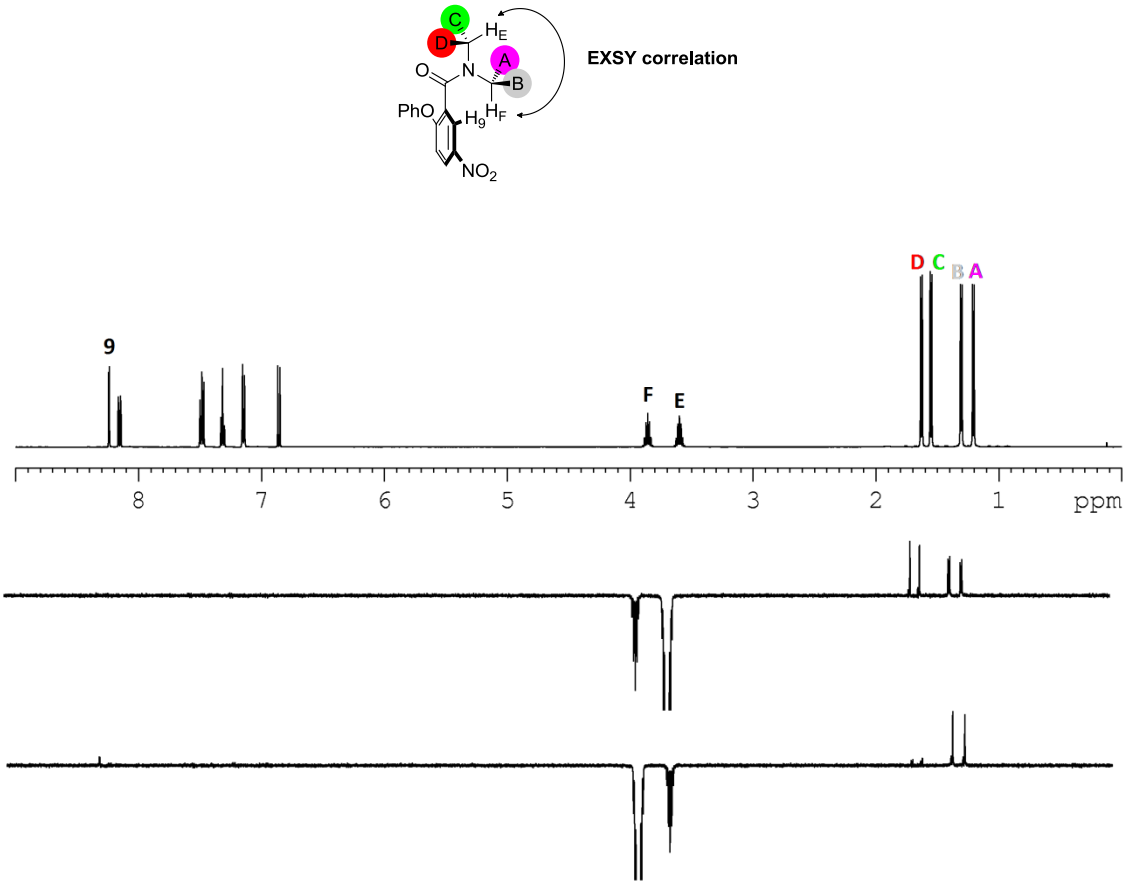


Figure 5.3. ^{1}H spectrum of **325** and EXSY spectra showing irradiation of H_E and H_F

Next the four doublets originating from the methyl groups were sequentially irradiated (Figure 5.4). Each of these four signals exhibited the same pattern of EXSY correlations – one to its diastereotopic partner and another to a methyl from the other isopropyl group. In no case was a third correlation observed.

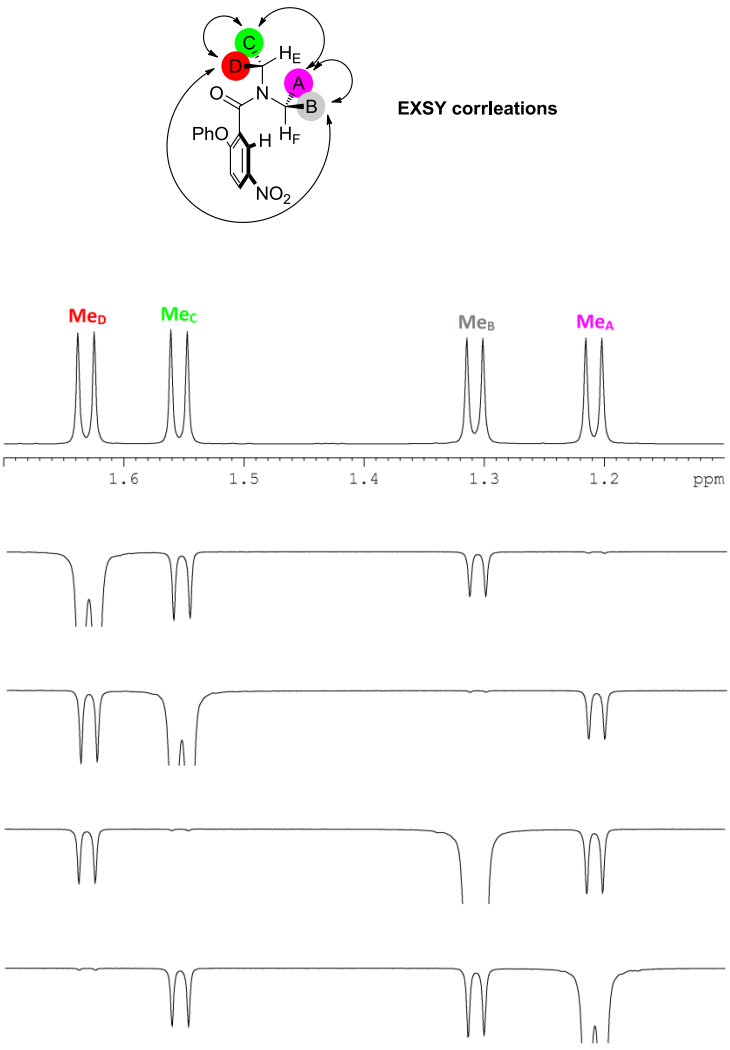
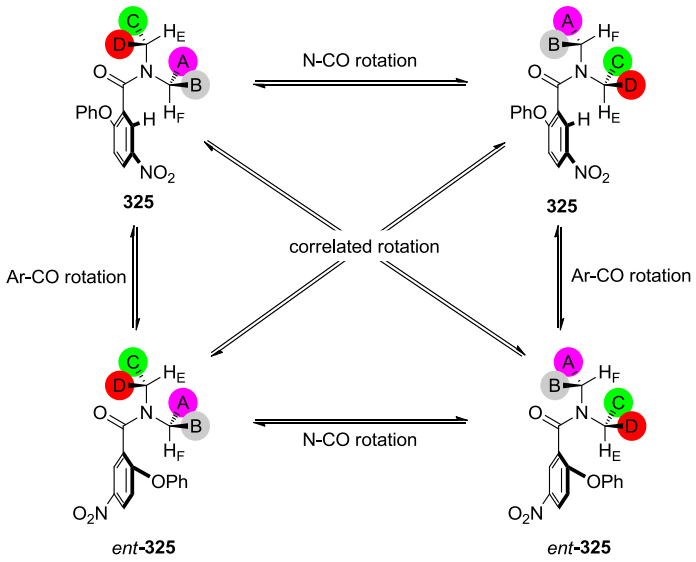


Figure 5.4. ^{1}H spectrum of **325** and EXSY correlations between methyl groups A-D

Clayden *et al.* have investigated the interconversion of stereoisomers of related hindered amides and have described three mechanistic possibilities (Scheme 5.14).[105] The first possibility is rotation about the Ar-CO axis, which would convert **325** to its enantiomer *ent*-**325** and result in exchange of methyl groups A ↔ B and C ↔ D. The second possibility is that isomerization of the amide takes place – that is to say that rotation about the N-CO bond occurs. This process would result in exchange of methyl groups A ↔ C and B ↔ D. The final possibility is that rotation about both Ar-CO and N-CO axes occurs *via* a correlated mechanism. This rotation would result in the exchange of methyl groups A ↔ D and B ↔ C. Our EXSY experiments clearly demonstrate that two (but not three) of these processes take place over

the 200 ms timescale observed. Moreover, the only process which can explain the observed interconversion of diastereotopic methyl groups is Ar-CO rotation. Since our assignments of the methyl groups within each diastereotopic pair are arbitrary, we cannot distinguish whether the second process operates *via* straightforward N-CO rotation or *via* a correlated mechanism. The exchange of $H_E \leftrightarrow H_F$ can also be explained by either of these processes. We concluded that enantiomers of **325** are not configurationally stable, interconverting on a timescale of the order of 200 ms.*

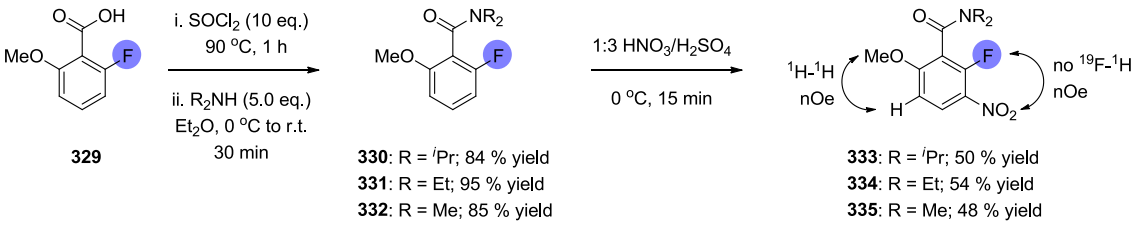


Scheme 5.14. Possible rotational exchange processes for **325** as described by Clayden *et al.*

Since **325** undergoes such rapid isomerization, we decided to synthesise a series of more hindered aryl fluorides possessing an additional *ortho*-methoxy substituent. To investigate the steric requirements of this system we set out to synthesise dimethyl, diethyl and diisopopyl analogues and investigate their conformational stability. These compounds were assembled from commercially available carboxylic acid **329** by amide formation followed by nitration under standard conditions (Scheme 5.15). For the diisopropyl amide **333**, we carried out

* This fits well with the work of Clayden *et al.*, who have reported that the majority of tertiary aromatic amides with a single *ortho* substituent are not atropisomeric at room temperature.[105] It would be interesting to investigate the effect of a quaternary *ortho* substituent, for example in **327**.

homo- and heteronuclear nOe experiments to tentatively assign the regioselectivity of the nitration reaction.



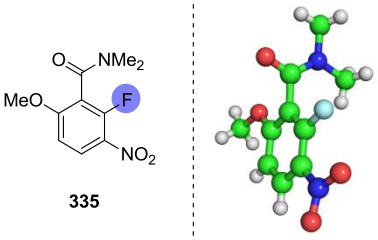
329

330: R = ^{i}Pr; 84 % yield
331: R = Et; 95 % yield
332: R = Me; 85 % yield

333: R = ^{i}Pr; 50 % yield
334: R = Et; 54 % yield
335: R = Me; 48 % yield

Scheme 5.15. Synthesis of methoxy substituted fluoroarenes

Fortunately, we were able to obtain a single crystal of **335** suitable for X-ray diffraction, which allowed us to unequivocally determine the structure of this material (Figure 5.5).*



335

Figure 5.5. X-ray crystal structure of **335**

We then analysed nitrated amides **333**, **334** and **335** by analytical chiral HPLC (Figure 5.6). The bulky diisopropyl amide **333** showed two peaks with clear baseline separation indicating it to be atropisomeric, but **334** and **335** with smaller ethyl and methyl amides exhibited chromatograms with a clear 'Batman effect'. Qualitatively, the conclusion is clear – the smaller the substituent on nitrogen the more rapidly the enantiomers interconvert. Using the method of Trapp *et al.* we were able to calculate the energetic barriers for enantiomerization of **334** and **335** along with the corresponding half-lives for racemization, which are shown below (Figure 5.6). The configurational stability of diisopropyl amide **333** was determined by

* X-ray data was collected and analysed by John Jolliffe.

monitoring the rate of racemization of an enantioenriched sample (obtained by semi-preparative chiral HPLC) over time.*

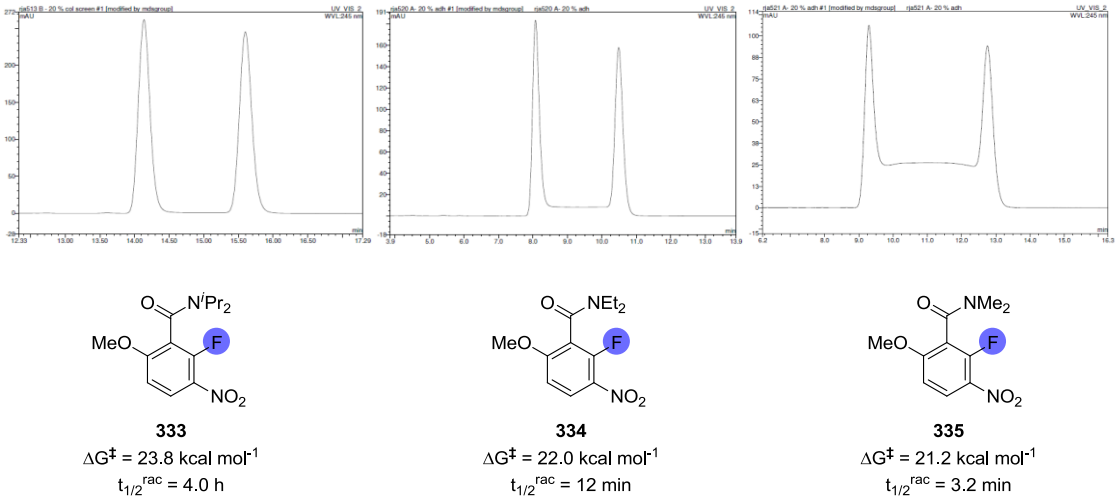


Figure 5.6. Analytical chiral HPLC spectra of nitrated aromatic amides

For the smallest compound in this series **335**, we demonstrated the impact of increased temperature upon the enantiomerization process by incrementally raising the temperature of the column oven. Over a 15 °C temperature range, we saw the Batman effect become increasingly pronounced up to a temperature of 40 °C, at which point coalescence of the peaks took place (Figure 5.7).

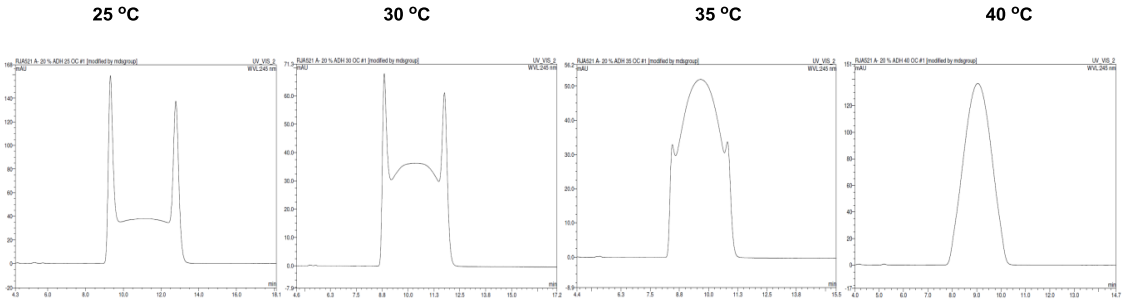
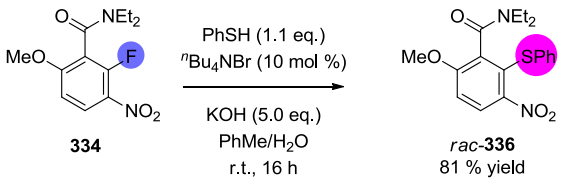


Figure 5.7. Analytical chiral HPLC spectra of **335** recorded at different temperatures

We selected ethyl derivative **334** as the starting material for a dynamically kinetically resolved S_NAr reaction as we knew that the enantiomers of this starting material would interconvert reasonably quickly ($t_{1/2}^{rac}$ = 12 min) under the reaction conditions. We subjected **334** to

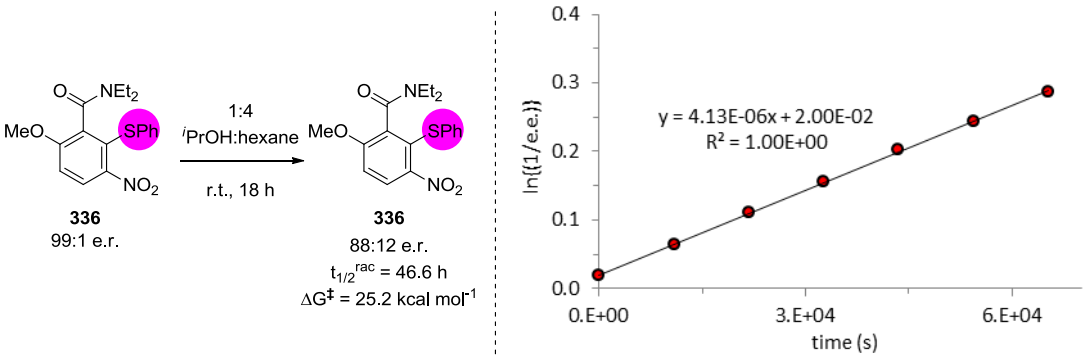
* See experimental section for details.

racemic phase-transfer conditions and were pleased to find that with thiophenol we observed substitution of the fluoride, affording **336** in 81 % yield (Scheme 5.16). The enantiomers of **336** were fully separated by HPLC and no Batman effect was observed.



Scheme 5.16. S_NAr reaction of **334** with thiophenol

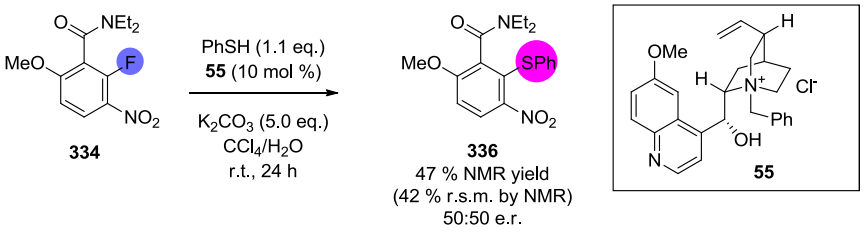
In order to probe the configurational stability of **336**, we used semi-preparative chiral HPLC to obtain an enantioenriched sample (99:1 e.r.). In an analogous manner to that described previously, a solution of this material was allowed to stand at room temperature and analysed by chiral HPLC every three hours (Scheme 5.17). After 18 hours we observed an overall decrease in enantioenrichment to 88:12 e.r. and were therefore able to determine that **336** possesses a half-life of racemization of 46.6 hours ($\Delta G^{\ddagger}$ = 25.2 kcal mol^{-1}).



Scheme 5.17. Determination of the rate of racemization of **336**

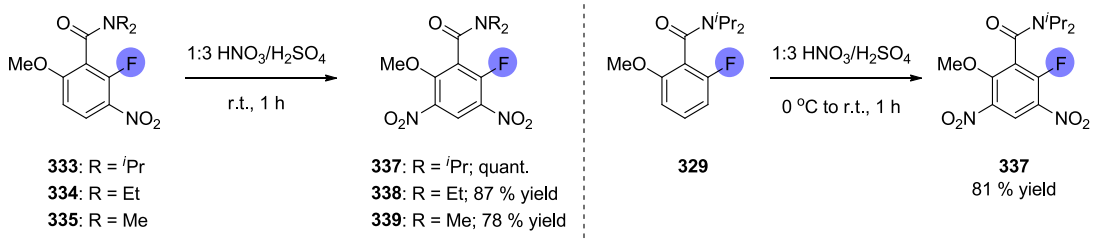
This result was extremely promising, since it indicated that we had identified a reactive system in which the starting material was dynamic ($t_{1/2}^{rac}$ = 12 min), but the product had a relatively high barrier to racemization ($t_{1/2}^{rac}$ = 46.6 hours) and were therefore in a position to attempt a dynamically kinetically resolved S_NAr reaction. Accordingly, we subjected **334** to thiophenol in the presence of *N*-benzylquninium chloride and after 24 h, we observed a 47 % NMR yield of

336. Unfortunately, analysis of this material by chiral HPLC indicated it to be racemic (Scheme 5.18).



Scheme 5.18. Attempted dynamic kinetic resolution of **334**

In order to achieve good S_NAr reactivity with other nucleophiles we believed it would be beneficial to increase the electrophilicity of the fluoroarene. We therefore subjected mono-nitrated compounds **333**, **334** and **335** to standard nitration conditions, and were pleased to obtain the corresponding dinitrated products in good yields. Conveniently, it also proved possible to obtain **337** directly from **330** *via* regioselective double nitration in 81 % yield.



Scheme 5.19. Synthesis of dinitrated analogues along with direct double nitration

We were interested to see what effect the additional nitro group would have upon the configurational stability of these aryl fluorides. Analysis by chiral HPLC revealed a similar pattern to that observed for the mono-nitrated analogues. **338** and **339** displayed a significant Batman effect, and using the method of Trapp *et al.*, we calculated these compounds to have racemization half-lives of 32 minutes and 4.0 minutes respectively. For the more hindered diisopropyl amide, two clear peaks were observed. Analysis of an enantioenriched sample of

337 over time allowed us to calculate a racemization half-life of 5.0 hours.* In all three cases the rate of racemisation was slightly retarded in comparison with the mono-nitrated analogues, which is likely due to the buttressing effect caused by the presence of the additional *meta*- substituent.[48]

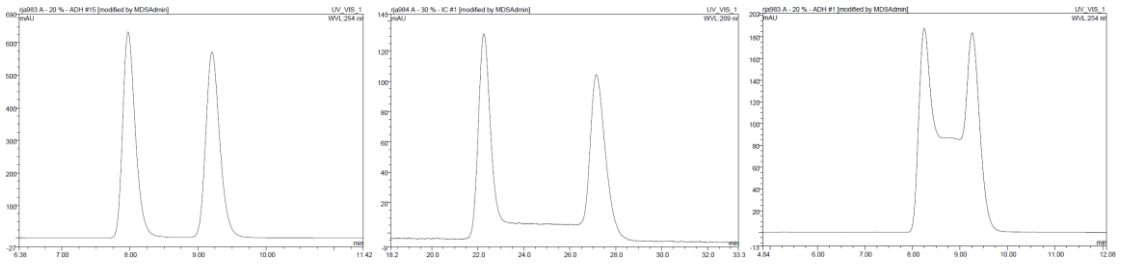
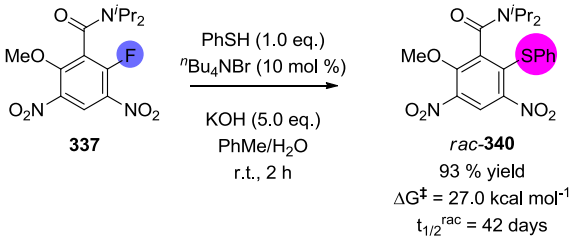


Figure 5.8. Analytical chiral HPLC spectra of dinitrated aromatic amides

We selected the most hindered aryl fluoride **337** and attempted a S_NAr reaction with thiophenol. We were pleased to isolate the substituted product **340** in 93 % yield and by monitoring the rate of racemization of an enantioenriched sample of the product **340** over time we were able to calculate that this material has a racemization half-life of 42 days.

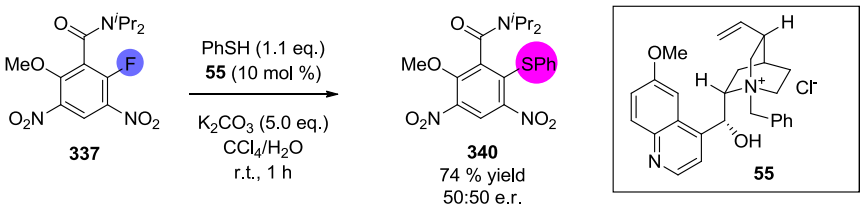


Scheme 5.20. S_NAr reaction of **337** with thiophenol

We next set out to investigate the asymmetric variant of this transformation. We found that employing our previously optimized conditions with 1.1 equivalents of thiophenol in the

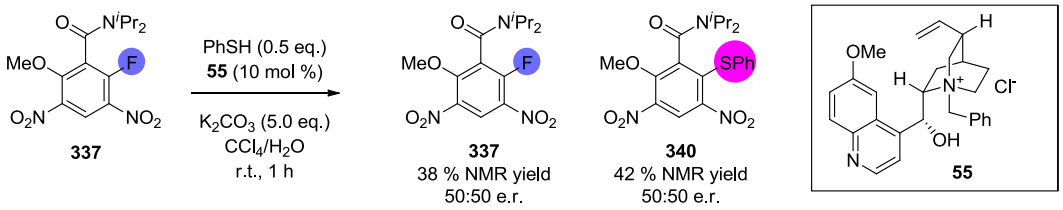
* See experimental section for details.

presence of *N*-benzyl quininium chloride we now obtained complete conversion to **340** within 1 hour, and the product was isolated in 74 % yield. This indicated that the additional nitro group had indeed resulted in enhanced reactivity. However, upon analysis by chiral HPLC, we found that this material was racemic. The poor enantioselectivity observed in this reaction is not surprising - if all of the starting material is consumed within 1 hour, but the $t_{1/2}^{rac}$ of the starting material is 5 hours, much of the undesired enantiomer must have undergone substitution.



Scheme 5.21. Attempted dynamic kinetic resolution of **337** with stoichiometric thiophenol

We therefore repeated the substitution reaction with a sub-stoichiometric quantity of thiophenol (0.5 eq.). Under these conditions, we observed a 42 % NMR yield of product **340** along with 38 % NMR yield of remaining starting material **337**. Unfortunately, analysis of these materials by chiral HPLC indicated both **337** and **340** to be racemic.



Scheme 5.22. Attempted dynamic kinetic resolution of **337** with sub-stoichiometric thiophenol

We do not currently have a clear explanation for the lack of asymmetric induction observed in these reactions. However, we believe that it is noteworthy that desymmetrization of the analogous amide substituted dichloropyrimidine **261** also led to racemic material (Chapter 2). Taken together, these results suggest that aromatic amide derived electrophiles are not good

substrates for the asymmetric S_NAr reaction. In order to carry out highly enantioselective substitution reactions with these substrates, significant re-optimization will be necessary.

5.5 Conclusion

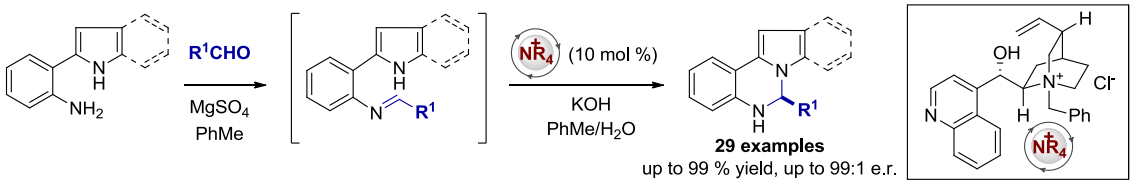
Following our work on the desymmetrization of prochiral dichloropyrimidines, we moved on to investigate the development of a kinetic resolution of non-symmetrical biaryls. We demonstrated proof of principle for this reaction, and were successfully able to resolve axially chiral chloropyrimidines, obtaining *S* factors in the range 3-30. The low conversions observed in these reactions prompted us to investigate aryl fluoride electrophiles, for which we hoped that a dynamic kinetic substitution might be feasible. We were able to identify a system possessing sufficient reactivity to readily undergo substitution, in which the enantiomers of the starting material rapidly interconvert, but the substituted product has a high barrier to enantiomeric interconversion. Under our previously optimized conditions, no asymmetric induction was observed in the substitution of this material by thiophenolate. Future work will probe the efficacy of different reaction conditions and alternative nucleophiles in this process.

6. Conclusions and Future Work

6.1. Conclusions

This thesis has focussed on the development of two new asymmetric processes in which the enantioselectivity is controlled by a chiral cation.

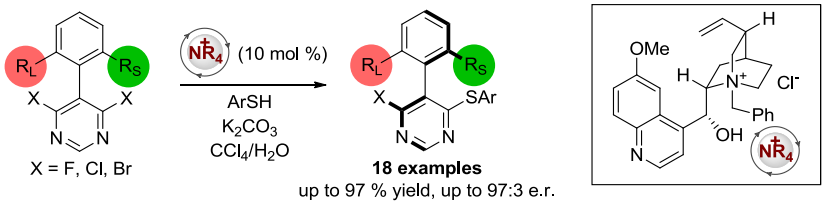
The first of these reactions is described in Chapter 2 and relates to the development of an asymmetric *N*-functionalization of pyrroles. The requisite substrates were prepared by magnesium sulfate mediated condensation of pyrolloanilines with aldehydes or ketones. Under asymmetric phase-transfer catalysed conditions a series of aldimine substrates underwent regioselective cyclization. The enantioselectivities obtained were variable and showed a strong dependence upon the steric and electronic properties of the aldehyde, although high enantioselectivities were observed in several cases.



Scheme 6.1. Cation-directed enantioselective *N*-functionalization of pyrroles

The synthetic utility of the cyclized products was explored by carrying out a range of derivatization processes including oxidation, *N*-protection and Friedel-Crafts acylation of the pyrrole.

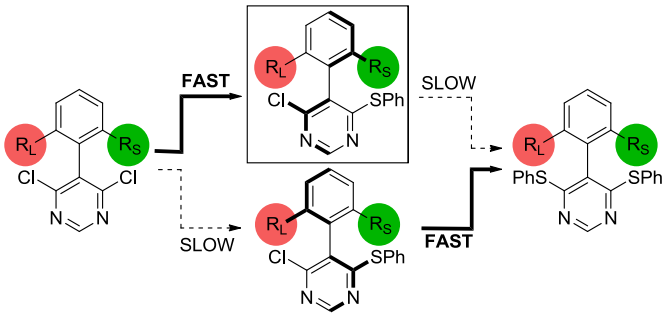
The third chapter of this thesis focussed on the development of a cation-directed method for the construction of axially chiral biaryls. Under optimized asymmetric phase-transfer conditions achiral dichloropyrimidines underwent a desymmetrizing S_NAr reaction with thiophenolate leading to atropisomeric products in up to 97:3 e.r.



Scheme 6.2. A cation-directed desymmetrizing S_NAr reaction

The products of the substitution reaction contain a second reactive aryl halide, which could be employed as a handle to carry out derivatization reactions, either through a second S_NAr reaction or in metal catalysed cross-coupling processes.

We have demonstrated that the high enantioselectivity observed in the desymmetrization process is a consequence of a kinetic resolution process, which reinforces the selectivity of the initial desymmetrization by scavenging the minor enantiomer.



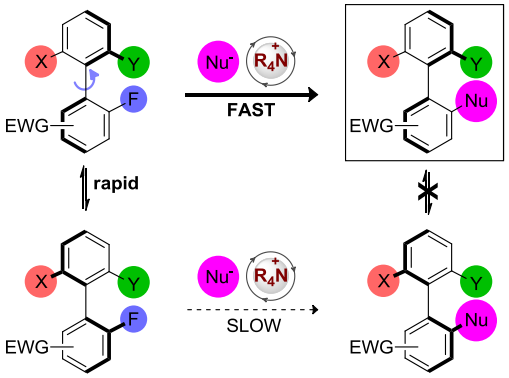
Scheme 6.3. Tandem desymmetrization/kinetic resolution mechanism

We went on to analyse the kinetic profile of the reaction through an initial rates investigation. This led us to conclude that the desymmetrization takes place according to the rate law shown below. From this, we tentatively propose that the reaction is takes place *via* an extractive mechanism in which the catalyst occupies an off-cycle dimeric resting state.

$$\frac{d[product]}{dt} = k[substrate][thiophenol]^{sat}[catalyst]^{0.5}$$

The fifth chapter describes the extension of the asymmetric S_NAr reaction to a kinetic resolution of axially chiral electrophiles. Although we observed promising enantioselectivities

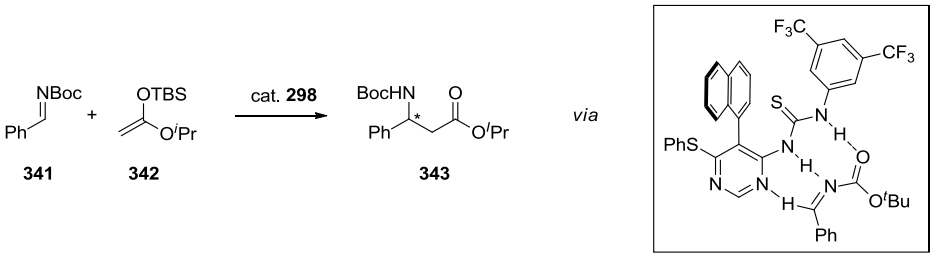
in these reactions, the conversions were low. As a consequence we investigated aryl fluoride electrophiles, which we hoped would prove suitable substrates for a dynamic kinetic resolution. Ultimately, we were able to identify a system in which the starting material underwent rapid interconversion and the product was configurationally robust. However, initial attempts to carry out an asymmetric substitution reactions have led to racemic products.



Scheme 6.4. Dynamic kinetic resolution *via* S_NAr with rapidly interconverting aryl fluorides

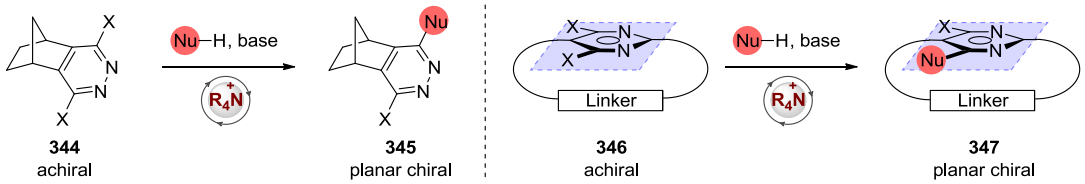
6.2. Future work

Future work in the group will aim to explore the utility of the products obtained from the desymmetrizing S_NAr reaction. We are particularly keen to probe the efficacy of thiourea **298** as an asymmetric catalyst for a Mukaiyama Mannich reaction (Scheme 6.5).[106] We hope that the catalyst will accelerate this reaction by hydrogen bonding to aldimine **341**, forcing attack by the silyl ketene acetal to take place on the lower face, away from the bulky naphthyl group.



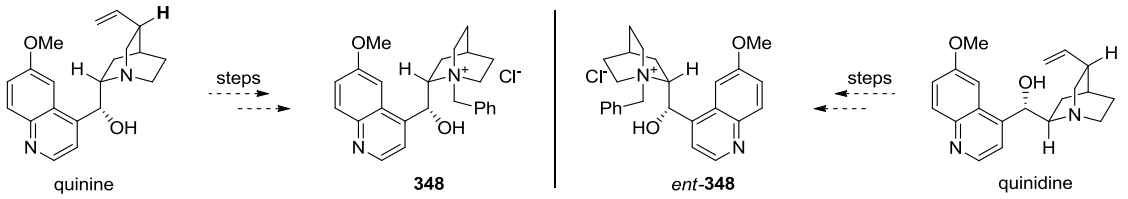
Scheme 6.5. Evaluation of **298** as a hydrogen bonding catalyst for a Mukaiyama Mannich reaction

We also aim to develop new desymmetrization processes, with a particular focus on the development of asymmetric S_NAr methodology targeting materials possessing planar chirality. We hope that a prochiral pyridazine substrate such as **344** could undergo a desymmetrizing S_NAr reaction resulting in a planar chiral product **345**. Additionally, we hope to carry out a cation-directed desymmetrization of a highly strained achiral cyclophane **346**, which would result in **347** (Scheme 6.6).



Scheme 6.6. Synthesis of planar chiral materials *via* desymmetrization of prochiral starting materials

Mechanistic analysis of the desymmetrization reaction will be continued, with an ultimate goal of identifying the origin of the changing enantioselectivity over the early period of the reaction. To this end, the rate of deprotonation of thiophenol along with partition coefficients for the various species involved will be determined. One particularly intriguing additional experiment to carry out would be to cleave the bridgehead olefinic substituent from quinine and quinidine, resulting in enantiomeric catalysts **348** and *ent*-**348**.[107]



Scheme 6.7. Future work – synthesis of enantiomeric catalysts to investigate non-linear effects

With these compounds it would be possible to investigate any potential non-linear effect which may arise as a consequence of catalyst aggregation or deaggregation.

7. Experimental

7.1 Experimental methods

Dichloromethane, diethyl ether, toluene, acetonitrile and methanol were purified by filtration through activated alumina columns employing the method of Grubbs *et al.*[108] Diisopropylamine was distilled over freshly ground potassium hydroxide and stored over potassium hydroxide under an inert argon atmosphere. Aldehydes were purchased from Sigma Aldrich and distilled or recrystallized before use. *n*-Butyllithium was purchased from Acros Organics and titrated against a known quantity of menthol in THF using 1,10-phenanthroline as the indicator. All other reagents and solvents were used as supplied. Petrol 30-40, petrol 40-60 and petrol 60-80 refer to the fractions of petroleum ether which boil in the range 30-40 ^{o}C, 40-60 ^{o}C and 60-80 ^{o}C respectively. Where mixtures of solvents are described, the stated ratios are volume:volume. Brine refers to a saturated aqueous solution of sodium chloride.

Column chromatography was carried out using Merck Geduran® Silicagel (40-63 μm particle size). Analytical thin layer chromatography was carried out using pre-coated, aluminium backed plates (Merck Kieselgel 60 F254). Visualisation was achieved with ultraviolet irradiation (254 nm) and staining with solutions of potassium permanganate or vanillin as appropriate. Potassium permanganate solution was made by dissolving potassium permanganate (2.5 g), potassium carbonate (13 g) and sodium hydroxide (0.63 g) in water (250 mL). Vanillin solution was made by dissolving 4-hydroxy-3-methoxybenzaldehyde (15 g), glacial acetic acid (1.5 mL) and concentrated sulfuric acid (1.5 mL) in ethanol (250 mL).

^{1}H NMR spectroscopy was carried out using either a Bruker AVC500 (500 MHz), AV400 (400 MHz), DPX400 (400 MHz) or DPX200 (200 MHz) spectrometer using the residual non-deuterated solvent signal as the internal reference. Chemical shifts are quoted in ppm,

based on appearance rather than interpretation. ^{1}H NMR spectra are reported as follows: ***^{1}H NMR* (*spectrometer frequency, solvent)*** *δ_H = chemical shift/ppm (multiplicity of peak, coupling constant, number of protons, assignment)*. The assignment refers to the numbering scheme shown in the diagrams prefacing each experimental procedure. The multiplicity is abbreviated in the following way: s = singlet; d = doublet; t = triplet; q = quartet; quint. = quintet; sept. = septet; m = multiplet; br = broad. ^{13}C NMR spectroscopy was carried out using either a Bruker AVC500, AV400 or DPX400 spectrometer. Spectra were recorded at either 101 MHz or 126 MHz using the central resonance of the solvent signal as the internal reference. ^{13}C NMR spectra are reported as follows: ***^{13}C NMR* (*spectrometer frequency, solvent)*** *δ_C = chemical shift/ppm (multiplicity, assignment*). Multiplicities are assigned as Quat., CH, CH_2 or CH_3. Assignments given refer to a combination of the numbering schemes shown along with other generic labels. A variety of additional spectroscopic techniques including COSY, DEPT, HSQC, HMBC and nOe were used to assign the one dimensional spectra.

Infrared spectra samples were prepared as a neat film and were recorded using a Bruker Tensor 27 FTIR spectrometer. Spectra are reported as follows: ***FTIR* (*neat)*** *λ/cm^{-1} = absorption maxima/cm^{-1}*. The additional abbreviation br = broad is used where appropriate.

LRMS was carried out using ESI and was performed on a Micromass LCT Premier spectrometer. HRMS was carried out using Bruker MicroTOF and Micromass GCT spectrometers under ESI or FI conditions respectively. Values are reported as a ratio of mass to charge in Daltons.

Melting points were determined using a Reichert melting point apparatus and are uncorrected.

Analytical chiral HPLC was carried out using a Dionex Ultimate 3000 HPLC system comprising a Dionex LPG 3400A pump, WPS-3000SL autosampler and TCC-3000SD column compartment, and a Daicel Chiralpak column (0.46 cm x 25 cm), equipped with an appropriate guard column

(0.4 cm x 1 cm). Semi-preparative chiral HPLC was carried out using the same system with a YMC chiral amylose-SA column.

Optical rotations were recorded on a Perkin-Elmer 241 polarimeter. Concentrations are quoted in g/100 mL.

7.2 General experimental procedures

General procedure A: imine formation/asymmetric cyclization

Imine Formation: A slurry of *the appropriate aniline*, *the appropriate aldehyde* and oven dried anhydrous magnesium sulfate in anhydrous toluene was stirred at room temperature for 16 hours and then filtered through a plug of Celite® washing with anhydrous diethyl ether. The filtrate was concentrated under reduced pressure. Cyclization: The crude imine thus obtained was dissolved in toluene and *the appropriate phase-transfer catalyst* was added. The resulting stirred suspension was cooled to *the appropriate temperature* and *the appropriate base* (precooled to *the appropriate temperature* if liquid) was added. The biphasic reaction mixture was rapidly stirred at *the appropriate temperature* for *the appropriate time*. After this time, water was added and the solution was allowed to warm to room temperature. The organic layer was separated and the aqueous layer was extracted three times with dichloromethane. The combined organic extracts were dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure.

General procedure B: imine formation/racemic cyclization

Imine Formation: A slurry of *the appropriate aniline*, *the appropriate aldehyde* and oven dried anhydrous magnesium sulfate in anhydrous toluene was stirred at room temperature for 16 hours and then filtered through a plug of Celite® washing with anhydrous diethyl ether. The filtrate was concentrated under reduced pressure. Cyclization: The crude imine thus obtained was dissolved in toluene and tetrabutylammonium bromide and *the appropriate base* were

added. The biphasic reaction mixture was rapidly stirred at room temperature for *the appropriate time*. After this time, water was added. The organic layer was separated and the aqueous layer was extracted three times with dichloromethane. The combined organic extracts were dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure.

General procedure C: copper catalysed malonate α-arylation[86]

An oven dried schlenk tube was charged sequentially with copper (I) iodide, 2-picolinic acid, cesium carbonate and *the appropriate aryl iodide*, if a solid. The atmosphere was purged with argon three times and anhydrous 1,4-dioxane was added followed by freshly distilled diethylmalonate and *the appropriate aryl iodide*, if a liquid (purified prior to use by filtering the neat liquid through a plug of neutral alumina). The resulting mixture was stirred at *the appropriate temperature* for *the appropriate time* and then cooled to room temperature and diluted with ethyl acetate and ammonium chloride. The organic layer was separated and the aqueous layer was extracted twice with ethyl acetate. The combined organic extracts were dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure.

General procedure D: pyrimidine formation/chlorination[109]

Pyrimidine formation: To a stirred room temperature suspension of sodium methoxide, prepared *in situ* by the portionwise addition of metallic sodium to anhydrous methanol, was added *the appropriate amidine or corresponding salt* in a single portion. The resulting suspension was stirred at room temperature for 30 minutes and then diluted with THF. A solution of *the appropriate α-aryl malonate* in a mixture of THF and methanol was added. The reaction mixture was stirred at *the appropriate temperature* for *the appropriate time* and then cooled to room temperature and concentrated to dryness under reduced pressure. The residue was suspended in water (c.a. 0.5 mL/mmol malonate), acidified with 1 M HCl and

cooled to 0 ^{o}C for 30 minutes. A solid was formed, which was isolated by vacuum filtration and washed five times with water and then dried under high vacuum to afford the corresponding aryl pyrimidine. Chlorination: A suspension of crude aryl pyrimidine, phosphorus(V) oxychloride and *N*,*N*-dimethylaniline was stirred at *the appropriate temperature* for *the appropriate time* and then cooled to room temperature and concentrated under reduced pressure. The residue was dissolved in dichloromethane and poured onto crushed ice and then allowed to warm to room temperature. The organic layer was separated and the aqueous layer was extracted twice with dichloromethane. The combined organic extracts were washed with 1 M HCl, dried over anhydrous magnesium sulfate and concentrated under reduced pressure.

General procedure E: asymmetric phase-transfer catalysed S_NAr

In a 7 mL screw capped vial, *the appropriate dihalopyrimidine* was dissolved in *the appropriate solvent* and *the appropriate phase-transfer catalyst*, thiophenol and *the appropriate base* were added sequentially. The atmosphere was purged with nitrogen, and the biphasic reaction mixture was rapidly stirred at room temperature for *the appropriate time* and then saturated aqueous ammonium chloride and dichloromethane were added. The organic layer was separated and the aqueous layer was extracted twice with dichloromethane. The combined organic extracts were dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure.

General procedure F: racemic phase-transfer catalysed S_NAr

The appropriate dihalopyrimidine was dissolved in toluene and tetrabutylammonium bromide, thiophenol and 50 % aqueous potassium hydroxide were added sequentially. The biphasic reaction mixture was rapidly stirred at room temperature for *the appropriate time* and then saturated aqueous ammonium chloride and dichloromethane were added. The organic layer

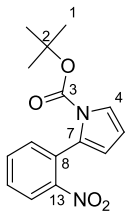
was separated and the aqueous layer was extracted twice with dichloromethane. The combined organic extracts were dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure.

General procedure G: kinetics of asymmetric phase-transfer catalysed S_NAr

In a 7 mL screw capped vial, *the appropriate dichloropyrimidine* was dissolved in *the appropriate solvent* and *the appropriate phase-transfer catalyst*, thiophenol and *the appropriate base* were added sequentially. The biphasic reaction mixture was rapidly stirred at room temperature. At known time intervals 5 μL aliquots were removed from the rapidly stirred reaction mixture and passed through a small plug of silica (c.a. 1 cm in a Pasteur pipette) eluting with 1:4 diethyl ether/dichloromethane (3 mL). The resulting solution was blown down and the residue was redissolved in 1:4 toluene/IPA and analysed by chiral HPLC (Chiralpak ADH, 20 % IPA, 80 % hexane, 1.0 mL/min, λ = 222 nm, 20 μL injection).

7.3 Experimental

***tert*-Butyl 2-(2-nitrophenyl)-1*H*-pyrrole-1-carboxylate, 47**



This compound was prepared by modification of a literature procedure.[39]

A stirred room temperature suspension of 1-iodo-2-nitrobenzene (2.00 g, 8.03 mmol), *N*-Boc-pyrrole-2-boronic acid (2.04 g, 9.67 mmol), SPhos (165 mg, 0.40 mmol) and palladium(II) acetate (45 mg, 0.20 mmol) in 1,4-dioxane (105 mL) was sparged with argon for 30 minutes. In a separate flask, an aqueous solution of potassium phosphate (3.0 M, 20 mL, 60 mmol) was sparged with argon for 30 minutes and then added *via* cannula to the above

stirred dioxane suspension. The resulting mixture was heated to 60 ^{o}C for 16 hours. The reaction mixture was cooled to room temperature, diluted with diethyl ether (100 mL) and 1 M sodium hydroxide (100 mL) was added. The organic layer was separated and the aqueous layer was extracted twice with diethyl ether. The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography eluting with 3:47 diethyl ether/petrol 40-60 to afford the title compound **47** as a viscous yellow oil which solidified upon standing to give a yellow solid (2.23 g, 96 %). The spectral data matched that previously reported in the literature.[39]

Melting point: 64-66 ^{o}C (diethyl ether/petrol 40-60) [lit. 78-79 ^{o}C];[39]

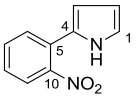
^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 8.14 (dd, J = 8.1, 1.2 Hz, 1H, H_9), 7.65 (td, J = 7.5, 1.3 Hz, 1H, H_{11}), 7.53 (td, J = 7.8, 1.6 Hz, 1H, H_{10}), 7.49 (dd, J = 7.6, 1.5 Hz, 1H, H_{12}), 7.44 (dd, J = 3.3, 1.8 Hz, 1H, H_4), 6.30 (t, J = 3.3 Hz, 1H, H_5), 6.23 (dd, J = 3.2, 1.7 Hz, 1H, H_6), 1.36 (s, 9H, H_1);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 148.9 (Quat), 148.5 (Quat), 132.9 (CH), 132.7 (CH), 130.1 (Quat), 129.5 (Quat), 128.6 (CH), 124.4 (CH), 122.6 (CH, C_4), 114.8 (CH, C_6), 110.9 (CH, C_5), 84.1 (Quat, C_2), 27.5 (CH_3, C_1);

FTIR (neat) ν/cm^{-1} = 2981, 1738, 1614, 1525, 1456, 1401, 1370, 1343, 1315, 1262, 1143, 1091, 1033;

LRMS (ESI^{+}) 311 ([M + Na]$^{+}$).

2-(2-Nitrophenyl)-1*H*-pyrrole, 49



This compound was prepared by modification of a literature procedure.[39]

A solution of Boc-protected pyrrole **47** (5.31 g, 18.4 mmol) in anhydrous methanol (130 mL) was stirred at room temperature. Sodium methoxide (2.98 g, 55.2 mmol) was added in one portion and the resulting mixture was heated to 70 ^{o}C for 3 hours. The reaction mixture was cooled to room temperature and concentrated to dryness under reduced pressure. The residue was quenched with water and extracted three times with dichloromethane. The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography eluting with 1:9 ethyl acetate/petrol 40-60 to afford the title compound **49** as a viscous orange oil (3.46 g, quant.). The spectral data matched that previously reported in the literature.[39]

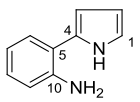
^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 8.92 (br s, 1H, N*H*), 7.72 (dd, J = 8.2, 1.1 Hz, 1H, H_6), 7.62-7.52 (m, 2H, H_8 and H_9), 7.35 (ddd, 1H, J = 7.9, 7.3, 1.3 Hz, H_7), 6.94-6.92 (m, 1H, H_1), 6.49-6.47 (m, 1H, H_3), 6.32 (td, J = 6.2, 2.6 Hz, 1H, H_2);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C =148.1 (Quat, C_{10}), 132.4 (CH, C_7), 130.8 (CH, C_6), 127.1 (CH, C_8), 127.0 (Quat, $C_{4/5}$), 126.3 (Quat, $C_{4/5}$), 124.4 (CH, C_9), 120.5 (CH, C_1), 111.0 (CH, C_3), 110.1 (CH, C_2);

FTIR (neat) ν/cm^{-1} = 3414, 3106, 1607, 1517, 1481, 1344, 1285, 1115, 1088, 1037;

LRMS (ESI$^-$) 187 ([M - H]$^-$).

2-(1*H*-Pyrrol-2-yl)aniline, 50



This compound was prepared by modification of a literature procedure.[39]

A solution of nitro compound **49** (3.46 g, 18.4 mmol) in anhydrous methanol (115 mL) was stirred at room temperature and Pd/C (346 mg, 10 wt. %) was added. The resulting stirred suspension was sparged with hydrogen for 30 minutes and then stirred under an atmosphere of hydrogen (balloon pressure) for 5 hours. The reaction mixture was filtered through a plug of celite, washing with dichloromethane and the filtrate was concentrated under reduced pressure to afford the title compound **50** as an off white solid (2.88 g, 99 %) which was used without further purification in all subsequent reactions. The spectral data matched that previously reported in the literature.[39]

Melting point: 96-99 ^{o}C (dichloromethane) [lit. 103-106 ^{o}C];[39]

^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 8.63 (br s, 1H, N*H* pyrrole), 7.27 (dd, J = 7.6, 1.6 Hz, 1H, H_6), 7.14 (td, J = 7.7, 1.5 Hz, 1H, H_8), 6.89-6.84 (m, 2H, H_1 and H_7), 6.79 (dd, J = 8.0, 1.1 Hz, 1H, H_9), 6.47-6.46 (m, 1H, H_3), 6.37 (dd, J = 6.1, 2.7 Hz, 1H, H_2), 3.97 (br s, 2H, N*H* aniline);

^{13}C NMR (126 MHz, $CDCl_3$) δ_C = 143.4 (Quat, C_{10}), 129.6 (Quat, C_4), 128.5 (CH, C_9), 127.9 (CH, C_7), 119.7 (Quat, C_5), 119.1 (CH, C_8), 118.1 (CH, C_1), 116.5 (CH, C_6), 109.4 (CH, C_2), 107.4 (CH, C_3);

FTIR (neat) ν/cm^{-1} = 3405 (br), 3102, 3056, 1614, 1494, 1470, 1304, 1105, 1034;

HRMS (ESI^{+}) calculated for $C_{10}H_{11}N_2$ = 159.0917, mass found = 159.0921.

Table 2.1 – Catalyst optimization

Entries 1-17: According to a modification of **General Procedure A**. Imine formation: pyrroloaniline **50** (120 mg, 0.76 mmol), benzaldehyde (109 μL, 0.99 mmol) and magnesium sulfate (457 mg, 3.79 mmol) in anhydrous toluene (24 mL). Cyclization: The crude residue from obtained from imine formation was dissolved in toluene (7.2 mL) and the resulting solution was divided into 12 portions of 0.6 mL (c.a. 0.06 mmol each). The remainder of the procedure

was carried out as described in the general procedure using *the appropriate catalyst* (0.006 mmol) and potassium hydroxide (50 % w/w, 50 μL, 0.89 mmol) at room temperature for 16 hours. An analytical HPLC sample of **52** was obtained by small scale preparative TLC (1:4 diethyl ether/petrol 40-60).

Table 2.2 – Solvent optimization

Entries 1-11: According to a modification of **General Procedure A**. Imine formation: pyrroloaniline **50** (110 mg, 0.70 mmol), benzaldehyde (100 μL, 0.90 mmol) and magnesium sulfate (419 mg, 3.48 mmol) in anhydrous toluene (22 mL). Cyclization: The crude residue from obtained from imine formation was dissolved in diethyl ether (5.5 mL) and the resulting solution was divided into 11 portions of 0.5 mL (c.a. 0.06 mmol each). The solvent was removed under reduced pressure and the residue was re-dissolved in *the appropriate solvent* (0.6 mL). The remainder of the procedure was carried out as described in the general procedure using *N*-benzylcinchoninium chloride (3 mg, 0.006 mmol) and potassium hydroxide (50 % w/w, 50 μL, 0.89 mmol) at room temperature for 16 hours. An analytical HPLC sample of **52** was obtained by small scale preparative TLC (1:4 diethyl ether/petrol 40-60).

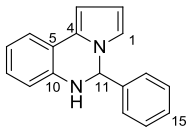
Scheme 2.11 – Base optimization

Entries with aqueous bases: According to a modification of **General Procedure A**. Imine formation: pyrroloaniline **50** (30 mg, 0.19 mmol), benzaldehyde (27 μL, 0.25 mmol) and magnesium sulfate (114 mg, 0.95 mmol) in anhydrous toluene (6 mL). Cyclization: The crude residue from obtained from imine formation was dissolved in toluene (1.8 mL) and the resulting solution was divided into 3 portions of 0.6 mL (c.a. 0.06 mmol each). The remainder of the procedure was carried out as described in the general procedure using *N*-benzylcinchoninium chloride (3 mg, 0.006 mmol) and the *appropriate base* (0.63 mmol) at

the appropriate temperature for *the appropriate time*. An analytical HPLC sample of **52** was obtained by small scale preparative TLC (1:4 diethyl ether/petrol 40-60).

Entries with solid bases: According to a modification of **General Procedure A**. Imine formation: pyrroloaniline **50** (90 mg, 0.57 mmol), benzaldehyde (82 μL, 0.74 mmol) and magnesium sulfate (342 mg, 2.84 mmol) in anhydrous toluene (18 mL). Cyclization: The crude residue from obtained from imine formation was dissolved in toluene (5.7 mL) and the resulting solution was divided into 3 portions of 1.9 mL (c.a. 0.19 mmol each). The remainder of the procedure was carried out as described in the general procedure using *N*-benzylcinchoninium chloride (8 mg, 0.019 mmol) and the *appropriate base* (1.9 mmol) at *the appropriate temperature* for *the appropriate time*. An analytical HPLC sample of **52** was obtained by small scale preparative TLC (1:4 diethyl ether/petrol 40-60).

5-Phenyl-5,6-dihydropyrrolo[1,2-*c*]quinazoline, 52



Asymmetric: According to **General Procedure A**. Imine formation: pyrroloaniline **50** (100 mg, 0.63 mmol), benzaldehyde (87 mg, 0.82 mmol) and magnesium sulfate (380 mg, 3.16 mmol) in anhydrous toluene (20 mL). Cyclization: *N*-benzylcinchoninium chloride (27 mg, 0.064 mmol) and potassium hydroxide (50 % w/w, 0.35 mL, 6.3 mmol) in toluene (6.3 mL) at -15 ^{o}C for 5 days yielded a crude reaction product. Purification *via* column chromatography eluting with 1:10 diethyl ether/petrol 40-60 afforded the title compound **52** as a white solid (132 mg, 85 %, 86:14 e.r.).

Racemic: According to **General Procedure B**. Imine formation: pyroloaniline **50** (100 mg, 0.63 mmol), benzaldehyde (87 mg, 0.82 mmol) and magnesium sulfate (380 mg, 3.16 mmol) in anhydrous toluene (20 mL). Cyclization: tetrabutylammonium bromide (20 mg, 0.062 mmol)

and potassium hydroxide (50 % w/w, 0.35 mL, 6.3 mmol) in toluene (6.3 mL) at room temperature for 2 hours afforded a crude product. Purification *via* column chromatography eluting with 1:10 diethyl ether/petrol 40-60 afforded the title compound *rac*-**52** as a white solid (124 mg, 80 %).

Melting point: 96-99 ^{o}C (diethyl ether/petrol 40-60);

^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 7.59-7.52 (m, 3H, H_6 and H_{13}), 7.49-7.44 (m, 3H, H_{14} and H_{15}), 7.06 (td, J = 7.6, 1.4 Hz, 1H, H_8), 6.93 (td, J = 7.6, 0.9 Hz, 1H, H_7), 6.70 (d, J = 7.9 Hz, 1H, H_9), 6.60 (dd, J = 3.6, 1.4 Hz, 1H, H_3), 6.24 (t, J = 3.2 Hz, 1H, H_2), 6.17 (dd, J = 2.5, 1.6 Hz, 1H, H_1), 6.17 (s, 1H, H_{11}), 4.32 (br s, 1H, N*H*);

^{13}C NMR (126 MHz, $CDCl_3$) δ_C = 139.3 (Quat, C_{10}), 138.4 (Quat, C_{12}), 129.9 (CH, C_{15}), 129.0 (Quat, C_4), 129.0 (CH, $C_{13/14}$), 128.3 (CH, $C_{13/14}$), 126.6 (CH, C_8), 122.5 (CH, C_6), 120.3 (CH, C_7), 118.2 (CH, C_1), 117.9 (Quat, C_5), 114.9 (CH, C_9), 109.4 (CH, C_2), 103.2 (CH, C_3), 71.0 (CH, C_{11});

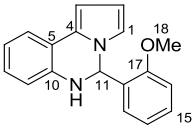
FTIR (neat) ν/cm^{-1} = 3357 (br), 3059, 1612, 1586, 1487, 1459, 1435, 1231, 1156, 1111;

HRMS (ESI^{+}) calculated for $C_{17}H_{15}N_2$ = 247.1230, mass found = 247.1230;

Chiral HPLC (Chiralpak IA, 5 % IPA, 95 % hexane, 1.0 mL/min, λ = 329 nm, 20 μL injection) τ_R (major) = 17.3 min, τ_R (minor) = 18.8 min;

$[\alpha]_D^{20}$ = +99 (*c* = 1.00, $CHCl_3$).

5-(2-Methoxyphenyl)-5,6-dihydropyrrolo[1,2-*c*]quinazoline, 69



Asymmetric: According to **General Procedure A**. Imine formation: pyrroloaniline **50** (50 mg, 0.32 mmol), *o*-anisaldehyde (56 mg, 0.41 mmol) and magnesium sulfate (190 mg, 1.58 mmol)

in anhydrous toluene (10 mL). Cyclization: *N*-benzylcinchoninium chloride (13 mg, 0.031 mmol) and potassium hydroxide (50 % w/w, 0.18 mL, 3.2 mmol) in toluene (3.2 mL) at -15 ^{o}C for 3 days and then at room temperature for 16 hours yielded a crude reaction product. Purification *via* column chromatography eluting with a gradient from petrol 40-60 to 3:17 diethyl ether/petrol 40-60 afforded the title compound **69** as an off white solid (67 mg, 77 %, 92:8 e.r.).

Racemic: According to **General Procedure B**. Imine formation: pyrroloaniline **50** (20 mg, 0.13 mmol), *o*-anisaldehyde (22 mg, 0.16 mmol) and magnesium sulfate (76 mg, 0.63 mmol) in anhydrous toluene (4 mL). Cyclization: tetrabutylammonium bromide (4 mg, 0.01 mmol) and potassium hydroxide (50 % w/w, 71 μL, 1.3 mmol) in toluene (1 mL) at room temperature for 2 hours afforded a crude product. An analytical HPLC sample of *rac*-**69** was obtained by small scale preparative TLC (1:4 diethyl ether/petrol 40-60).

Melting Point 38-41 ^{o}C (diethyl ether/petrol 40-60);

^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 7.52 (dd, J = 7.6, 1.3 Hz, 1H, H_6), 7.26 (td, J = 7.9, 1.8 Hz, 1H, H_{15}), 6.96 (td, J = 7.6, 1.4 Hz, 1H, H_8), 6.93 (d, J = 8.2 Hz, 1H, H_{16}), 6.84-6.78 (m, 2H, H_7 and H_{14}), 6.70 (s, 1H, H_{11}), 6.62 (dd, J = 7.9, 0.6 Hz, 1H, H_9), 6.59 (dd, J = 3.6, 1.4 Hz, 1H, H_3), 6.55 (dd, J = 2.5, 1.6 Hz, 1H, H_1), 6.48 (dd, J = 7.6, 1.6 Hz, 1H, H_{13}), 6.31 (dd, J = 3.5, 2.8 Hz, 1H, H_2), 4.80 (br s, 1H, N*H*), 3.95 (s, 3H, H_{18});

^{13}C NMR (126 MHz, $CDCl_3$) δ_C = 156.0 (Quat, C_{17}), 138.4 (Quat, C_{10}), 129.7 (CH, C_{15}), 128.8 (Quat, C_4), 128.4 (Quat, C_{12}), 126.8 (CH, C_{13}), 126.5 (CH, C_8), 122.2 (CH, C_6), 121.0 (CH, C_{14}), 119.7 (CH, C_7), 118.5 (CH, C_1), 117.5 (Quat, C_5), 115.1 (CH, C_9), 110.2 (CH, C_{16}), 109.4 (CH, C_2), 102.6 (CH, C_3), 65.3 (CH, C_{11}), 55.5 (CH_3, C_{18});

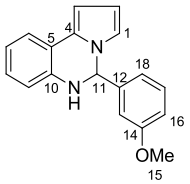
FTIR (neat) ν/cm^{-1} = 3388 (br), 3057, 2938, 1589, 1490, 1463, 1434, 1292, 1237, 1110, 1074, 1024;

HRMS (FI^+) calculated for $C_{18}H_{16}N_2O$ = 276.1263, mass found = 276.1265;

Chiral HPLC (Chiralpak AS, 5 % IPA, 95 % hexane, 1.0 mL/min, λ = 332 nm, 15 μL injection) τ_R (minor) = 10.9 min, τ_R (major) = 12.9 min;

$[\alpha]_D^{20}$ = +357 (*c* = 0.50, $CHCl_3$).

5-(3-Methoxyphenyl)-5,6-dihydropyrrolo[1,2-*c*]quinazoline, 70



Asymmetric: According to **General Procedure A**. Imine formation: pyrroloaniline **50** (50 mg, 0.32 mmol), *m*-anisaldehyde (56 mg, 0.41 mmol) and magnesium sulfate (190 mg, 1.58 mmol) in anhydrous toluene (10 mL). Cyclization: *N*-benzylcinchoninium chloride (13 mg, 0.031 mmol) and potassium hydroxide (50 % w/w, 0.18 mL, 3.2 mmol) in toluene (3.2 mL) at -15 °C for 4 days and then at room temperature for 16 hours yielded a crude reaction product. Purification *via* column chromatography eluting with a gradient from petrol 40-60 to 1:4 diethyl ether/petrol 40-60 afforded the title compound **70** as a light brown solid (75 mg, 86 %, 82:18 e.r.).

Racemic: According to **General Procedure B**. Imine formation: pyrroloaniline **50** (20 mg, 0.13 mmol), *m*-anisaldehyde (22 mg, 0.16 mmol) and magnesium sulfate (76 mg, 0.63 mmol) in anhydrous toluene (4 mL). Cyclization: tetrabutylammonium bromide (4 mg, 0.01 mmol) and potassium hydroxide (50 % w/w, 71 μL, 1.3 mmol) in toluene (1 mL) at room temperature for 2 hours afforded a crude product. An analytical HPLC sample of *rac*-**70** was obtained by small scale preparative TLC (1:4 diethyl ether/petrol 40-60).

Melting Point: 86-88 °C (diethyl ether/petrol 40-60);

^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 7.55 (dd, J = 7.7, 1.4 Hz, 1H, H_6), 7.36 (t, J = 7.4 Hz, 1H, H_{17}), 7.12-7.09 (m, 2H, H_{13} and H_{18}), 7.04 (td, J = 7.6, 1.4 Hz, 1H, H_8), 7.01-6.99 (m, 1H, H_{16}), 6.91 (td, J = 7.6, 0.9 Hz, 1H, H_7), 6.71 (dd, J = 7.7, 0.8 Hz, 1H, H_9), 6.58 (dd, J = 3.5, 1.6 Hz, 1H, H_3), 6.23 (t, 3.2 Hz, 1H, H_2), 6.21 (dd, J = 2.8, 1.6 Hz, 1H, H_1), 6.13 (s, 1H, H_{11}), 4.34 (br s, 1H, N*H*), 3.81 (s, 3H, H_{15});

^{13}C NMR (126 MHz, $CDCl_3$) δ_C = 160.2 (Quat, C_{14}), 139.9 (Quat, C_{12}), 139.3 (Quat, C_{10}), 130.0 (CH, C_{17}), 128.9 (Quat, C_4), 126.6 (CH, C_8), 122.4 (CH, C_6), 120.6 (CH, C_{18}), 120.3 (CH, C_7), 118.2 (CH, C_1), 117.8 (Quat, C_5), 115.8 (CH, C_{16}), 114.9 (CH, C_9), 113.1 (CH, C_{13}), 109.4 (CH, C_2), 130.1 (CH, C_3), 70.9 (CH, C_{11}), 55.3 (CH_3, C_{15});

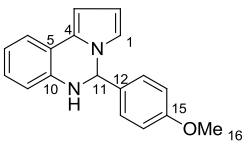
FTIR (neat) ν/cm^{-1} = 3359 (br), 3058, 2938, 1601, 1588, 1487, 1458, 1437, 1285, 1256, 1232, 1155, 1044;

HRMS (FI$^+$) calculated for $C_{18}H_{16}N_2O$ = 276.1263, mass found = 276.1257;

Chiral HPLC (Chiralpak AS, 5 % IPA, 95 % hexane, 1.0 mL/min, λ = 327 nm, 15 μL injection) τ_R (minor) = 19.0 min, τ_R (major) = 21.4 min;

$[\alpha]_D^{20}$ +75 (*c* = 1.00, $CHCl_3$).

5-(4-Methoxyphenyl)-5,6-dihydropyrrolo[1,2-*c*]quinazoline, 71



Asymmetric: According to **General Procedure A**. Imine formation: pyrroloaniline **50** (50 mg, 0.32 mmol), *p*-anisaldehyde (56 mg, 0.41 mmol) and magnesium sulfate (190 mg, 1.58 mmol) in anhydrous toluene (10 mL). Cyclization: *N*-benzylcinchoninium chloride (13 mg, 0.031 mmol) and potassium hydroxide (50 % w/w, 0.18 mL, 3.2 mmol) in toluene (3.2 mL) at -15 ^{o}C for

4 days yielded a crude reaction product. Purification *via* column chromatography eluting with a gradient from petrol 40-60 to 1:4 diethyl ether/petrol 40-60 afforded the title compound **71** as a brown solid (64 mg, 73 %, 78:22 e.r.).

Racemic: According to **General Procedure B**. Imine formation: pyrroloaniline **50** (20 mg, 0.13 mmol), *p*-anisaldehyde (22 mg, 0.16 mmol) and magnesium sulfate (76 mg, 0.63 mmol) in anhydrous toluene (4 mL). Cyclization: tetrabutylammonium bromide (4 mg, 0.01 mmol) and potassium hydroxide (50 % w/w, 71 μL, 1.3 mmol) in toluene (1 mL) at room temperature for 2 hours afforded a crude product. An analytical HPLC sample of *rac*-**71** was obtained by small scale preparative TLC (1:4 diethyl ether/petrol 40-60).

Melting Point: 130-140 ^{o}C (diethyl ether/petrol 40-60);

^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 7.54 (dd, J = 7.9, 1.3 Hz, 1H, H_6), 7.48 (d, J = 8.5 Hz, 2H, H_{13}), 7.05 (td, J = 7.6, 1.4 Hz, 1H, H_8), 6.98 (d, J = 8.8 Hz, 2H, H_{14}), 6.91 (td, J = 7.6, 1.4 Hz, 1H, H_7), 6.71 (d, J = 7.9 Hz, 1H, H_9), 6.57 (dd, J = 3.6, 1.4 Hz, 1H, H_3), 6.22 (dd, J = 3.6, 2.7 Hz, 1H, H_2), 6.14 (dd, J = 2.7, 1.4 Hz, 1H, H_1), 6.09 (s, 1H, H_{11}), 4.29 (br s, 1H, N*H*), 3.86 (s, 3H, H_{16});

^{13}C NMR (126 MHz, $CDCl_3$) δ_C = 160.8 (Quat, C_{15}), 139.6 (Quat, C_{10}), 130.2 (Quat, C_{12}), 129.7 (CH, C_{13}), 129.0 (Quat, C_4), 126.5 (CH, C_8), 122.4 (CH, C_6), 120.2 (CH, C_7), 118.1 (CH, C_1), 117.9 (Quat, C_5), 114.8 (CH, C_9), 114.3 (CH, C_{14}), 109.2 (CH, C_2), 103.1 (CH, C_3), 70.5 (CH, C_{11}), 55.4 (CH_3, C_{16});

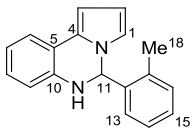
FTIR (neat) ν/cm^{-1} = 3359 (br), 2933, 1610, 1587, 1512, 1487, 1439, 1246, 1172, 1068;

HRMS (FI^{+}) calculated for $C_{18}H_{16}N_2O$ = 276.1263, mass found = 276.1259;

Chiral HPLC (Chiralpak ADH, 30 % IPA, 70 % hexane, 1.0 mL/min, λ = 230 nm, 15 μL injection) τ_R (minor) = 11.3 min, τ_R (major) = 15.4 min;

$[\alpha]_D^{20}$ +58 (*c* = 0.50, $CHCl_3$).

5-(*o*-Tolyl)-5,6-dihydropyrrolo[1,2-*c*]quinazoline, 72



Asymmetric: According to **General Procedure A**. Imine formation: pyrroloaniline **50** (100 mg, 0.63 mmol), *o*-tolualdehyde (99 mg, 0.82 mmol) and magnesium sulfate (380 mg, 3.16 mmol) in anhydrous toluene (20 mL). Cyclization: *N*-benzylcinchoninium chloride (27 mg, 0.064 mmol) and potassium hydroxide (50 % w/w, 0.35 mL, 6.3 mmol) in toluene (6.3 mL) at -15 ^{o}C for 5 days yielded a crude reaction product. Purification *via* column chromatography eluting with 1:19 diethyl ether/petrol 40-60 afforded the title compound **72** as a pale yellow solid (120 mg, 73 %, 96:4 e.r.).

Racemic: According to **General Procedure B**. Imine formation: pyrroloaniline **50** (200 mg, 1.26 mmol), *o*-tolualdehyde (198 mg, 1.64 mmol) and magnesium sulfate (759 mg, 6.30 mmol) in anhydrous toluene (40 mL). Cyclization: tetrabutylammonium bromide (41 mg, 0.13 mmol) and potassium hydroxide (50 % w/w, 0.71 mL, 13 mmol) in toluene (12.6 mL) at room temperature for 1 hour afforded a crude product. Purification *via* column chromatography eluting with 1:19 diethyl ether/petrol 40-60 afforded the title compound *rac*-**72** as a pale yellow solid (264 mg, 80 %).

Melting point: 102-104 ^{o}C (diethyl ether/petrol 40-60);

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.57 (d, J = 7.8 Hz, 2H, H_6 and H_{13}), 7.39 (td, J = 7.5, 1.4, 1H, H_{15}), 7.31 (t, J = 7.7 Hz, 2H, H_{14} and H_{16}), 7.07 (td, J = 7.7, 1.5 Hz, 1H, H_8), 6.92 (td, J = 7.5, 1.1 Hz, 1H, H_7), 6.71 (dd, J = 7.8, 0.7 Hz, 1H, H_9), 6.59 (dd, J = 3.7, 1.5, 1H, H_3), 6.41 (s, 1H, H_{11}), 6.24 (dd, J = 3.4, 2.9 Hz, 1H, H_2), 6.14 (dd, J = 2.7, 1.5, 1H, H_1), 4.23 (br s, 1H, N*H*), 2.45 (s, 3H, H_{18});

^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 139.8 (Quat, C_{10}), 137.5 (Quat, C_{17}), 135.6 (Quat, C_{12}), 131.3 (CH, C_{16}), 129.7(CH, C_{15}), 129.1 (CH, C_{13}), 128.9 (Quat, C_4), 126.8 (CH, C_{14}), 126.6 (CH, C_8), 122.6 (CH, C_6), 120.3 (CH, C_7), 117.9 (CH, C_1), 117.9 (Quat, C_5), 114.9 (CH, C_9), 109.4 (CH, C_2), 103.2 (CH, C_3), 68.3 (CH, C_{11}), 19.1 (CH_3, C_{18});

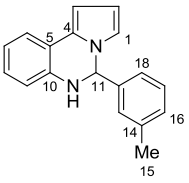
FTIR (neat) ν/cm^{-1} = 3362 (br), 3057, 1612, 1587, 1488, 1461, 1435, 1286, 1254, 1231, 1069;

HRMS (FI^+) calculated for $C_{18}H_{16}N_2$ = 260.1313, mass found = 260.1314;

Chiral HPLC (Chiralpak IA, 5 % IPA, 95 % hexane, 1.0 mL/min, λ = 328 nm, 20 μL injection) τ_R (major) = 9.7 min, τ_R (minor) = 13.8 min;

$[\alpha]_D^{20}$ +80 (*c* = 1.00, $CHCl_3$).

5-(*m*-Tolyl)-5,6-dihydropyrrolo[1,2-*c*]quinazoline, 73



Asymmetric: According to **General Procedure A**. Imine formation: pyrroloaniline **50** (50 mg, 0.32 mmol), *m*-tolualdehyde (49 mg, 0.41 mmol) and magnesium sulfate (190 mg, 1.58 mmol) in anhydrous toluene (10 mL). Cyclization: *N*-benzylcinchoninium chloride (13 mg, 0.031 mmol) and potassium hydroxide (50 % w/w, 0.18 mL, 3.2 mmol) in toluene (3.2 mL) at -15 ^oC for 5 days yielded a crude reaction product. Purification *via* column chromatography eluting with a gradient from petrol 40-60 to 7:93 diethyl ether/petrol 40-60 afforded the title compound **73** as a yellow oil (61 mg, 74 %, 89:11 e.r.).

Racemic: According to **General Procedure B**. Imine formation: pyrroloaniline **50** (20 mg, 0.13 mmol), *m*-tolualdehyde (20 mg, 0.17 mmol) and magnesium sulfate (76 mg, 0.63 mmol) in anhydrous toluene (4 mL). Cyclization: tetrabutylammonium bromide (4 mg, 0.01 mmol)

and potassium hydroxide (50 % w/w, 71 μL, 1.3 mmol) in toluene (1 mL) at room temperature for 2 hours afforded a crude product. An analytical HPLC sample of *rac*-**73** was obtained by small scale preparative TLC (1:4 diethyl ether/petrol 40-60).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.57 (dd, J = 7.7, 1.3 Hz, 1H, H_6), 7.42-7.28 (m, 4H, H_{13}, H_{16}, H_{17} and H_{18}), 7.06 (td, J = 7.3, 1.3 Hz, 1H, H_8), 6.92 (td, J = 7.3, 1.4 Hz, 1H, H_7), 6.70 (dd, J = 7.8, 1.0, 1H, H_9), 6.60 (dd, J = 3.4, 1.5 Hz, 1H, H_3), 6.25 (dd, J = 3.4, 2.9 Hz, 1H, H_2), 6.18 (dd, J = 2.7, 1.5 Hz, 1H, H_1), 6.10 (s, 1H, H_{11}), 4.31 (br s, 1H, N*H*), 2.42 (s, 3H, H_{15});

^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 139.5 (Quat, C_{10}), 138.9 (Quat, C_{14}), 138.3 (Quat, C_{12}), 130.7 (CH, C_{16}), 129.0 (Quat, C_4), 128.9(1) (CH, $C_{13/17}$), 128.8(7) (CH, $C_{13/17}$), 126.6 (CH, C_8), 125.5 (CH, C_{18}), 122.5 (CH, C_6), 120.3 (CH, C_7), 118.3 (CH, C_1), 117.9 (Quat, C_5), 114.9 (CH, C_9), 109.4 (CH, C_2), 103.2 (CH, C_3), 71.0 (CH, C_{11}), 21.5 (CH_3, C_{15});

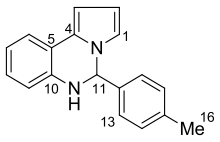
FTIR (neat) ν/cm^{-1} = 3363 (br), 3057, 2919, 1612, 1588, 1487, 1458, 1438, 1305, 1285, 1254, 1231, 1069;

HRMS (FI$^+$) calculated for $C_{18}H_{16}N_2$ = 260.1313, mass found = 260.1317;

Chiral HPLC (Chiralpak IA, 5 % IPA, 95 % hexane, 1.0 mL/min, λ = 330 nm, 15 μL injection) τ_R (major) = 14.2 min, τ_R (minor) = 16.1 min;

$[\alpha]_D^{20}$ +76 (*c* = 1.00, $CHCl_3$).

5-(*p*-Tolyl)-5,6-dihydropyrrolo[1,2-*c*]quinazoline, 74



Asymmetric: According to **General Procedure A**. Imine formation: pyrroloaniline **50** (50 mg, 0.32 mmol), *p*-tolualdehyde (49 mg, 0.41 mmol) and magnesium sulfate (190 mg, 1.58 mmol)

in anhydrous toluene (10 mL). Cyclization: *N*-benzylcinchoninium chloride (13 mg, 0.031 mmol) and potassium hydroxide (50 % w/w, 0.18 mL, 3.2 mmol) in toluene (3.2 mL) at -15 ^{o}C for 5 days yielded a crude reaction product. Purification *via* column chromatography eluting with a gradient from petrol 40-60 to 1:9 diethyl ether/petrol 40-60 afforded the title compound **74** as a yellow oil (78 mg, 95 %, 76:24 e.r.).

Racemic: According to **General Procedure B**. Imine formation: pyrroloaniline **50** (20 mg, 0.13 mmol), *p*-tolualdehyde (20 mg, 0.17 mmol) and magnesium sulfate (76 mg, 0.63 mmol) in anhydrous toluene (4 mL). Cyclization: tetrabutylammonium bromide (4 mg, 0.01 mmol) and potassium hydroxide (50 % w/w, 71 μL, 1.3 mmol) in toluene (1 mL) at room temperature for 2 hours afforded a crude product. An analytical HPLC sample of *rac*-**74** was obtained by small scale preparative TLC (1:4 diethyl ether/petrol 40-60).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 7.55 (dd, J = 7.6, 1.3 Hz, 1H, H_6), 7.44 (d, J = 7.9 Hz, 2H, H_{13}), 7.27 (d, J = 7.9 Hz, 2H, H_{14}), 7.05 (td, J = 7.6, 1.4 Hz, 1H, H_8), 6.91 (td, J = 7.6, 1.3 Hz, 1H, H_7), 6.70 (dd, J = 8.1, 1.3 Hz, 1H, H_9), 6.57 (dd, J = 3.8, 1.6 Hz, 1H, H_3), 6.22 (dd, J = 3.7, 2.7 Hz, 1H, H_2), 6.16 (dd, J = 2.8, 1.6 Hz, 1H, H_1), 6.12 (s, 1H, H_{11}), 4.30 (br s, 1H, N*H*), 2.43 (s, 3H, H_{16});

^{13}C NMR (126 MHz, $CDCl_3$) δ_C = 139.9 (Quat, C_{15}), 139.5 (Quat, C_{10}), 135.3 (Quat, C_{12}), 129.6 (CH, C_{14}), 129.0 (Quat, C_4), 128.2 (CH, C_{13}), 126.5 (CH, C_8), 122.4 (CH, C_6), 120.2 (CH, C_7), 118.1 (CH, C_1), 117.9 (Quat, C_5), 114.8 (CH, C_9), 109.3 (CH, C_2), 103.1 (CH, C_3), 70.8 (CH, C_{11}), 21.3 (CH_3, C_{16});

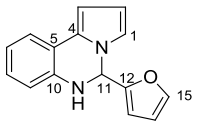
FTIR (neat) ν/cm^{-1} = 3363 (br), 3032, 2921, 1613, 1588, 1487, 1438, 1303, 1285, 1254, 1231, 1068;

HRMS (FI^{+}) calculated for $C_{18}H_{16}N_2$ = 260.1313, mass found = 260.1317;

Chiral HPLC (Chiralpak ADH, 20 % IPA, 80 % hexane, 1.0 mL/min, λ = 332 nm, 15 μL injection) τ_R (minor) = 10.3 min, τ_R (major) = 14.2 min;

$[\alpha]_D^{20}$ +41 (*c* = 1.00 $CHCl_3$).

5-(Furan-2-yl)-5,6-dihydropyrrolo[1,2-*c*]quinazoline, 75



Asymmetric: According to **General Procedure A**. Imine formation: pyrroloaniline **50** (50 mg, 0.32 mmol), furfural (39 μL, 0.47 mmol) and magnesium sulfate (190 mg, 1.58 mmol) in anhydrous toluene (10 mL). Cyclization: *N*-benzylcinchoninium chloride (13 mg, 0.031 mmol) and potassium hydroxide (50 % w/w, 0.18 mL, 3.2 mmol) in toluene (3.2 mL) at -15 ^oC for 2 days yielded a crude reaction product. Purification *via* column chromatography eluting with a gradient from petrol 40-60 to 1:9 diethyl ether/petrol 40-60 afforded the title compound **75** as a yellow oil (67 mg, 90 %, 70:30 e.r.).

Racemic: According to **General Procedure B**. Imine formation: pyrroloaniline **50** (20 mg, 0.13 mmol), furfural (16 μL, 0.19 mmol) and magnesium sulfate (76 mg, 0.63 mmol) in anhydrous toluene (4 mL). Cyclization: tetrabutylammonium bromide (4 mg, 0.01 mmol) and potassium hydroxide (50 % w/w, 71 μL, 1.3 mmol) in toluene (1 mL) at room temperature for 2 hours afforded a crude product. An analytical HPLC sample of *rac*-**75** was obtained by small scale preparative TLC (1:4 diethyl ether/petrol 40-60).

^1H NMR (500 MHz, $CDCl_3$) δ_H = 7.50 (dd, J = 7.6, 1.3 Hz, 1H, H_6), 7.43 (dd, J = 1.9, 0.6 Hz, 1H, H_{15}), 7.04 (td, J = 7.7, 1.2 Hz, 1H, H_8), 6.90 (td, J = 7.5, 1.1 Hz, 1H, H_7), 6.74 (dd, J = 7.9, 0.6 Hz, 1H, H_9), 6.55-6.53 (m, 2H, H_1 and H_3), 6.36 (s, 1H, H_{11}), 6.33 (dd, J = 3.2, 1.9 Hz, 1H, H_{14}), 6.28 (t, J = 3.2 Hz, 1H, H_2), 6.21 (d, J = 3.2 Hz, 1H, H_{13}), 4.49 (br s, 1H, N*H*);

^{13}C NMR (126 MHz, $CDCl_3$) δ_C = 151.7 (Quat, C_{12}), 143.1 (CH, C_{15}), 137.9 (Quat, C_{10}), 128.0 (Quat, C_4), 126.7 (CH, C_8), 122.4 (CH, C_6), 120.6 (CH, C_7), 118.0 (CH, C_1), 117.9 (Quat, C_5), 115.5 (CH, C_9), 110.5 (CH, C_{14}), 109.7 (CH, C_2), 108.7 (CH, C_{13}), 103.2 (CH, C_3), 64.4 (CH, C_{11});

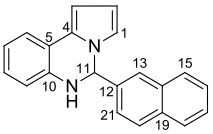
FTIR (neat) ν/cm^{-1} = 3366 (br), 3118, 2918, 1613, 1588, 1556, 1489, 1439, 1284, 1236, 1069, 1011;

HRMS (ESI^+) calculated for $C_{15}H_{12}N_2NaO$ = 259.0842, mass found = 259.0841;

Chiral HPLC (Chiralpak IA, 10 % IPA, 90 % hexane, 1.0 mL/min, λ = 328 nm, 15 μL injection) τ_R (minor) = 13.9 min, τ_R (major) = 14.8 min;

$[\alpha]_D^{20}$ = +53 (*c* = 0.52, $CHCl_3$).

5-(Naphthalen-2-yl)-5,6-dihydropyrrolo[1,2-*c*]quinazoline, 76



Asymmetric:

Imine Formation: A slurry of pyrroloaniline **50** (50 mg, 0.32 mmol), 2-naphthaldehyde (99 mg, 0.63 mmol) and oven dried anhydrous magnesium sulfate (190 mg, 1.6 mmol) in anhydrous toluene (10 mL) was stirred at room temperature for 24 hours. After this time a further portion of oven dried anhydrous magnesium sulfate (190 mg, 1.6 mmol) was added and the mixture was stirred at room temperature for 24 hours and then filtered through a plug of Celite® washing with anhydrous diethyl ether. The filtrate was concentrated under reduced pressure.

Cyclization: The crude imine thus obtained was dissolved in toluene (3.2 mL) and *N*-benzylcinchoninium chloride (13 mg, 0.031 mmol) was added. The resulting stirred

suspension was cooled to 0 °C and aqueous potassium hydroxide (50 % w/w, 0.18 mL, 3.2 mmol) precooled to 0 °C was added. The biphasic reaction mixture was rapidly stirred at 0 °C for 5 days. After this time, water was added and the solution was allowed to warm to room temperature. The organic layer was separated and the aqueous layer was extracted three times with dichloromethane. The combined organic extracts were dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. TLC (1:1 dichloromethane/petrol 40-60) indicated that an inseparable mixture of **76** and residual 2-naphthaldehyde were present.

Reduction of excess aldehyde: The crude residue thus obtained was dissolved in anhydrous methanol (3.2 mL). Sodium borohydride (45 mg, 1.2 mmol) was added in one portion and the resulting solution was stirred at room temperature for 1.5 hours. The reaction mixture was diluted with diethyl ether and water was added. The organic layer was separated and the aqueous layer was extracted twice with diethyl ether. The combined organic extracts were dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. Purification of the residue *via* column chromatography eluting with a gradient from petrol 40-60 to 1:19 diethyl ether/petrol 40-60 afforded the title compound **76** as a white solid (77 mg, 82 %, 91:9 e.r.).

Racemic:

Imine formation: A slurry of pyrroloaniline **50** (20 mg, 0.13 mmol), 2-naphthaldehyde (39 mg, 0.25 mmol) and oven dried anhydrous magnesium sulfate (76 mg, 0.63 mmol) in anhydrous toluene (4 mL) was stirred at room temperature for 24 hours. After this time a further portion of oven dried anhydrous magnesium sulfate (76 mg, 0.63 mmol) was added and the mixture was stirred at room temperature for 24 hours and then filtered through a plug of Celite® washing with anhydrous diethyl ether. The filtrate was concentrated under reduced pressure.

Cyclization: The crude imine thus obtained was dissolved in toluene (1 mL) and tetrabutylammonium bromide (4 mg, 0.01 mmol) and aqueous potassium hydroxide (50 % w/w, 71 μL, 1.3 mmol) were added. The biphasic reaction mixture was rapidly stirred at room temperature for 16 hours. After this time water was added. The organic layer was separated and the aqueous layer was extracted three times with dichloromethane. The combined organic extracts were dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. An analytical HPLC sample of *rac*-**76** was obtained by small scale preparative TLC (1:1 dichloromethane/petrol 40-60).

Melting Point: 136-138 ^{o}C (diethyl ether/petrol 40-60);

^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 8.00-7.87 (m, 4H, H_{13}, H_{15}, H_{18} and H_{20}), 7.67 (dd, J = 8.5, 1.6 Hz, 1H, H_{21}), 7.61-7.54 (m, 3H, H_6, H_{16} and H_{17}), 7.06 (td, J = 7.6, 1.4 Hz, 1H, H_8), 6.93 (td, J = 7.6, 0.9 Hz, 1H, H_7), 6.72 (dd, J = 7.8, 0.9 Hz, 1H, H_9), 6.62 (dd, J = 3.6, 1.4 Hz, 1H, H_3), 6.31 (s, 1H, H_{11}), 6.24 (t, J = 3.3 Hz, 1H, H_2), 6.16 (dd, J = 2.8, 1.6 Hz, 1H, H_1), 4.38 (br s, 1H, N*H*);

^{13}C NMR (126 MHz, $CDCl_3$) δ_C = 139.3 (Quat, C_{10}), 135.6 (Quat, C_{12}), 134.1 (Quat, C_{19}), 133.0 (Quat, C_{14}), 129.2 (CH, C_{20}), 129.0 (Quat, C_4), 128.3 (CH, $C_{13/15/18}$), 128.1 (CH, $C_{13/15/18}$), 127.9 (CH, $C_{13/15/18}$), 127.0 (CH, $C_{16/17}$), 126.6(2) (CH, $C_{8/16/17}$), 126.6(0) (CH, $C_{8/16/17}$), 125.1 (CH, C_{21}), 122.5 (CH, C_6), 120.3 (CH, C_7), 118.3 (CH, C_1), 117.8 (Quat, C_5), 114.9 (CH, C_9), 109.5 (CH, C_2), 103.2 (CH, C_3), 71.1 (CH, C_{11});

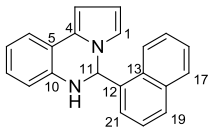
FTIR (neat) ν/cm^{-1} = 3368 (br), 3057, 1612, 1588, 1488, 1433, 1302, 1285, 1253, 1232, 1112, 1069;

HRMS (FI^+) calculated for $C_{21}H_{16}N_2$ = 296.1313, mass found = 296.1319;

Chiral HPLC (Chiralpak ADH, 20 % IPA, 80 % hexane, 1.0 mL/min, λ = 328 nm, 30 μL injection) τ_R (major) = 15.7 min, τ_R (minor) = 18.1 min;

$[\alpha]_D^{20}$ = +97 (*c* = 0.53, $CHCl_3$).

5-(Naphthalen-1-yl)-5,6-dihydropyrrolo[1,2-*c*]quinazoline, 77



Asymmetric:

Imine Formation: A slurry of pyrroloaniline **50** (50 mg, 0.32 mmol), 1-naphthaldehyde (99 mg, 0.63 mmol) and oven dried anhydrous magnesium sulfate (190 mg, 1.6 mmol) in anhydrous toluene (10 mL) was stirred at room temperature for 24 hours. After this time a further portion of oven dried anhydrous magnesium sulfate (190 mg, 1.6 mmol) was added and the mixture was stirred at room temperature for 24 hours and then filtered through a plug of Celite® washing with anhydrous diethyl ether. The filtrate was concentrated under reduced pressure.

Cyclization: The crude imine thus obtained was dissolved in toluene (3.2 mL) and *N*-benzylcinchoninium chloride (13 mg, 0.031 mmol) was added. The resulting stirred suspension was cooled to 0 ^oC and aqueous potassium hydroxide (50 % w/w, 0.18 mL, 3.2 mmol) precooled to 0 ^oC was added. The biphasic reaction mixture was rapidly stirred at 0 ^oC for 5 days. After this time, water was added and the solution was allowed to warm to room temperature. The organic layer was separated and the aqueous layer was extracted three times with dichloromethane. The combined organic extracts were dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. TLC (1:1 dichloromethane/petrol 40-60) indicated that an inseparable mixture of **77** and residual 1-naphthaldehyde were present.

Reduction of excess aldehyde: The crude residue thus obtained was dissolved in anhydrous methanol (3.2 mL). Sodium borohydride (45 mg, 1.2 mmol) was added in one portion and the resulting solution was stirred at room temperature for 1.5 hours. The reaction mixture was diluted with diethyl ether and water was added. The organic layer was separated and the aqueous layer was extracted twice with diethyl ether. The combined organic extracts were dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. Purification of the residue *via* column chromatography eluting with a gradient from petrol 40-60 to 1:19 diethyl ether/petrol 40-60 afforded the title compound **77** as a white solid (75 mg, 80 %, 88:12 e.r.).

Racemic:

Imine formation: A slurry of pyrroloaniline **50** (20 mg, 0.13 mmol), 1-naphthaldehyde (39 mg, 0.25 mmol) and oven dried anhydrous magnesium sulfate (76 mg, 0.63 mmol) in anhydrous toluene (4 mL) was stirred at room temperature for 24 hours. After this time a further portion of oven dried anhydrous magnesium sulfate (76 mg, 0.63 mmol) was added and the mixture was stirred at room temperature for 24 hours and then filtered through a plug of Celite® washing with anhydrous diethyl ether. The filtrate was concentrated under reduced pressure.

Cyclization: The crude imine thus obtained was dissolved in toluene (1 mL) and tetrabutylammonium bromide (4 mg, 0.01 mmol) and aqueous potassium hydroxide (50 % w/w, 71 μL, 1.3 mmol) were added. The biphasic reaction mixture was rapidly stirred at room temperature for 16 hours. After this time, water was added. The organic layer was separated and the aqueous layer was extracted three times with dichloromethane. The combined organic extracts were dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. An analytical HPLC sample of *rac*-**77** was obtained by small scale preparative TLC (1:1 dichloromethane/petrol 40-60).

Melting Point: 148-152 ^{o}C (diethyl ether/petrol 40-60);

^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 8.31 (d, J = 8.5 Hz, 1H, H_{14}), 7.98-7.93 (m, 2H, H_{17} and H_{19}), 7.62-7.58 (m, 2H, H_6 and H_{21}), 7.55-7.45 (m, 3H, H_{15}, H_{16} and H_{20}), 7.04 (td, J = 7.6, 1.4 Hz, 1H, H_8), 6.93 (td, J = 7.6, 1.2 Hz, 1H, H_7), 6.93 (s, 1H, H_{11}), 6.65 (dd, J = 7.9, 0.9 Hz, 1H, H_9), 6.62 (dd, J = 3.6, 1.4 Hz, 1H, H_3), 6.19 (dd, J = 3.8, 2.5 Hz, 1H, H_2), 6.13 (dd, J = 2.8, 1.6 Hz, 1H, H_1), 4.41 (br s, 1H, N*H*);

^{13}C NMR (126 MHz, $CDCl_3$) δ_C = 139.5 (Quat, C_{10}), 134.3 (Quat, C_{18}), 132.8 (Quat, C_{12}), 131.1 (Quat, C_{13}), 130.7 (CH, C_{19}), 128.9 (CH, C_{17}), 128.8 (Quat, C_4), 127.6 (CH, C_{21}), 126.7 (CH, $C_{8/15}$), 126.6 (CH, $C_{8/15}$), 126.2 (CH, C_{16}), 125.2 (CH, C_{20}), 124.1 (CH, C_{14}), 122.5 (CH, C_6), 120.3 (CH, C_7), 118.6 (CH, C_1), 117.9 (Quat, C_5), 114.9 (CH, C_9), 109.5 (CH, C_2), 103.1 (CH, C_3), 70.1 (CH, C_{11});

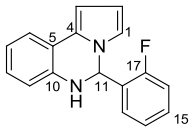
FTIR (neat) ν/cm^{-1} = 3366 (br), 3055, 1612, 1587, 1488, 1460, 1433, 1304, 1285, 1234, 1112;

HRMS (FI^{+}) calculated for $C_{21}H_{16}N_2$ = 296.1313, mass found = 296.1307;

Chiral HPLC (Chiralpak ADH, 20 % IPA, 80 % hexane, 1.0 mL/min, λ = 221 nm, 20 μL injection) τ_R (major) = 10.1 min, τ_R (minor) = 13.1 min;

$[\alpha]_D^{20}$ = +150 (*c* = 1.00, $CHCl_3$).

5-(2-Fluorophenyl)-5,6-dihydropyrrolo[1,2-*c*]quinazoline, 80



Asymmetric: According to **General Procedure A**. Imine formation: pyrroloaniline **50** (50 mg, 0.32 mmol), *o*-fluorobenzaldehyde (51 mg, 0.41 mmol) and magnesium sulfate (190 mg, 1.58 mmol) in anhydrous toluene (10 mL). Cyclization: *N*-benzylcinchoninium chloride (13 mg, 0.031 mmol) and potassium hydroxide (50 % w/w, 0.18 mL, 3.2 mmol) in toluene (3.2 mL)

at -15 ^{o}C for 4 days and then at room temperature for 16 hours yielded a crude reaction product. Purification of the residue *via* column chromatography eluting with a gradient from petrol 40-60 to 1:9 diethyl ether/petrol 40-60 afforded the title compound **80** as a yellow oil (71 mg, 85 %, 81:19 e.r.).

Racemic: According to **General Procedure B**. Imine formation: pyrroloaniline **50** (20 mg, 0.13 mmol), *o*-fluorobenzaldehyde (20 mg, 0.16 mmol) and magnesium sulfate (76 mg, 0.63 mmol) in anhydrous toluene (4 mL). Cyclization: tetrabutylammonium bromide (4 mg, 0.01 mmol) and potassium hydroxide (50 % w/w, 71 μL, 1.3 mmol) in toluene (1 mL) at room temperature for 3 hours yielded a crude product. An analytical HPLC sample of *rac*-**80** was obtained by small scale preparative TLC (1:4 diethyl ether/petrol 40-60).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 7.53 (dd, J = 7.9, 1.3 Hz, 1H, H_6), 7.34-7.29 (m, 1H, H_{15}), 7.12 (ddd, J = 10.2, 8.4, 0.8 Hz, 1H, H_{16}), 7.05 (td, J = 7.1, 0.8 Hz, 1H, H_{14}), 7.01 (td, J = 7.6, 0.8 Hz, 1H, H_8), 6.91-6.85 (m, 2H, H_7 and H_{13}), 6.69 (s, 1H, H_{11}), 6.67 (dd, J = 8.0, 0.8 Hz, 1H, H_9), 6.59 (dd, J = 3.5, 1.6 Hz, 1H, H_3), 6.47 (dd, J = 2.7, 1.4 Hz, 1H, H_1), 6.30 (dd, J = 3.5, 2.8 Hz, 1H, H_2), 4.48 (br s, 1H, N*H*);

^{13}C NMR (126 MHz, $CDCl_3$) δ_C = 160.0 (d, J = 160.0 Hz, Quat, C_{17}), 138.1 (Quat, C_{10}), 130.7 (d, J = 8.6 Hz, CH, C_{15}), 128.7 (Quat, C_4), 128.1 (d, J = 2.9 Hz, CH, C_{13}), 127.1 (d, J = 11.4 Hz, Quat, C_{12}), 126.8 (CH, C_8), 124.8 (d, J = 3.8 Hz, CH, C_{14}), 122.4 (CH, C_6), 120.3 (CH, C_7), 118.3 (CH, C_1), 117.6 (Quat, C_5), 115.4 (d, J = 21.0 Hz, CH, C_{16}), 115.2 (CH, C_9), 109.9 (CH, C_2), 103.2 (CH, C_3), 64.1 (d, J = 4.8 Hz, CH, C_{11});

^{19}F NMR (470 MHz, $CDCl_3$) δ_F = -120.3 (s);

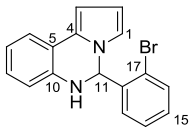
FTIR (neat) ν/cm^{-1} = 3361 (br), 3061, 1613, 1588, 1489, 1458, 1437, 1306, 1288, 1259, 1233, 1076;

HRMS (FI^+) calculated for $C_{17}H_{13}N_2F$ = 264.1063, mass found = 264.1074;

Chiral HPLC (Chiralpak ODH, 30 % IPA, 70 % hexane, 1.0 mL/min, λ = 231 nm, 30 μL injection) τ_R (major) = 8.7 min, τ_R (minor) = 11.6 min;

$[\alpha]_D^{20}$ = +148 (*c* = 0.52, $CHCl_3$).

5-(2-Bromophenyl)-5,6-dihydropyrrolo[1,2-*c*]quinazoline, 81



Asymmetric: According to **General Procedure A**. Imine formation: pyrroloaniline **50** (50 mg, 0.32 mmol), *o*-bromobenzaldehyde (76 mg, 0.41 mmol) and magnesium sulfate (190 mg, 1.58 mmol) in anhydrous toluene (10 mL). Cyclization: *N*-benzylcinchoninium chloride (13 mg, 0.031 mmol) and potassium hydroxide (50 % w/w, 0.18 mL, 3.2 mmol) in toluene (3.2 mL) at -15 °C for 4 days and then at room temperature for 16 hours yielded a crude reaction product. Purification *via* column chromatography eluting with a gradient from petrol 40-60 to 1:19 diethyl ether/petrol 40-60 afforded the title compound **81** as a yellow oil (73 mg, 71 %, 82:18 e.r.).

Racemic: According to **General Procedure 2**. Imine formation: pyrroloaniline **50** (20 mg, 0.13 mmol), *o*-bromobenzaldehyde (30 mg, 0.16 mmol) and magnesium sulfate (76 mg, 0.63 mmol) in anhydrous toluene (4 mL). Cyclization: tetrabutylammonium bromide (4 mg, 0.01 mmol) and potassium hydroxide (50 % w/w, 71 μL, 1.3 mmol) in toluene (1 mL) at room temperature for 3 hours afforded a crude product. An analytical HPLC sample of *rac*-**81** was obtained by small scale preparative TLC (1:9 diethyl ether/petrol 40-60).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 7.61-7.57 (m, 1H, H_{16}), 7.54 (dd, J = 7.7, 1.4 Hz, 1H, H_6), 7.20-7.15 (m, 2H, H_{14} and H_{15}), 6.99 (td, J = 7.6, 1.3 Hz, 1H, H_8), 6.86 (td, J = 7.6, 0.9 Hz, 1H, H_7), 6.74-

6.69 (m, 2H, H_{11} and H_{13}), 6.64 (dd, J = 7.9, 0.6 Hz, 1H, H_9), 6.61 (dd, J = 3.6, 1.4 Hz, 1H, H_3), 6.48 (dd, J = 2.7, 1.4 Hz, 1H, H_1), 6.31 (dd, J = 3.5, 2.8 Hz, 1H, H_2), 4.81 (br s, 1H, N*H*);

^{13}C NMR (126 MHz, $CDCl_3$) δ_C = 138.8 (Quat, C_{12}), 137.5 (Quat, C_{10}), 132.9 (CH, C_{16}), 130.4 (CH, C_{15}), 128.6 (Quat, C_4), 128.2(3) (CH, $C_{13/14}$), 128.2(0) (CH, $C_{13/14}$), 126.8 (CH, C_8), 122.3 (CH, C_6), 121.8 (Quat, C_{17}), 120.1 (CH, C_7), 118.4 (CH, C_1), 117.4 (Quat, C_5), 115.1 (CH, C_9), 110.0 (CH, C_2), 103.0 (CH, C_3), 69.3 (CH, C_{11});

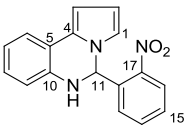
FTIR (neat) ν/cm^{-1} = 3362, 3060, 1613, 1588, 1490, 1442, 1306, 1289, 1253, 1236, 1046;

HRMS (FI$^+$) calculated for $C_{17}H_{13}N_2Br$ = 324.0262, mass found = 324.0264;

Chiral HPLC (Chiralpak ADH, 20 % IPA, 80 % hexane, 1.0 mL/min, λ = 330 nm, 30 μL injection) τ_R (major) = 7.8 min, τ_R (minor) = 10.1 min;

$[\alpha]_D^{20}$ = +232 (*c* = 1.01, $CHCl_3$).

5-(2-Nitrophenyl)-5,6-dihydropyrrolo[1,2-c]quinazoline, 82



Asymmetric: According to **General Procedure A**. Imine formation: pyrroloaniline **50** (50 mg, 0.32 mmol), *o*-nitrobenzaldehyde (62 mg, 0.41 mmol) and magnesium sulfate (190 mg, 1.6 mmol) in anhydrous toluene (10 mL). Cyclization: *N*-benzylcinchoninium chloride (13 mg, 0.031 mmol) and potassium hydroxide (50 % w/w, 0.18 mL, 3.2 mmol) in toluene (3.2 mL) at -15 ^{o}C for 5 days yielded a crude reaction product. Purification *via* column chromatography eluting with a gradient from petrol to 1:9 diethyl ether/petrol 40-60 afforded the title compound **82** as a brown solid (34 mg, 37 %, 56:44 e.r.).

Racemic: According to **General Procedure B**. Imine formation: pyrroloaniline **50** (20 mg, 0.13 mmol), *o*-nitrobenzaldehyde (25 mg, 0.16 mmol) and magnesium sulfate (76 mg, 0.63 mmol) in anhydrous toluene (4 mL). Cyclization: tetrabutylammonium bromide (4 mg, 0.01 mmol) and potassium hydroxide (50 % w/w, 0.07 mL, 1.3 mmol) in toluene (1 mL) at room temperature for 2 hours afforded a crude product. An analytical HPLC sample of *rac*-**82** was obtained by small scale preparative TLC (1:4 diethyl ether/petrol 40-60).

Melting Point: 114-116 ^{o}C (diethyl ether/petrol 40-60);

^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 8.09-8.05 (m, 1H, H_{16}), 7.55 (dd, J = 7.6, 1.3 Hz, 1H, H_6), 7.42-7.37 (m, 2H, H_{Ar}), 7.00 (s, 1H, H_{11}), 6.98 (td, J = 7.7, 1.1 Hz, 1H, H_8), 6.85 (td, J = 7.6, 0.9 Hz, 1H, H_7), 6.64 (dd, J = 3.6, 1.4 Hz, 1H, H_3), 6.61 (dd, J = 8.1, 0.8 Hz, 1H, H_9), 6.57 (dd, J = 2.7, 1.4 Hz, 1H, H_1), 6.47-6.42 (m, 1H, H_{Ar}), 6.36 (dd, J = 3.8, 2.8, 1H, H_2), 5.21 (br s, 1H, N*H*);

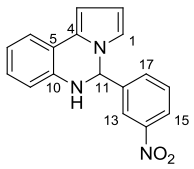
^{13}C NMR (126 MHz, $CDCl_3$) δ_C = 146.6 (Quat, C_{Ar}), 136.7 (Quat, C_{Ar}), 136.3 (Quat, C_{Ar}), 134.5 (CH, C_{Ar}), 129.3 (CH, C_{Ar}), 128.9 (Quat, C_{Ar}), 127.8 (CH, C_{Ar}), 127.1 (CH, C_8), 125.3 (CH, C_{16}), 122.2 (CH, C_6), 120.0 (CH, C_7), 118.6 (CH, C_1), 116.9 (Quat, C_{Ar}), 115.5 (CH, C_9), 110.7 (CH, C_2), 103.0 (CH, C_3), 66.0 (CH, C_{11});

FTIR (neat) ν/cm^{-1} = 3410, 3067, 1525, 1491, 1342, 1307, 1239;

HRMS (FI^{+}) calculated for $C_{17}H_{13}N_3O_2$ = 291.1008, mass found = 291.1012;

Chiral HPLC (Chiralpak ADH, 30 % IPA, 70 % hexane, 1.0 mL/min, λ = 245 nm, 30 μL injection) τ_R (major) = 11.2 min, τ_R (minor) = 14.3 min.

5-(3-Nitrophenyl)-5,6-dihydropyrrolo[1,2-c]quinazoline, 83



Asymmetric: According to **General Procedure A**. Imine formation: pyrroloaniline **50** (50 mg, 0.32 mmol), *m*-nitrobenzaldehyde (62 mg, 0.41 mmol) and magnesium sulfate (190 mg, 1.6 mmol) in anhydrous toluene (10 mL). Cyclization: *N*-benzylcinchoninium chloride (13 mg, 0.031 mmol) and potassium hydroxide (50 % w/w, 0.18 mL, 3.2 mmol) in toluene (3.2 mL) at -15 ^{o}C for 5 days yielded a crude reaction product. Purification *via* column chromatography eluting with a gradient from petrol to 3:7 diethyl ether/petrol 40-60 afforded the title compound **83** as a brown solid (73 mg, 79 %, 65:35 e.r.).

Racemic: According to **General Procedure B**. Imine formation: pyrroloaniline **50** (20 mg, 0.13 mmol), *m*-nitrobenzaldehyde (25 mg, 0.16 mmol) and magnesium sulfate (76 mg, 0.63 mmol) in anhydrous toluene (4 mL). Cyclization: tetrabutylammonium bromide (4 mg, 0.01 mmol) and potassium hydroxide (50 % w/w, 0.07 mL, 1.3 mmol) in toluene (1 mL) at room temperature for 2 hours afforded a crude product. An analytical HPLC sample of *rac*-**83** was obtained by small scale preparative TLC (2:3 diethyl ether/petrol 40-60).

Melting Point: 41-44 ^{o}C (diethyl ether/petrol 40-60);

^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 8.29-8.27 (m, 1H, H_{13}), 8.22 (ddd, J = 8.2, 2.2, 0.9 Hz, 1H, H_{Ar}), 7.65 (d, J = 7.9 Hz, 1H, H_{Ar}), 7.55-7.52 (m, 2H, H_6 and H_{Ar}), 7.05 (td, J = 7.6, 1.4 Hz, 1H, H_8), 6.93 (td, J = 7.5, 1.2 Hz, 1H, H_7), 6.72 (dd, J = 7.9, 0.9 Hz, 1H, H_9), 6.61 (dd, J = 3.6, 1.4 Hz, 1H, H_3), 6.29 (dd, J = 3.6, 2.7 Hz, 1H, H_2), 6.26 (s, 1H, H_{11}), 6.23 (dd, J = 2.7, 1.4 Hz, 1H, H_1), 4.47 (br s, 1H, N*H*);

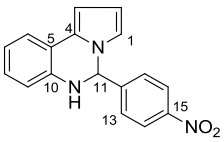
^{13}C NMR (126 MHz, $CDCl_3$) δ_C = 148.5 (Quat, C_{Ar}), 141.5 (Quat, C_{Ar}), 138.0 (Quat, C_{Ar}), 133.8 (CH, C_{Ar}), 130.1 (CH, C_{Ar}), 128.6 (Quat, C_{Ar}), 126.9 (CH, C_8), 124.4 (CH, C_{Ar}), 122.7 (CH, C_{13}), 122.5 (CH, C_6), 120.9 (CH, C_7), 118.1 (CH, C_1), 117.8 (Quat, C_5), 115.5 (CH, C_9), 110.3 (CH, C_2), 103.7 (CH, C_3), 69.8 (CH, C_{11});

FTIR (neat) ν/cm^{-1} = 3367, 3067, 1613, 1588, 1527, 1488, 1348, 1305, 1286, 1254, 1234;

HRMS (FI$^+$) calculated for $C_{17}H_{13}N_3O_2$ = 291.1008, mass found = 291.1006;

Chiral HPLC (Chiralpak ADH, 30 % IPA, 70 % hexane, 1.0 mL/min, λ = 245 nm, 30 μL injection) τ_R (minor) = 10.9 min, τ_R (major) = 11.9 min;

5-(4-Nitrophenyl)-5,6-dihydropyrrolo[1,2-c]quinazoline, 84



Asymmetric: According to **General Procedure A**. Imine formation: pyrroloaniline **50** (50 mg, 0.32 mmol), *p*-nitrobenzaldehyde (62 mg, 0.41 mmol) and magnesium sulfate (190 mg, 1.6 mmol) in anhydrous toluene (10 mL). Cyclization: *N*-benzylcinchoninium chloride (13 mg, 0.031 mmol) and potassium hydroxide (50 % w/w, 0.18 mL, 3.2 mmol) in toluene (3.2 mL) at -15 ^{o}C for 5 days yielded a crude reaction product. Purification *via* column chromatography eluting with a gradient from petrol to 3:7 diethyl ether/petrol 40-60 afforded the title compound **84** as a brown solid (31 mg, 34 %, 54:46 e.r.).

Racemic: According to **General Procedure B**. Imine formation: pyrroloaniline **50** (20 mg, 0.13 mmol), *p*-nitrobenzaldehyde (25 mg, 0.16 mmol) and magnesium sulfate (76 mg, 0.63 mmol) in anhydrous toluene (4 mL). Cyclization: tetrabutylammonium bromide (4 mg, 0.01 mmol) and potassium hydroxide (50 % w/w, 0.07 mL, 1.3 mmol) in toluene (1 mL) at

room temperature for 2 hours afforded a crude product. An analytical HPLC sample of *rac*-**84** was obtained by small scale preparative TLC (2:3 diethyl ether/petrol 40-60).

Melting Point: 164-166 ^{o}C (diethyl ether/petrol 40-60);

^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 8.22 (d, J = 8.8 Hz, 2H, H_{14}), 7.55-7.51 (m, 3H, H_6 and H_{13}), 7.05 (td, J = 7.6, 1.4 Hz, 1H, H_8), 6.93 (td, J = 7.6, 1.2 Hz, 1H, H_7), 6.72 (dd, J = 7.9, 0.9 Hz, 1H, H_9), 6.60 (dd, J = 3.6, 1.4 Hz, 1H, H_3), 6.31 (s, 1H, H_{11}), 6.29 (dd, J = 3.7, 3.0 Hz, 1H, H_2), 6.26 (dd, J = 2.8, 1.4 Hz, 1H, H_1), 4.41 (br s, 1H, N*H*);

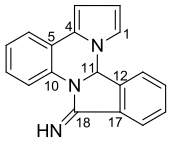
^{13}C NMR (126 MHz, $CDCl_3$) δ_C =148.5 (Quat, C_{Ar}), 146.2 (Quat, C_{Ar}), 137.7 (Quat, C_{Ar}), 128.5 (Quat, C_{Ar}), 128.5 (CH, C_{13}), 126.9 (CH, C_8), 124.1 (CH, C_{14}), 122.5 (CH, C_6), 121.0 (CH, C_7), 118.1 (CH, C_1), 117.8 (Quat, C_5), 115.6 (CH, C_9), 110.3 (CH, C_2), 103.6 (CH, C_3), 69.8 (CH, C_{11});

FTIR (neat) ν/cm^{-1} = 3370, 3074, 1609, 1589, 1519, 1489, 1345, 1286, 1234, 1109, 1072;

HRMS (FI^{+}) calculated for $C_{17}H_{13}N_3O_2$ = 291.1008, mass found = 291.1016;

Chiral HPLC (Chiralpak ADH, 30 % IPA, 70 % hexane, 1.0 mL/min, λ = 222 nm, 30 μL injection) τ_R (minor) = 10.1 min, τ_R (major) = 11.8 min.

Isoindolo[2,1-*a*]pyrrolo[1,2-*c*]quinazolin-9(13*bH*)-imine, 85



Asymmetric: According to **General Procedure A**. Imine formation: pyrroloaniline **50** (50 mg, 0.32 mmol), 2-cyanobenzaldehyde (54 mg, 0.41 mmol) and magnesium sulfate (190 mg, 1.58 mmol) in anhydrous toluene (10 mL). Cyclization: *N*-benzylcinchoninium chloride (13 mg, 0.031 mmol) and potassium hydroxide (50 % w/w, 0.18 mL, 3.2 mmol) in toluene (3.2 mL) at -15 ^{o}C for 5 days yielded a crude reaction product. Purification *via* column chromatography

eluting with diethyl ether afforded the title compound **85** as an off white solid (81 mg, 94 %, 61:39 e.r.).

Racemic: According to **General Procedure B**. Imine formation: pyrroloaniline **50** (20 mg, 0.13 mmol), 2-cyanobenzaldehyde (22 mg, 0.17 mmol) and magnesium sulfate (76 mg, 0.63 mmol) in anhydrous toluene (4 mL). Cyclization: tetrabutylammonium bromide (4 mg, 0.01 mmol) and potassium hydroxide (50 % w/w, 71 μL, 1.3 mmol) in toluene (1 mL) at room temperature for 2 hours afforded a crude product. An analytical HPLC sample of *rac*-**85** was obtained by small scale preparative TLC (diethyl ether).

Melting Point: 64 -68 ^{o}C (diethyl ether);

^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 7.93 (br d, J = 7.6 Hz, 1H, H_{16}), 7.89 (d, J = 7.3 Hz, 1H, H_{13}), 7.85 (br s, 1H, H_9), 7.74-7.69 (m, 2H, H_6 and H_{14}), 7.66 (t, J = 7.4 Hz, 1H, H_{15}), 7.35 (td, J = 7.6, 1.4 Hz, 1H, H_8), 7.28 (td, J = 7.6, 0.9 Hz, 1H, H_7), 6.98 (dd, J = 2.8, 1.3 Hz, 1H, H_1), 6.64 (dd, J = 3.8, 1.3 Hz, 1H, H_3), 6.43 (s, 1H, H_{11}), 6.32 (dd, J = 3.6, 2.9 Hz, 1H, H_2). The N*H* signal was absent in $CHCl_3$ but was observed as a broad singlet at δ = 8.44 ppm in d_6-DMSO;

^{13}C NMR (126 MHz, $CDCl_3$) δ_C = 161.0 (Quat, C_{18}), 136.4 (Quat, C_{12}), 134.0 (Quat, C_{17}), 131.4 (CH, C_{14}), 131.2 (Quat, C_{10}), 130.3 (CH, C_{15}), 127.8 (Quat, C_4), 126.5 (CH, C_8), 125.4 (CH, C_7), 124.5 (CH, C_{13}), 123.2 (CH, $C_{6/16}$), 123.1 (CH, $C_{6/16}$), 123.1 (Quat, C_5), 122.2 (CH, C_9), 116.4 (CH, C_1), 110.2 (CH, C_2), 105.5 (CH, C_3), 71.2 (C_{11});

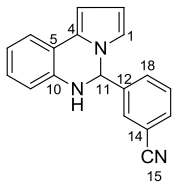
FTIR (neat) ν/cm^{-1} = 3303, 1644, 1601, 1487, 1468, 1395, 1297;

HRMS (FI^{+}) calculated for $C_{18}H_{16}N_2O$ = 271.1109, mass found = 271.1110;

Chiral HPLC (Chiralpak ADH, 30 % IPA, 70 % hexane, 1.0 mL/min, λ = 211 nm, 20 μL injection) τ_R (minor) = 12.1 min, τ_R (major) = 16.2 min.

$[\alpha]_D^{20}$ = -71 (*c* = 0.38, $CHCl_3$).

3-(5,6-Dihydropyrrolo[1,2-*c*]quinazolin-5-yl)benzonitrile, 86



Asymmetric: According to **General Procedure A**. Imine formation: pyrroloaniline **50** (50 mg, 0.32 mmol), 3-cyanobenzaldehyde (54 mg, 0.41 mmol) and magnesium sulfate (190 mg, 1.58 mmol) in anhydrous toluene (10 mL). Cyclization: *N*-benzylcinchoninium chloride (13 mg, 0.031 mmol) and potassium hydroxide (50 % w/w, 0.18 mL, 3.2 mmol) in toluene (3.2 mL) at -15 ^{o}C for 4 days yielded a crude reaction product. Purification *via* column chromatography eluting with a gradient from petrol 40-60 to 3:7 diethyl ether/petrol 40-60 afforded the title compound **86** as a white solid (79 mg, 92 %, 70:30 e.r.).

Racemic: According to **General Procedure B**. Imine formation: pyrroloaniline **50** (20 mg, 0.13 mmol), 3-cyanobenzaldehyde (22 mg, 0.17 mmol) and magnesium sulfate (76 mg, 0.63 mmol) in anhydrous toluene (4 mL). Cyclization: tetrabutylammonium bromide (4 mg, 0.01 mmol) and potassium hydroxide (50 % w/w, 71 μL, 1.3 mmol) in toluene (1 mL) at room temperature for 2 hours afforded a crude product. An analytical HPLC sample of *rac*-**86** was obtained by small scale preparative TLC (1:1 diethyl ether/petrol 40-60).

Melting Point: 32-34 ^{o}C (diethyl ether/petrol 40-60);

^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 7.71-7.67 (m, 2H, H_{13} and H_{16}), 7.63 (dt, J = 7.7, 1.2 Hz, 1H, H_{18}), 7.56-7.49 (m, 2H, H_6 and H_{17}), 7.05 (td, J = 7.6, 1.4 Hz, 1H, H_8), 6.93 (td, J = 7.6, 0.9 Hz, 1H, H_7), 6.72 (dd, J = 7.9, 0.9 Hz, 1H, H_9), 6.59 (dd, J = 3.6, 1.4 Hz, 1H, H_3), 6.28 (dd, J = 3.5, 2.8 Hz, 1H, H_2), 6.22 (s, 1H, H_{11}), 6.20 (dd, J = 2.7, 1.4 Hz, 1H, H_1), 4.40 (br s, 1H, N*H*);

^{13}C NMR (126 MHz, $CDCl_3$) δ_C = 140.8 (Quat, C_{12}), 138.0 (Quat, C_{10}), 133.2 (CH, C_{16}), 132.2 (CH, C_{18}), 131.4 (CH, C_{13}), 129.9 (CH, C_{17}), 128.7 (Quat, C_4), 126.8 (CH, C_8), 122.5 (CH, C_6), 120.9 (CH,

C_7), 118.3 (Quat, C_{15}), 118.0 (CH, C_1), 117.8 (Quat, C_5), 115.4 (CH, C_9), 113.1 (Quat, C_{14}), 110.2 CH, C_2), 103.6 (CH, C_3), 69.9 (CH, C_{11});

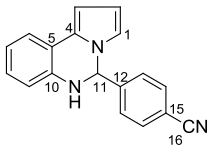
FTIR (neat) ν/cm^{-1} = 3350 (br), 3061, 2231, 1613, 1589, 1554, 1488, 1287;

HRMS (FI$^+$) calculated for $C_{18}H_{16}N_2O$ = 271.1109, mass found = 271.1110;

Chiral HPLC (Chiralpak ADH, 15 % IPA, 85 % hexane, 1.0 mL/min, λ = 328 nm, 20 μL injection) τ_R (minor) = 19.4 min, τ_R (major) = 20.8 min;

$[\alpha]_D^{20}$ = +57 (*c* = 1.00, $CHCl_3$).

4-(5,6-Dihydropyrrolo[1,2-*c*]quinazolin-5-yl)benzonitrile, 87



Asymmetric: According to **General Procedure A**. Imine formation: pyrroloaniline **50** (50 mg, 0.32 mmol), 4-cyanobenzaldehyde (54 mg, 0.41 mmol) and magnesium sulfate (190 mg, 1.58 mmol) in anhydrous toluene (10 mL). Cyclization: *N*-benzylcinchoninium chloride (13 mg, 0.031 mmol) and potassium hydroxide (50 % w/w, 0.18 mL, 3.2 mmol) in toluene (3.2 mL) at -15 ^{o}C for 5 days and then at room temperature for 16 hours yielded a crude reaction product. Purification *via* column chromatography eluting with a gradient from petrol 40-60 to 3:7 diethyl ether/petrol 40-60 afforded the title compound **87** as a white solid (65 mg, 76 %, 62:38 e.r.).

Racemic: According to **General Procedure B**. Imine formation: pyrroloaniline **50** (20 mg, 0.13 mmol), 4-cyanobenzaldehyde (22 mg, 0.17 mmol) and magnesium sulfate (76 mg, 0.63 mmol) in anhydrous toluene (4 mL). Cyclization: tetrabutylammonium bromide (4 mg, 0.01 mmol) and potassium hydroxide (50 % w/w, 71 μL, 1.3 mmol) in toluene (1 mL) at room

temperature for 2 hours afforded a crude product. An analytical HPLC sample of *rac*-**87** was obtained by small scale preparative TLC (1:1 diethyl ether/petrol 40-60).

Melting Point: 180-183 ^{o}C (diethyl ether/petrol 40-60);

^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 7.67 (d, J = 8.2 Hz, 2H, H_{14}), 7.53 (dd, J = 7.9, 1.3 Hz, 1H, H_6), 7.48 (d, J = 8.2 Hz, 2H, H_{13}), 7.05 (td, J = 7.6, 1.4 Hz, 1H, H_8), 6.92 (td, J = 7.5, 1.1 Hz, 1H, H_7), 6.71 (dd, J = 7.6, 0.6 Hz, 1H, H_9), 6.59 (dd, J = 3.6, 1.4 Hz, 1H, H_3), 6.28 (dd, J = 3.6, 2.7 Hz, 1H, H_2), 6.24 (s, 1H, H_{11}), 6.23 (dd, J = 2.7, 1.4 Hz, 1H, H_1), 4.40 (br s, 1H, N*H*);

^{13}C NMR (126 MHz, $CDCl_3$) δ_C = 144.3 (Quat, C_{12}), 137.9 (Quat, C_{10}), 132.7 (CH, C_{14}), 128.6 (Quat, C_4), 128.3 (CH, C_{13}), 126.9 (CH, C_8), 122.5 (CH, C_6), 120.8 (CH, C_7), 118.3 (Quat, C_{16}), 118.1 (CH, C_1), 117.8 (Quat, C_5), 115.4 (CH, C_9), 113.4 (Quat, C_{15}), 110.2 (CH, C_2), 103.5 (CH, C_3), 70.1 (CH, C_{11});

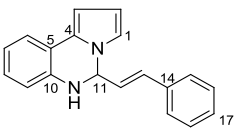
FTIR (neat) ν/cm^{-1} = 3345 (br), 3061, 2228, 1612, 1589, 1552, 1488, 1285, 1234, 1071;

HRMS (FI^{+}) calculated for $C_{18}H_{13}N_3$ = 271.1109, mass found = 271.1110;

Chiral HPLC (Chiralpak ADH, 30 % IPA, 70 % hexane, 1.0 mL/min, λ = 327 nm, 20 μL injection) τ_R (minor) = 10.8 min, τ_R (major) = 12.9 min;

$[\alpha]_D^{20}$ = +42 (*c* = 0.48, $CHCl_3$).

(*E*)-5-Styryl-5,6-dihydropyrrolo[1,2-*c*]quinazoline, 88



Asymmetric: According to **General Procedure A**. Imine formation: pyrroloaniline **50** (50 mg, 0.32 mmol), *trans*-cinnamaldehyde (46 mg, 0.35 mmol) and magnesium sulfate (190 mg, 1.58 mmol) in anhydrous toluene (10 mL). Cyclization: *N*-benzylcinchoninium chloride (13 mg,

0.031 mmol) and potassium hydroxide (50 % w/w, 0.18 mL, 3.2 mmol) in toluene (3.2 mL) at room temperature for 2 days yielded a crude reaction product. Purification *via* column chromatography eluting with a gradient from petrol 40-60 to 1:4 diethyl ether/petrol 40-60 afforded the title compound **88** as a yellow oil (85 mg, 99 %, 60:40 e.r.).

Racemic: According to **General Procedure B**. Imine formation: pyrroloaniline **50** (20 mg, 0.13 mmol), *trans*-cinnamaldehyde (18 mg, 0.14 mmol) and magnesium sulfate (76 mg, 0.63 mmol) in anhydrous toluene (4 mL). Cyclization: tetrabutylammonium bromide (4 mg, 0.01 mmol) and potassium hydroxide (50 % w/w, 71 μL, 1.3 mmol) in toluene (1 mL) at room temperature for 2 hours afforded a crude product. An analytical HPLC sample of *rac*-**88** was obtained by small scale preparative TLC (1:4 diethyl ether/petrol 40-60).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 7.51 (dd, J = 7.9, 1.3 Hz, 1H, H_6), 7.43 (dt, J = 7.3, 1.6 Hz, 2H, H_{15}), 7.40-7.31 (m, 3H, H_{16} and H_{17}), 7.05 (td, J = 7.6, 1.5 Hz, 1H, H_8), 6.89 (td, J = 7.5, 1.1 Hz, 1H, H_7), 6.79 (d, J = 16.1 Hz, 1H, H_{13}), 6.73 (dd, J = 7.9, 0.6 Hz, 1H, H_9), 6.69 (dd, J = 2.5, 1.6 Hz, 1H, H_1), 6.56 (dd, J = 3.6, 1.4 Hz, 1H, H_3), 6.43 (dd, J = 15.8, 7.9 Hz, 1H, H_{12}), 6.30 (dd, J = 3.5, 2.8 Hz, 1H, H_2), 5.81 (d, J = 7.9 Hz, 1H, H_{11}), 4.24 (br s, 1H, N*H*);

^{13}C NMR (126 MHz, $CDCl_3$) δ_C = 138.3 (Quat, C_{10}), 135.6 (CH, C_{13}), 135.2 (Quat, C_{14}), 128.7(8) (CH, C_{17}), 128.7(7) (CH, C_{16}), 127.7 (Quat, C_4) C, 127.0 (CH, C_{15}), 126.6 (CH, C_8), 126.0 (CH, C_{12}), 122.4 (CH, C_6), 120.2 (CH, C_7), 117.6 (Quat, C_5), 117.3 (CH, C_1), 114.9 (CH, C_9), 109.6 (CH, C_2), 103.3 (CH, C_3), 69.8 (CH, C_{11});

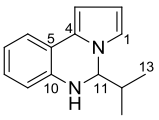
FTIR (neat) ν/cm^{-1} = 3368 (br), 3058, 1669, 1612, 1588, 1488, 1434, 1285, 1229, 1072;

HRMS (ESI^+) calculated for $C_{19}H_{16}N_2Na$ = 295.1206, mass found = 295.1207;

Chiral HPLC (Chiralpak IA, 10 % IPA, 90 % hexane, 1.0 mL/min, λ = 328 nm, 15 μL injection) τ_R (minor) = 15.5 min, τ_R (major) = 16.9 min;

$[\alpha]_D^{20}$ = - 46 (*c* = 0.24, $CHCl_3$).

5-Isopropyl-5,6-dihydropyrrolo[1,2-*c*]quinazoline, 89



Asymmetric: According to **General Procedure A**. Imine formation: pyrroloaniline **50** (50 mg, 0.32 mmol), isobutyraldehyde (0.14 mL, 1.5 mmol) and magnesium sulfate (190 mg, 1.58 mmol) in anhydrous toluene (10 mL). Cyclization: *N*-benzylcinchoninium chloride (13 mg, 0.031 mmol) and potassium hydroxide (50 % w/w, 0.18 mL, 3.2 mmol) in toluene (3.2 mL) at room temperature for 24 hours yielded a crude reaction product. Purification *via* column chromatography eluting with a gradient from petrol 40-60 to 1:9 diethyl ether/petrol 40-60 afforded the title compound **89** as a white solid (56 mg, 83 %, 77:23 e.r.).

Racemic: According to **General Procedure B**. Imine formation: pyrroloaniline **50** (20 mg, 0.13 mmol), isobutyraldehyde (58 μL, 0.64 mmol) and magnesium sulfate (76 mg, 0.63 mmol) in anhydrous toluene (4 mL). Cyclization: tetrabutylammonium bromide (4 mg, 0.01 mmol) and potassium hydroxide (50 % w/w, 71 μL, 1.3 mmol) in toluene (1 mL) at room temperature for 2 hours yielded a crude reaction product. An analytical HPLC sample of *rac*-**89** was obtained by small scale preparative TLC (1:4 diethyl ether/petrol 40-60).

Melting Point: 63-65 ^oC (diethyl ether/petrol 40-60);

^1H NMR (400 MHz, $CDCl_3$) δ_H = 7.47 (dd, J = 7.8, 1.2 Hz, 1H, H_6), 7.05 (td, J = 7.6, 1.3 Hz, 1H, H_8), 6.84 (td, J = 7.5, 1.1 Hz, 1H, H_7), 6.71-6.67 (m, 2H, H_9 and H_1), 6.48 (dd, J = 3.7, 1.5 Hz, 1H, H_3), 6.28 (dd, J = 3.4, 2.7 Hz, 1H, H_2), 5.02 (d, J = 6.1 Hz, 1H, H_{11}), 4.26 (br s, 1H, N*H*), 2.23 (octet, J = 6.7 Hz, 1H, H_{12}), 0.95 (t, J = 6.8 Hz, 6H, H_{13});

^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 138.4 (Quat, C_{10}), 127.6 (Quat, C_4), 126.7 (CH, C_8), 122.2 (CH, C_6), 119.7 (CH, C_7), 115.5 (CH, C_1), 118.1 (Quat, C_5), 115.0 (CH, C_9), 108.9 (CH, C_2), 102.5 (CH, C_3), 73.2 (CH, C_{11}), 33.9 (CH, C_{12}), 19.0 (CH_3, C_{13}), 17.3 (CH_3, $C_{13'}$);

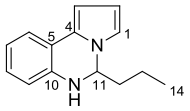
FTIR (neat) ν/cm^{-1} = 3396 (br), 2961, 2871, 1612, 1588, 1492, 1467, 1307, 1290, 1258, 1236, 1071;

HRMS (ESI$^+$) calculated for $C_{14}H_{17}N_2$ = 213.1386, mass found = 213.1391;

Chiral HPLC (Chiralpak ADH, 5 % IPA, 95 % hexane, 1.0 mL/min, λ = 327 nm, 15 μL injection) τ_R (minor) = 13.0 min, τ_R (major) = 13.9 min;

$[\alpha]_D^{20}$ = -44 (*c* = 1.00, $CHCl_3$).

5-Propyl-5,6-dihydropyrrolo[1,2-*c*]quinazoline, 90



Asymmetric: According to **General Procedure A**. Imine formation: pyrroloaniline **50** (50 mg, 0.32 mmol), *n*-butyraldehyde (0.14 mL, 1.6 mmol) and magnesium sulfate (190 mg, 1.58 mmol) in anhydrous toluene (10 mL). Cyclization: *N*-benzylcinchoninium chloride (13 mg, 0.031 mmol) and potassium hydroxide (50 % w/w, 0.18 mL, 3.2 mmol) in toluene (3.2 mL) at room temperature for 24 hours yielded a crude reaction product. Purification *via* column chromatography eluting with a gradient from petrol 40-60 to 1:9 diethyl ether/petrol 40-60 afforded the title compound **90** as a colourless oil (56 mg, 83 %, 83:17 e.r.).

Racemic: According to **General Procedure B**. Imine formation: pyrroloaniline **50** (20 mg, 0.13 mmol), *n*-butyraldehyde (57 μL, 0.63 mmol) and magnesium sulfate (76 mg, 0.63 mmol) in anhydrous toluene (4 mL). Cyclization: tetrabutylammonium bromide (4 mg, 0.01 mmol) and potassium hydroxide (50 % w/w, 71 μL, 1.3 mmol) in toluene (1 mL) at room temperature

for 2 hours afforded a crude product. An analytical HPLC sample of *rac*-**90** was obtained by small scale preparative TLC (1:4 diethyl ether/petrol 40-60).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.49 (dd, J = 7.6, 1.2 Hz, 1H, H_6), 7.05 (td, J = 7.6, 1.3 Hz, 1H, H_8), 6.88 (td, J = 7.5, 1.1 Hz, 1H, H_7), 6.73-6.70 (m, 2H, H_9 and H_1), 6.50 (dd, J = 3.7, 1.5 Hz, 1H, H_3), 6.30 (dd, J = 3.3, 3.1 Hz, 1H, H_2), 5.25 (dd, J = 6.7, 5.3 Hz, 1H, H_{11}), 4.15 (br s, 1H, N*H*), 1.98-1.81 (m, 2H, H_{12}), 1.56-1.37 (m, 2H, H_{13}), 0.98 (t, J = 7.3 Hz, 3H, H_{14});

^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 138.4 (Quat, C_{10}), 127.7 (Quat, C_4), 126.7 (CH, C_8), 122.4 (CH, C_6), 120.2 (CH, C_7), 118.3 (Quat, C_5), 117.1 (CH, C_1), 115.6 (CH, C_9), 109.3 (CH, C_2), 102.9 (CH, C_3), 67.7 (CH, C_{11}), 37.7 (CH_2, C_{12}), 18.2 (CH_2, C_{13}), 13.9 (CH_3, C_{14});

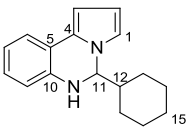
FTIR (neat) ν/cm^{-1} = 3372 (br), 2958, 2932, 1612, 1588, 1553, 1490, 1305, 1238;

HRMS (ESI$^+$) calculated for $C_{14}H_{17}N_2$ = 213.1386, mass found = 213.1393;

Chiral HPLC (Chiralpak ADH, 5 % IPA, 95 % hexane, 1.0 mL/min, λ = 326 nm, 15 μL injection) τ_R (major) = 13.8 min, τ_R (minor) = 14.8 min;

$[\alpha]_D^{20}$ = -43 (*c* = 1.00, $CHCl_3$).

5-Cyclohexyl-5,6-dihydropyrrolo[1,2-*c*]quinazoline, 91



Asymmetric: According to **General Procedure A**. Imine formation: pyrroloaniline **50** (50 mg, 0.32 mmol), cyclohexanecarboxaldehyde (0.19 mL, 1.6 mmol) and magnesium sulfate (190 mg, 1.58 mmol) in anhydrous toluene (10 mL). Cyclization: *N*-benzylcinchoninium chloride (13 mg, 0.031 mmol) and potassium hydroxide (50 % w/w, 0.18 mL, 3.2 mmol) in toluene (3.2 mL) at room temperature for 24 hours yielded a crude reaction product. Purification *via* column

chromatography eluting with a gradient from petrol 40-60 to 1:9 diethyl ether/petrol 40-60 afforded the title compound **91** as a white solid (69 mg, 86 %, 92:8 e.r.).

Racemic: According to **General Procedure B**. Imine formation: pyrroloaniline **50** (100 mg, 0.63 mmol), cyclohexanecarboxaldehyde (0.38 mL, 3.1 mmol) and magnesium sulfate (380 mg, 3.16 mmol) in anhydrous toluene (20 mL). Cyclization: tetrabutylammonium bromide (20 mg, 0.063 mmol) and potassium carbonate (33 % w/w, 1.7 mL, 6.2 mmol) in toluene (6.3 mL) at room temperature for 16 hours afforded a crude product. Purification *via* column chromatography eluting with 1:9 diethyl ether/petrol 40-60 afforded the title compound *rac*-**91** as a white solid (111 mg, 70 %).

Melting Point: 89-91 ^{o}C (diethyl ether/petrol 40-60);

^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 7.45 (dd, J = 7.7, 1.4 Hz, 1H, H_6), 7.04 (td, J = 7.6, 1.4 Hz, 1H, H_8), 6.83 (td, J = 7.5, 1.1 Hz, 1H, H_7), 6.69 (d, J = 7.9 Hz, 1H, H_9), 6.65 (dd, J = 2.5, 1.6 Hz, 1H, H_1), 6.45 (dd, J = 3.6, 1.4 Hz, 1H, H_3), 6.24 (dd, J = 3.5, 2.8 Hz, 1H, H_2), 4.99 (d, J = 6.6 Hz, 1H, H_{11}), 4.35 (br s, 1H, N*H*), 1.89-1.80 (m, 1H, H_{12}), 1.78-1.70 (m, 3H, H_{Cy}), 1.67-1.61 (m, 1H, H_{Cy}), 1.55-1.48 (m, 1H, H_{Cy}), 1.21-0.99 (m, 5H, H_{Cy});

^{13}C NMR (126 MHz, $CDCl_3$) δ_C = 138.2 (Quat, C_{10}), 127.3 (Quat, C_4), 126.6 (CH, C_8), 122.1 (CH, C_6), 119.6 (CH, C_7), 118.7 (CH, C_1), 118.2 (Quat, C_5), 115.0 (CH, C_9), 108.5 (CH, C_2), 102.4 (CH, C_3), 72.8 (CH, C_{11}), 43.2 (CH, C_{12}), 29.4 (CH_2, C_{13}), 27.9 (CH_2, $C_{13'}$), 26.0 (CH_2, $C_{14/14'/15}$), 25.8 (CH_2, $C_{14/14'/15}$), 25.6 (CH_2, $C_{14/14'/15}$);

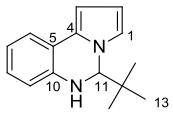
FTIR (neat) ν/cm^{-1} = 3393 (br), 2925, 2852, 1612, 1587, 1554, 1491, 1448, 1308, 1258, 1237, 1071;

HRMS (ESI^{+}) calculated for $C_{17}H_{21}N_2$ = 253.1699, mass found = 253.1695;

Chiral HPLC (Chiralpak ADH, 25 % IPA, 75 % hexane, 1.0 mL/min, λ = 330 nm, 15 μL injection) τ_R (major) = 6.0 min, τ_R (minor) = 6.7 min;

$[\alpha]_D^{20}$ = -52 (*c* = 1.00, $CHCl_3$).

5-(*tert*-Butyl)-5,6-dihydropyrrolo[1,2-*c*]quinazoline, 92



Asymmetric: According to **General Procedure A**. Imine formation: pyrroloaniline **50** (50 mg, 0.32 mmol), pivaldehyde (0.17 mL, 1.6 mmol) and magnesium sulfate (190 mg, 1.58 mmol) in anhydrous toluene (10 mL). Cyclization: *N*-benzylcinchoninium chloride (13 mg, 0.031 mmol) and potassium hydroxide (50 % w/w, 0.18 mL, 3.2 mmol) in toluene (3.2 mL) at room temperature for 24 hours yielded a crude reaction product. Purification *via* column chromatography eluting with a gradient from petrol 40-60 to 1:4 diethyl ether/petrol 40-60 afforded the title compound **92** as a white solid (60 mg, 84 %, 72:28 e.r.).

Racemic: According to **General Procedure B**. Imine formation: pyrroloaniline **50** (100 mg, 0.63 mmol), pivaldehyde (0.34 mL, 3.1 mmol) and magnesium sulfate (380 mg, 3.16 mmol) in anhydrous toluene (20 mL). Cyclization: tetrabutylammonium bromide (20 mg, 0.062 mmol) and aqueous potassium carbonate (33 % w/w, 1.7 mL, 6.2 mmol) in toluene (6.3 mL) at room temperature for 16 hours afforded a crude product. Purification *via* column chromatography eluting with a gradient from petrol 40-60 to 1:4 diethyl ether/petrol 40-60 afforded the title compound *rac*-**92** as a white solid (106 mg, 74 %).

Melting Point: 97-99 ^oC (diethyl ether/petrol 40-60);

^1H NMR (500 MHz, $CDCl_3$) δ_H = 7.43 (dd, J = 7.6, 1.6 Hz, 1H, H_6), 7.01 (td, J = 7.6, 1.4 Hz, 1H, H_8), 6.78 (td, J = 7.5, 1.1 Hz, 1H, H_7), 6.67 (dd, J = 2.5, 1.6 Hz, 1H, H_1), 6.64 (dd, J = 7.9, 0.9 Hz, 1H,

H_9), 6.47 (dd, J = 3.6, 1.4 Hz, 1H, H_3), 6.28 (dd, J = 3.5, 2.8 Hz, 1H, H_2), 5.05 (s, 1H, H_{11}), 4.39 (br s, 1H, N*H*), 0.92 (s, 9H, H_{13});

^{13}C NMR (126 MHz, $CDCl_3$) δ_C = 138.8 (Quat, C_{10}), 128.0 (Quat, C_4), 126.7 (CH, C_8), 121.8 (CH, C_6), 120.1 (CH, C_1), 118.8 (CH, C_7), 117.8 (Quat, C_5), 113.5 (CH, C_9), 108.3 (CH, C_2), 101.8 (CH, C_3), 76.1 (CH, C_{11}), 40.8 (Quat, C_{12}), 26.5 (CH_3, C_{13});

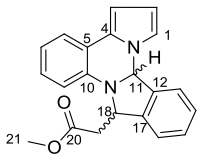
FTIR (neat) ν/cm^{-1} = 3422 (br), 2959, 2867, 1613, 1585, 1496, 1306, 1285, 1264, 1234, 1088, 1071;

HRMS (ESI$^+$) calculated for $C_{15}H_{19}N_2$ = 227.1543, mass found = 227.1542;

Chiral HPLC (Chiralpak IA, 5 % IPA, 95 % hexane, 1.0 mL/min, λ = 334 nm, 20 μL injection) τ_R (major) = 10.5 min, τ_R (minor) = 12.0 min;

$[\alpha]_D^{20}$ = +22 (*c* = 1.00, $CHCl_3$).

Methyl 2-(9,13b-dihydroisoindolo[2,1-a]pyrrolo[1,2-c]quinazolin-9-yl)acetate, 94



94a and **94b**

Asymmetric: According to **General Procedure A**. Imine formation: pyrroloaniline **50** (29 mg, 0.18 mmol), (*E*)-methyl 3-(2-formylphenyl)acrylate (46 mg, 0.24 mmol) and magnesium sulfate (224 mg, 1.86 mmol) in anhydrous toluene (6 mL). Cyclization: *N*-benzylcinchoninium chloride (8 mg, 0.019 mmol) and potassium hydroxide (50 % w/w, 0.10 mL, 1.9 mmol) in toluene (3.2 mL) at -15 ^{o}C for 4 days yielded a crude reaction product. ^{1}H NMR of the crude residue (200 MHz, $CDCl_3$) indicated a mixture of diastereoisomers (3:1 **94a**:**94b**) was present. The residue was purified by column chromatography eluting with 1:9 diethyl ether/petrol 40-60 to afford **94** as a 3:1 mixture of **94a**:**94b** (49 mg, 81 %).

Racemic: According to **General Procedure B**. Imine formation: pyrroloaniline **50** (30 mg, 0.18 mmol), (*E*)-methyl 3-(2-formylphenyl)acrylate (47 mg, 0.25 mmol) and magnesium sulfate (230 mg, 1.90 mmol) in anhydrous toluene (6 mL). Cyclization: tetrabutylammonium bromide (6 mg, 0.019 mmol) and potassium hydroxide (50 % w/w, 0.11 mL, 1.9 mmol) in toluene (1.9 mL) at room temperature for 2.5 hours afforded a crude product. ^{1}H NMR of the crude residue (200 MHz, $CDCl_3$) indicated a mixture of diastereoisomers (5:4 **94a**:**94b**) was present. An analytical quantity of each diastereoisomer was obtained by column chromatography eluting with 1:9 diethyl ether/petrol 40-60. A yield was not calculated.

Data for **94a**: (yellow oil, 89:11 e.r.)

^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 7.75-7.71 (m, 1H, H_{13}), 7.63 (dd, J = 7.4, 1.4 Hz, 1H, H_6), 7.48-7.43 (m, 2H, H_{14} and H_{15}), 7.34-7.30 (m, 1H, H_{16}), 7.25 (dd, J = 7.9, 0.9 Hz, 1H, H_9), 7.18 (td, J = 7.5, 1.7 Hz, 1H, H_8), 7.14 (td, J = 7.3, 1.4 Hz, 1H, H_7), 6.70 (dd, J = 2.7, 1.4 Hz, 1H, H_1), 6.55 (dd, J = 3.6, 1.4 Hz, 1H, H_3), 6.31 (d, J = 1.3 Hz, 1H, H_{11}), 6.26 (t, J = 3.2 Hz, 1H, H_2), 4.95-4.91 (m, 1H, H_{18}), 3.66 (s, 3H, H_{21}), 3.25 (dd, J = 15.9, 3.9 Hz, 1H, H_{19}), 2.96 (dd, J = 16.1, 7.6 Hz, 1H, $H_{19'}$);

^{13}C NMR (126 MHz, $CDCl_3$) δ_C = 171.3 (Quat, C_{20}), 142.6 (Quat, C_{17}), 137.6 (Quat, C_{10}), 136.9 (Quat, C_{12}), 129.3 (CH, C_{15}), 127.9 (Quat, C_4), 127.7 (CH, C_{14}), 126.2 (CH, C_8), 124.1 (2 x CH, C_7 and C_{13}), 123.2 (Quat, C_5), 122.9 (CH, $C_{6/16}$), 122.8 (CH, $C_{6/16}$), 122.4 (CH, C_9), 116.7 (CH, C_1), 109.8 (CH, C_2), 103.6 (CH, C_3), 74.0 (CH, C_{11}), 63.9 (CH, C_{18}), 51.7 (CH_3, C_{21}), 39.3 (CH_2, C_{19});

FTIR (neat) ν/cm^{-1} = 3047, 2950, 1735, 1606, 1575, 1552, 1379, 1269, 1157;

HRMS (ESI^{+}) calculated for $C_{17}H_{15}N_2$ = 330.1368, mass found = 330.1357;

Chiral HPLC (Chiralpak ADH, 5 % IPA, 95 % hexane, 1.0 mL/min, λ = 242 nm, 20 μL injection) τ_R (minor) = 12.5 min, τ_R (major) = 13.7 min.

Data for **94b**: (yellow oil, 90:10 e.r.)

^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 7.76 (d, J = 6.9 Hz, 1H, H_{13}), 7.62 (dd, J = 7.9, 1.3 Hz, 1H, H_6), 7.53-7.44 (m, 3H, H_{14}, H_{15} and H_{16}), 7.21 (t, J = 7.6 Hz, 1H, H_8), 7.14 (dd, J = 7.9, 0.9 Hz, 1H, H_9), 7.07 (td, J = 7.6, 1.2 Hz, 1H, H_7), 6.79 (dd, J = 2.5, 1.6 Hz, 1H, H_1), 6.54 (dd, J = 3.6, 1.4 Hz, 1H, H_3), 6.30 (s, 1H, H_{11}), 6.28 (t, J = 3.2 Hz, 1H, H_2), 5.57 (dd, J = 9.1, 4.1 Hz, 1H, H_{18}), 3.53 (s, 3H, H_{21}), 2.69 (dd, J = 15.8, 4.1 Hz, 1H, H_{19}), 2.10 (dd, J = 15.8, 9.1 Hz, 1H, $H_{19'}$);

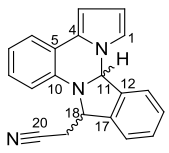
^{13}C NMR (126 MHz, $CDCl_3$) δ_C = 171.8 (Quat, C_{20}), 143.0 (Quat, C_{17}), 136.8 (Quat, C_{10}), 135.4 (Quat, C_{12}), 129.5 (CH, C_{15}), 128.4 (Quat, C_4), 128.1 (CH, C_{14}), 126.5 (CH, C_8), 124.8 (CH, C_{13}), 123.6(6) (Quat, C_5), 123.6(5) (CH, C_{16}), 122.8 (CH, $C_{6/7}$), 122.7 (CH, $C_{6/7}$), 120.4 (CH, C_9), 115.3 (CH, C_1), 109.7 (CH, C_2), 104.0 (CH, C_3), 73.4 (CH, C_{11}), 62.8 (CH, C_{18}), 51.5 (CH_3, C_{21}), 39.0 (CH_2, C_{19});

FTIR (neat) ν/cm^{-1} = 3045, 2950 , 1731, 1605, 1574, 1487, 1380, 1277, 1156;

HRMS (ESI$^+$) calculated for $C_{21}H_{18}N_2O_2$ = 330.1368, mass found = 330.1368;

Chiral HPLC (Chiralpak ADH, 5 % IPA, 95 % hexane, 1.0 mL/min, λ = 242 nm, 20 μL injection) τ_R (minor) = 9.2 min, τ_R (major) = 9.9 min.

2-(9,13b-Dihydroisoindolo[2,1-a]pyrrolo[1,2-c]quinazolin-9-yl)acetonitrile, 95



95a and **95b**

Asymmetric: According to **General Procedure A**. Imine formation: pyrroloaniline **50** (33 mg, 0.21 mmol), (*E*)-3-(2-formylphenyl)acrylonitrile (43 mg, 0.27 mmol) and magnesium sulfate (251 mg, 2.08 mmol) in anhydrous toluene (6.6 mL). Cyclization: *N*-benzylcinchoninium chloride (9 mg, 0.021 mmol) and potassium hydroxide (50 % w/w, 0.12 mL, 2.1 mmol) in

toluene (2.1 mL) at -15 °C for 4 days yielded a crude reaction product. ^{1}H NMR of the crude residue (200 MHz, $CDCl_3$) indicated a single diastereomer, **95a** was present. The residue was purified by column chromatography eluting with a gradient from petrol 40-60 to 1:4 diethyl ether/petrol 40-60 to afford **95a** as a brown solid (33 mg, 53 %, 84:16 e.r.).

Racemic: According to **General Procedure B**. Imine formation: pyrroloaniline **50** (33 mg, 0.21 mmol), (*E*)-3-(2-formylphenyl)acrylonitrile (43 mg, 0.27 mmol) and magnesium sulfate (251 mg, 2.08 mmol) in anhydrous toluene (6.6 mL). Cyclization: tetrabutylammonium bromide (7 mg, 0.021 mmol) and potassium hydroxide (50 % w/w, 0.12 mL, 2.1 mmol) in toluene (2.1 mL) at room temperature for 16 hours afforded a crude product. ^{1}H NMR of the crude residue (200 MHz, $CDCl_3$) indicated a mixture of diastereoisomers (3:7 **95a**:**95b**) was present. The residue was purified by column chromatography eluting with a gradient from petrol 40-60 to 1:4, enabling complete separation of the diastereomers affording *rac*-**95a** as a brown solid (12 mg, 19 %) and *rac*-**95b** as a yellow solid (32 mg, 52 %).

Data for **95a**

Melting point: 168-170 °C;

^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 7.80-7.86 (m, 1H, H_{13}), 7.68-7.64 (m, 1H, H_6), 7.56-7.51 (m, 2H, H_{14} and H_{15}), 7.45-7.40 (m, 1H, H_{16}), 7.24-7.20 (m, 3H, H_7, H_8 and H_9), 6.66 (dd, J = 2.7, 1.4 Hz, 1H, H_1), 6.57 (dd, J = 3.6, 1.4 Hz, 1H, H_3), 6.37 (d, J = 1.3 Hz, 1H, H_{11}), 6.26 (t, J = 3.2 Hz, 1H, H_2), 4.65-4.62 (m, 1H, H_{18}), 3.18 (dd, J = 17.2, 5.5 Hz, 1H, H_{19}), 3.14 (dd, J = 17.4, 3.2 Hz, 1H, $H_{19'}$);

^{13}C NMR (126 MHz, $CDCl_3$) δ_C = 140.2 (Quat, C_{17}), 137.3 (Quat, C_{12}), 136.8 (Quat, C_{10}), 129.9 (CH, C_{15}), 128.7 (CH, C_{14}), 127.6 (Quat, C_4), 126.4 (CH, C_8), 125.3 (CH, $C_{7/9}$), 124.6 (CH, C_{13}), 124.0 (Quat, C_5), 123.4 (CH, $C_{7/9}$), 123.2 (CH, C_6), 122.4 (CH, C_{16}), 117.0 (CH, C_1), 116.7 (Quat, C_{20}), 109.9 (CH, C_2), 104.0 (CH, C_3), 74.3 (CH, C_{11}), 63.7 (CH, C_{18}), 24.0 (CH_2, C_{19});

FTIR (neat) ν/cm^{-1} = 3048, 2924, 2250, 1715, 1606, 1575, 1552, 1484, 1379, 1273, 1222, 1068;

HRMS (ESI^+) calculated for $C_{20}H_{15}N_3$ = 297.1266, mass found = 297.1273;

Chiral HPLC (Chiralpak ADH, 10 % IPA, 90 % hexane, 1.0 mL/min, λ = 208 nm, 20 μL injection) τ_R (minor) = 15.4 min, τ_R (major) = 20.4 min;

$[\alpha]_D^{20}$ = – 265 (c = 0.34, $CHCl_3$).

Data for *rac*-**95b**

Melting point: 60-66 ^oC;

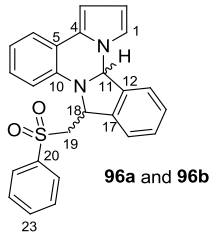
^1H NMR (500 MHz, $CDCl_3$) δ_H = 7.81 (dd, J = 6.4, 2.0 Hz, 1H, H_{13}), 7.75 (dd, J = 6.5, 2.0 Hz, 1H, H_{16}), 7.64 (dd, J = 8.0, 1.4 Hz, 1H, H_6), 7.62-7.55 (m, 2H, H_{14} and H_{15}), 7.24 (td, J = 7.6, 1.2 Hz, 1H, H_8), 7.15-7.11 (m, 2H, H_7 and H_9), 6.80 (dd, J = 2.8, 1.3 Hz, 1H, H_1), 6.56 (dd, J = 3.6, 1.4 Hz, 1H, H_3), 6.31 (s, 1H, H_{11}), 6.30 (t, J = 3.2 Hz, 1H, H_2), 5.34 (dd, J = 9.6, 3.3 Hz, 1H, H_{18}), 2.74 (dd, J = 16.7, 3.5 Hz, 1H, H_{19}), 2.01 (dd, J = 16.7, 9.5 Hz, 1H, $H_{19'}$);

^{13}C NMR (126 MHz, $CDCl_3$) δ_C = 140.7 (Quat, C_{17}), 135.7 (Quat, C_{10}), 135.6 (Quat, C_{12}), 129.9 (CH, C_{15}), 129.0 (CH, C_{14}), 127.9 (Quat, C_4), 126.8 (CH, C_8), 125.0 (CH, C_{13}), 123.9(3) (CH, C_{16}), 123.8(6) (Quat, C_5), 123.6 (CH, $C_{7/9}$), 123.1 (CH, C_6), 120.2 (CH, $C_{7/9}$), 117.0 (Quat, C_{20}), 115.7 (CH, C_1), 110.0 (CH, C_2), 104.6 (CH, C_3), 73.3 (CH, C_{11}), 62.4 (CH, C_{18}), 22.6 (CH_2, C_{19});

FTIR (neat) ν/cm^{-1} = 3047, 2866, 2248, 1706, 1605, 1574, 1549, 1487, 1381, 1278, 1069;

HRMS (ESI^+) calculated for $C_{20}H_{15}N_3$ = 297.1266, mass found = 297.1257.

9-((Phenylsulfonyl)methyl)-9,13b-dihydroisoindolo[2,1-a]pyrrolo[1,2-c]quinazoline, 96



96a and **96b**

Asymmetric: According to **General Procedure A**. Imine formation: pyrroloaniline **50** (33 mg, 0.21 mmol), (*E*)-2-(2-(phenylsulfonyl)vinyl)benzaldehyde (74 mg, 0.27 mmol) and magnesium sulfate (251 mg, 2.08 mmol) in anhydrous toluene (6.6 mL). Cyclization: *N*-benzylcinchoninium chloride (9 mg, 0.021 mmol) and potassium hydroxide (50 % w/w, 0.12 mL, 2.1 mmol) in toluene (2.1 mL) at -15 ^{o}C for 4 days yielded a crude reaction product. ^{1}H NMR of the crude residue (200 MHz, $CDCl_3$) indicated a mixture of diastereoisomers (7:2 **96a**:**96b**) was present. The residue was purified by column chromatography eluting with 3:7 diethyl ether/petrol 40-60 to afford **96** as a 7:2 mixture of diastereoisomers (**96a**:**96b**) (56 mg, 65 %). Analytical samples of each diastereoisomer were obtained by column chromatography.

Racemic: According to **General Procedure B**. Imine formation: pyrroloaniline **50** (33 mg, 0.21 mmol), (*E*)-2-(2-(phenylsulfonyl)vinyl)benzaldehyde (74 mg, 0.27 mmol) and magnesium sulfate (251 mg, 2.08 mmol) in anhydrous toluene (6.6 mL). Cyclization: tetrabutylammonium bromide (7 mg, 0.021 mmol) and potassium hydroxide (50 % w/w, 0.12 mL, 2.1 mmol) in toluene (2.1 mL) at room temperature for 6 hours afforded a crude product. ^{1}H NMR of the crude residue (200 MHz, $CDCl_3$) indicated a mixture of diastereoisomers (7:2 **96a**:**96b**) was present. The residue was purified by column chromatography eluting with 3:7 diethyl ether/petrol 40-60 to afford *rac*-**96** (42 mg, 49 %). Analytical samples of each diastereoisomer were obtained by column chromatography.

Data for **96a** (white solid, 63:37 e.r.)

Melting point: 78-82 ^{o}C (diethyl ether/petrol 40-60);

^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 7.87-7.83 (m, 2H, H_{21}), 7.76-7.73 (m, 1H, H_{16}), 7.73-7.70 (m, 1H, H_{13}), 7.60 (tt, J = 7.3, 1.3 Hz, 1H, H_{23}), 7.54 (dd, J = 7.3, 1.3 Hz, 1H, H_6), 7.51-7.45 (m, 4H, H_{14}, H_{15} and H_{22}), 7.08-6.99 (m, 3H, H_7, H_8 and H_9), 6.80 (dd, J = 2.8, 1.6 Hz, 1H, H_1), 6.51 (dd, J = 3.6, 1.4 Hz, 1H, H_3), 6.28 (dd, J = 3.5, 2.8 Hz, 1H, H_2), 6.27 (d, J = 1.6 Hz, 1H, H_{11}), 5.16 (d, J = 7.9 Hz, 1H, H_{18}), 4.09 (dd, J = 15.0, 1.4 Hz, 1H, H_{19}), 3.64 (dd, J = 15.1, 7.9 Hz, 1H, $H_{19'}$);

^{13}C NMR (126 MHz, $CDCl_3$) δ_C = 141.6 (Quat, C_{17}), 139.4 (Quat, C_{20}), 136.6(0) (Quat, $C_{10/12}$), 136.5(8) (Quat, $C_{10/12}$), 133.9 (CH, C_{23}), 129.9 (CH, C_{15}), 129.3 (CH, C_{22}), 128.2 (CH, C_{14}), 128.0 (CH, C_{21}), 127.8 (Quat, C_4), 126.5 (CH, C_6), 123.9 (CH, C_{16}), 123.8 (CH, C_{13}), 122.9(4) (CH, C_8), 122.8(7) (CH, C_6), 121.5 (Quat, C_5), 118.8 (CH, C_9), 116.4 (CH, C_1), 110.2 (CH, C_2), 103.7 (CH, C_3), 73.5 (CH, C_{11}), 61.2 (CH, C_{18}), 60.3 (CH_2, C_{19});

FTIR (neat) ν/cm^{-1} = 3064, 2924, 1708, 1606, 1577, 1492, 1382, 1306, 1151, 1084;

HRMS (FI^{+}) calculated for $C_{25}H_{20}N_2O_2S$ = 412.1245, mass found = 412.1266;

Chiral HPLC (Chiralpak ADH, 20 % IPA, 80 % hexane, 1.0 mL/min, λ = 245 nm, 20 μL injection) τ_R (major) = 10.4 min, τ_R (minor) = 11.5 min.

Data for **96b** (white solid, 64:36 e.r.)

Melting point: 176-178 ^{o}C (diethyl ether/petrol 40-60);

^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 8.02 (d, J = 7.3 Hz, 1H, H_{16}), 7.83 (dt, J = 8.7, 1.2 Hz, 2H, H_{21}), 7.75 (dd, J = 6.9, 1.4 Hz, 1H, H_{13}), 7.67 (tt, J = 7.5, 1.2 Hz, 1H, H_{23}), 7.59-7.52 (m, 5H, H_6, H_{14}, H_{15} and H_{22}), 7.07 (td, J = 7.3, 1.9 Hz, 1H, H_8), 7.04 (td, J = 7.1, 1.8 Hz, 1H, H_7), 6.81 (dd, J = 2.7, 1.4 Hz, 1H, H_1), 6.75-6.73 (m, 1H, H_9), 6.50 (dd, J = 3.5, 1.3 Hz, 1H, H_3), 6.26 (dd, J = 3.5, 2.8 Hz,

1H, H_2), 6.25 (s, 1H, H_{11}), 5.63 (d. J = 8.8 Hz, 1H, H_{18}), 3.31 (dd, J = 14.7, 1.1 Hz, 1H, H_{19}), 2.96 (dd, J = 14.7, 9.0 Hz, 1H, $H_{19'}$);

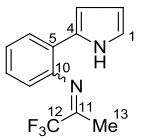
^{13}C NMR (126 MHz, $CDCl_3$) δ_C = 141.8 (Quat, C_{17}), 139.2 (Quat, C_{20}), 135.6 (Quat, C_{10}), 135.0 (Quat, C_{12}), 133.9 (CH, C_{23}), 130.0 (CH, C_{15}), 129.4 (CH, C_{22}), 128.5 (CH, C_{14}), 128.2 (Quat, C_4), 128.1 (CH, C_{21}), 126.8 (CH, C_8), 125.2 (CH, C_{16}), 124.5 (CH, C_{13}), 123.5 (Quat, C_5), 122.9 (CH, $C_{6/7}$), 122.8 (CH, $C_{6/7}$), 119.3 (CH, C_9), 115.4 (CH, C_1), 109.9 (CH, C_2), 104.3 (CH, C_3), 73.2 (CH, C_{11}), 59.4 (CH, C_{18}), 58.8 (CH_2, C_{19});

FTIR (neat) ν/cm^{-1} = 3058, 2918, 1605, 1574, 1548, 1487, 1307, 1153, 1085;

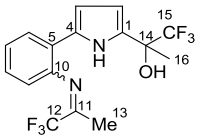
HRMS (ESI^+) calculated for $C_{20}H_{15}N_3$ = 412.1245, mass found = 412.1260;

Chiral HPLC (Chiralpak ODH, 30 % IPA, 70 % hexane, 1.0 mL/min, λ = 245 nm, 50 μL injection) τ_R (minor) = 16.4 min, τ_R (major) = 23.8 min.

2-(1*H*-Pyrrol-2-yl)-*N*-(1,1,1-trifluoropropan-2-ylidene)aniline, 96



96



97

A slurry of pyrroloaniline **50** (300 mg, 1.90 mmol), 1,1,1-trifluoroacetone (1.7 mL, 19.0 mmol) and oven dried anhydrous magnesium sulfate (1.14 g, 9.47 mmol) in anhydrous toluene (45 mL) was stirred at room temperature for 16 hours and then filtered through a plug of Celite® washing with anhydrous diethyl ether. The filtrate was concentrated under reduced pressure. Purification of the residue *via* column chromatography eluting with 1:19 diethyl ether/petrol 40-60 afforded the title compound **96** as a yellow oil (203 mg, 42%) along with by-product **97** as a yellow oil (334 mg, 48 %).

Data for **96**:

^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 9.58 (br s, 1H, N*H*), 7.72 (dd, J = 7.9, 1.3 Hz, 1H, H_6), 7.24 (td, J = 7.6, 1.4 Hz, 1H, H_7), 7.18 (td, J = 7.6, 1.3 Hz, 1H, H_8), 6.89-6.87 (m, 1H, H_1), 6.71 (dd, J = 7.9, 1.3 Hz, 1H, H_9), 6.62-6.59 (m, 1H, H_3), 6.27 (dd, J = 6.1, 2.7 Hz, 1H, H_2), 2.10 (s, 3H, H_{13});

^{13}C NMR (126 MHz, $CDCl_3$) δ_C = 158.0 (q, J = 33.7 Hz, Quat, C_{11}), 142.0 (Quat, C_{10}), 130.3 (Quat, C_4), 127.6 (CH, C_6), 127.1 (CH, C_7), 126.5 (CH, C_8), 125.1 (Quat, C_5), 120.2 (q, J = 278.5 Hz, Quat, C_{12}), 119.9 (CH, C_9), 119.6 (CH, C_3), 109.5 (CH, C_2), 108.0 (CH, C_1), 15.3 (CH_3, C_{13});

^{19}F NMR (470 MHz, $CDCl_3$) δ_F = -74.1 (s);

FTIR (neat) ν/cm^{-1} = 3412 (br), 1683, 1596, 1484, 1433, 1333, 1220, 1186, 1137, 1113, 1038;

HRMS (ESI$^+$) calculated for $C_{13}H_{12}F_3N_2$ = 253.0947, mass found = 253.0956.

Data for **97**:

^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 9.87 (br s, 1H, N*H*), 7.69 (dd, J = 7.6, 1.6 Hz, 1H, H_6), 7.24 (td, J = 7.5, 1.5 Hz, 1H, H_7), 7.20 (td, J = 7.5, 1.5 Hz, 1H, H_8), 6.71 (dd, J = 7.7, 1.4 Hz, 1H, H_9), 6.54 (dd, J = 3.8, 2.8 Hz, 1H, $H_{2/3}$), 6.26 (t, J = 3.2 Hz, 1H, $H_{2/3}$), 2.44 (s, 1H, O*H*), 2.11 (s, 3H, H_{13}), 1.77 (s, 3H, H_{16});

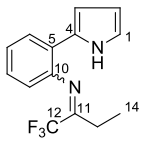
^{13}C NMR (126 MHz, $CDCl_3$) δ_C = 157.8 (q, J = 33.9 Hz, Quat, C_{11}), 141.6 (Quat, C_{10}), 130.5 (Quat, C_4), 129.7 (Quat. C_1), 127.2 (CH, C_6), 126.7 (CH, C_7), 126.3 (CH, C_8), 125.1 (q, J = 284.8 Hz, Quat, C_{15}), 124.1 (Quat, C_5), 119.7 (q, J = 278.4 Hz, Quat, C_{12}), 119.6 (CH, C_9), 107.8 (CH, $C_{2/3}$), 107.7 CH, $C_{2/3}$), 72.1 (q, J = 30.6 Hz, Quat, C_{14}), 22.5 (CH_3, C_{16}), 14.9 (CH_3, C_{13});

^{19}F NMR (470 MHz, $CDCl_3$) δ_F = -74.4 (s), -81.8 (s);

FTIR (neat) ν/cm^{-1} = 3400 (br), 1683, 1504, 1461, 1335, 1221, 1138, 1113, 1055;

HRMS (ESI$^+$) calculated for $C_{16}H_{14}F_6N_2NaO$ = 387.0903, mass found = 387.0895.

2-(1*H*-Pyrrol-2-yl)-*N*-(1,1,1-trifluorobutan-2-ylidene)aniline, 98



A slurry of pyrroloaniline **50** (100 mg, 0.63 mmol), 1,1,1-trifluorobutanone (0.43 mL, 3.17 mmol) and oven dried anhydrous magnesium sulfate (380 mg, 3.16 mmol) in anhydrous toluene (20 mL) was stirred at room temperature for 24 hours. At this point TLC (1:4 diethyl ether/petrol 40-60) showed formation of no new products. 1,1,1-Trifluorobutanone (0.86 mL, 6.3 mmol) and oven dried anhydrous magnesium sulfate (761 mg, 6.32 mmol) were added and the resulting slurry was heated to 50 ^{o}C in a sealed vial for 20 hours, cooled to room temperature and then filtered through a plug of Celite® washing with anhydrous diethyl ether. The filtrate was concentrated under reduced pressure. Purification of the residue *via* column chromatography eluting with 1:19 diethyl ether/petrol 40-60 afforded the title compound **98** as a yellow oil (103 mg, 61 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 9.39 (br s, 1H, N*H*), 7.68 (d, J = 7.8 Hz, 1H, H_6), 7.24-7.14 (m, 2H, H_7 and H_8), 6.87-6.83 (m, 1H, H_1), 6.68 (d, J = 7.6 Hz, 1H, H_9), 6.59-6.54 (m, 1H, H_3), 6.28-6.23 (m, 1H, H_2), 2.44 (q, J = 7.7 Hz, 2H, H_{13}), 1.06 (t, J = 7.6 Hz, 3H, H_{14});

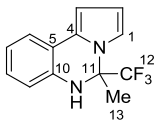
^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 162.8 (q, J = 31.8 Hz, Quat, C_{11}), 142.2 (Quat, C_{10}), 129.7 (Quat, C_4), 127.2 (CH, C_6), 126.2 (CH, C_7), 126.0 (CH, C_8), 123.9 (Quat, C_5), 119.9 (q, J = 280.0 Hz, Quat, C_{12}), 119.0 (CH, $C_{1/9}$), 118.9 (CH, $C_{1/9}$), 109.1 (CH, C_2), 107.6 (CH, C_3), 22.3 (CH_2, C_{13}), 10.7 (CH_3, C_{14});

^{19}F NMR (376 MHz, $CDCl_3$) δ_F = -71.4 (s);

FTIR (neat) ν/cm^{-1} = 3416 (br), 2987, 1679, 1484, 1342, 1216, 1184, 1126, 1038;

HRMS (ESI^+) calculated for $C_{14}H_{13}F_3N_2Na$ = 289.0923, mass found = 289.0928.

5-Methyl-5-(trifluoromethyl)-5,6-dihydropyrrolo[1,2-*c*]quinazoline, 99



Asymmetric: Imine **96** (100 mg, 0.40 mmol) was dissolved in toluene (4.0 mL) and *N*-benzylcinchoninium chloride (17 mg, 0.040 mmol) was added. The resulting stirred suspension was cooled to -15 ^{o}C and aqueous potassium hydroxide (50 % w/w, 0.22 mL, 3.9 mmol) precooled to -15 ^{o}C was added. The biphasic reaction mixture was rapidly stirred at -15 ^{o}C for 1 hour. After this time, water was added and the solution was allowed to warm to room temperature. The organic layer was separated and the aqueous layer was extracted three times with dichloromethane. The combined organic extracts were dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. Purification of the residue *via* column chromatography eluting with 1:9 diethyl ether/petrol 40-60 afforded the title compound **99** as a white solid (96 mg, 96 %, 99:1 e.r.).

Racemic: Imine **96** (66 mg, 0.26 mmol) was dissolved in toluene (2.6 mL) and tetrabutylammonium bromide (8 mg, 0.02 mmol) and aqueous potassium hydroxide (50 % w/w, 0.15 mL, 2.6 mmol) were added. The biphasic reaction mixture was rapidly stirred at room temperature for 10 minutes. Water was added and the organic layer was separated. The aqueous layer was extracted three times with dichloromethane and the combined organic extracts were dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. Purification of the residue *via* column chromatography eluting with 1:9 diethyl ether/petrol 40-60 afforded the title compound *rac*-**99** as a white solid (62 mg, 94 %).

Melting Point: 101-104 ^{o}C (diethyl ether/petrol 40-60);

^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 7.48 (dd, J = 7.8, 1.3 Hz, 1H, H_6), 7.05 (td, J = 7.7, 1.3 Hz, 1H, H_8), 6.88 (td, J = 7.8, 1.1 Hz, 1H, H_7), 6.85-6.82 (m, 1H, H_1), 6.71 (dd, J = 7.8, 0.7 Hz, 1H, H_9), 6.57 (dd, J = 3.7, 1.5 Hz, 1H, H_3), 6.37 (t, J = 3.3 Hz, 1H, H_2), 4.36 (br s, 1H, N*H*), 1.99-1.97 (m, 3H, H_{13});

^{13}C NMR (126 MHz, $CDCl_3$) δ_C = 136.1 (Quat, C_{10}), 128.3 (Quat, C_4), 127.0 (CH, C_8), 124.7 (q, J = 294.8 Hz, Quat, C_{12}), 122.2 (CH, C_6), 120.4 (CH, C_7), 117.3 (CH, C_1), 116.4 (Quat, C_5), 113.9 (CH. C_9), 110.7 (CH, C_2), 103.6 (CH, C_3), 70.5 (q, J = 30.4 Hz, Quat, C_{11}), 22.0 (CH_3, C_{13});

^{19}F NMR (376 MHz, $CDCl_3$) δ_F = -81.6 (s);

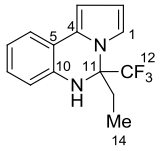
FTIR (neat) ν/cm^{-1} = 3395 (br), 3065, 1614, 1593, 1493, 1307, 1284, 1261, 1247, 1165, 1127, 1094;

HRMS (ESI^+) calculated for $C_{13}H_{11}F_3N_2Na$ = 275.0767, mass found = 257.0770;

Chiral HPLC (Chiralpak IA, 1. 5 % IPA, 98.5 % hexane, 1.0 mL/min, λ = 323 nm, 20 μL injection) τ_R (major) = 14.9 min, τ_R (minor) = 18.9 min;

$[\alpha]_D^{20}$ = +7 (*c* = 1.00 , $CHCl_3$).

5-Ethyl-5-(trifluoromethyl)-5,6-dihydropyrrolo[1,2-*c*]quinazoline, 100



Asymmetric: Imine **98** (81 mg, 0.30 mmol) was dissolved in toluene (3.0 mL) and *N*-benzylcinchoninium chloride (13 mg, 0.031 mmol) was added. The resulting stirred suspension was cooled to -15 ^{o}C and aqueous potassium hydroxide (50 % w/w, 0.17 mL, 3.0 mmol) precooled to -15 ^{o}C was added. The biphasic reaction mixture was rapidly stirred at -15 ^{o}C for 4 hours. After this time, water was added and the solution was allowed to warm to

room temperature. The organic layer was separated and the aqueous layer was extracted three times with dichloromethane. The combined organic extracts were dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. Purification of the residue *via* column chromatography eluting with 7:93 diethyl ether/petrol 40-60 afforded the title compound **100** as a white solid (73 mg, 90 %, 98:2 e.r.).

Racemic: Imine **98** (16 mg, 0.060 mmol) was dissolved in toluene (1.0 mL) and tetrabutylammonium bromide (2 mg, 0.006 mmol) and aqueous potassium hydroxide (50 % w/w, 34 μL, 0.6 mmol) were added. The biphasic reaction mixture was rapidly stirred at room temperature for 10 minutes. Water was added and the organic layer was separated. The aqueous layer was extracted three times with dichloromethane and the combined organic extracts were dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. Purification of the residue *via* column chromatography eluting with 1:19 diethyl ether/petrol 40-60 afforded the title compound *rac*-**100** as a white solid (15 mg, 94 %).

Melting Point: 175-178 ^{o}C (diethyl ether/petrol 40-60);

^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 7.46 (dd, J = 7.6, 1.3 Hz, 1H, H_6), 7.04 (td, J = 7.6, 1.4 Hz, 1H, H_8), 6.85 (td, J = 7.5, 1.0 Hz, 1H, H_7), 6.81-6.79 (m, 1H, H_1), 6.69 (dd, J = 8.0, 0.9 Hz, 1H, H_9), 6.56 (dd, J = 1.4, 3.7 Hz, 1H, H_3), 6.37 (t, J = 3.4 Hz, 1H, H_2), 4.13 (br s, 1H, N*H*), 2.53 (dq, J = 14.8, 7.4 Hz, 1H, H_{13}), 2.04 (dq, J = 14.8, 7.5 Hz, 1H, $H_{13'}$), 1.10 (t, J = 7.3 Hz, 3H, H_{14});

^{13}C NMR (126 MHz, $CDCl_3$) δ_C = 136.5 (Quat, C_{10}), 128.6 (Quat, C_4), 127.0 (CH, C_8), 125.0 (q, J = 300.9 Hz, Quat, C_{12}), 122.1 (CH, C_6), 120.0 (CH, C_7), 117.4 (CH, C_1), 115.6 (Quat, C_5), 113.6 (CH, C_9), 110.9 (CH, C_2), 103.3 (CH, C_3), 73.8 (q, J = 29.2 Hz, Quat, C_{11}), 25.9 (CH_2, C_{13}), 5.8 (CH_3, C_{14});

^{19}F NMR (470 MHz, $CDCl_3$) δ_F = -81.3 (s);

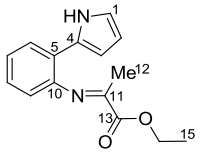
FTIR (neat) ν/cm^{-1} = 3379 (br), 2982, 1617, 1596, 1494, 1310, 1258, 1175, 1161, 1152, 1122, 1080;

HRMS (ESI^+) calculated for $C_{14}H_{13}F_3N_2Na$ = 289.0923, mass found = 289.0923;

Chiral HPLC (Chiralpak ODH, 50 % IPA, 50 % hexane, 1.0 mL/min, λ = 225 nm, 10 μL injection) τ_R (major) = 3.9 min, τ_R (minor) = 5.2 min;

$[\alpha]_D^{20}$ = -31.7 (*c* = 1.00 , $CHCl_3$).

Ethyl 2-((2-(1H-pyrrol-2-yl)phenyl)imino)propanoate, 101



A slurry of pyrroloaniline **50** ((50 mg, 0.32 mmol)), ethyl pyruvate (0.18 mL, 1.6 mmol) and oven dried anhydrous magnesium sulfate (190 mg, 1.6 mmol) in anhydrous toluene (10 mL) was stirred at room temperature for 2 hours and then filtered through a plug of Celite® washing with anhydrous diethyl ether. The filtrate was concentrated under reduced pressure. Purification of the residue *via* column chromatography eluting with a gradient from petrol 40-60 to 1:4 diethyl ether/petrol 40-60 afforded the title compound **101** as a yellow oil (58 mg, 72 %).

^{1}H NMR (500 MHz, $CDCl_3$)* δ_H = 10.53 (br s, 1H, N*H*), 7.77 (dd, J = 7.8, 1.3 Hz, 1H, H_6), 7.21 (td, J = 7.6, 1.4 Hz, 1H, H_7), 7.14 (td, J = 7.6, 1.5 Hz, 1H, H_8), 6.87 (td, J = 2.6, 1.5 Hz, 1H, H_1), 6.74 (dd, J = 7.7, 1.1 Hz, 1H, H_9), 6.69 (ddd, J = 3.7, 2.4, 1.4 Hz, 1H, H_3), 6.27 (dt, J = 3.5, 2.7 Hz, 1H, H_2), 4.44 (q, J = 7.0 Hz, 2H, H_{14}), 2.23 (s, 3H, H_{12}), 1.49 (t, J = 6.9 Hz, 3H, H_{15});

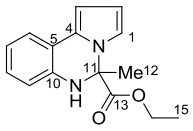
* The ^{1}H NMR also contained c.a. 6 % of an uncharacterised impurity with peaks consistent with an alternative stereoisomer of the imine; δ_H = 4.34 (q, J = 7.2 Hz, 2H), 2.49 (s, 3H), 1.39 (t, J = 7.3 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C = 164.6 (Quat, C_{13}), 159.2 (Quat, C_{11}), 142.2 (Quat, C_{10}), 130.5 (Quat, C_4), 126.6 (CH, C_7), 126.4 (CH, C_6), 125.4 (CH, C_8), 125.2 (Quat, C_5), 119.5 (CH, C_9), 119.1 (CH, C_1), 108.9 (CH, C_2), 107.1 (CH, C_3), 62.3 (CH_2, C_{14}), 17.0 (CH_3, C_{12}), 14.2 (CH_3, C_{15});

FTIR (neat) ν/cm^{-1} = 3338 (br, N-H), 2982 (C-H), 1723 (C=O), 1654 (C=N), 1593, 1480, 1365, 1290, 1142, 1109, 1038;

HRMS (ESI^+) calculated for $C_{15}H_{16}N_2NaO_2$ = 279.1104, mass found = 279.1103.

Ethyl 5-methyl-5,6-dihydropyrrolo[1,2-*c*]quinazoline-5-carboxylate, 104



Asymmetric: Imine **101** (44 mg, 0.17 mmol) was dissolved in toluene (1.7 mL) and *N*-benzylcinchoninium chloride (7 mg, 0.02 mmol) and aqueous potassium hydroxide (50 % w/w, 0.10 mL, 1.8 mmol) was added. The biphasic reaction mixture was rapidly stirred at room temperature for 2 hours. After this time, water was added and the solution was allowed to warm to room temperature. The organic layer was separated and the aqueous layer was extracted three times with dichloromethane. The combined organic extracts were dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. Purification of the residue *via* column chromatography eluting with dichloromethane afforded the title compound **104** as a colourless oil (23 mg, 52 %, 63:37 e.r.).

Racemic: Imine **101** (23 mg, 0.090 mmol) was dissolved in toluene (0.9 mL) and tetrabutylammonium bromide (3 mg, 0.009 mmol) and aqueous potassium hydroxide (50 % w/w, 50 μL, 0.9 mmol) were added. The biphasic reaction mixture was rapidly stirred at room temperature for 30 minutes. Water was added and the organic layer was separated. The aqueous layer was extracted three times with dichloromethane and the combined organic

extracts were dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. An analytical HPLC sample of *rac*-**104** was obtained by small scale preparative TLC (1:1 diethyl ether/petrol 40-60).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 7.46 (dd, J = 7.7, 1.1 Hz, 1H, H_6), 7.04 (td, J = 7.6, 1.2 Hz, 1H, H_8), 6.90-6.86 (m, 2H, H_1 and H_7), 6.76 (dd, J = 7.9, 0.6 Hz, 1H, H_9), 6.54 (dd, J = 3.6, 1.4 Hz, 1H, H_3), 6.34 (dd, J = 3.6, 3.0 Hz, 1H, H_2), 4.69 (br s, N*H*), 4.06 (dq, J = 11.5, 7.3 Hz, 1H, H_{14}), 4.03 (dq, J = 11.3, 7.3 Hz, 1H, $H_{14'}$), 2.02 (s, 3H, H_{12}), 1.07 (t, J = 7.1 Hz, 3H, H_{15});

^{13}C NMR (126 MHz, $CDCl_3$) δ_C = 172.0 (Quat, C_{13}), 137.6 (Quat, C_{10}), 128.2 (Quat, C_4), 126.7 (CH, C_8), 122.4 (CH, C_6), 120.7 (CH, C_7), 117.5 (Quat, C_5), 117.2 (CH, C_1), 115.0 (CH, C_9), 109.8 (CH, C_2), 103.4 (CH, C_3), 72.1 (Quat, C_{11}), 62.1 (CH_2, C_{14}), 24.3 (CH_3, C_{12}), 14.0 (CH_3, C_{15});

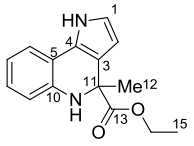
FTIR (neat) ν/cm^{-1} = 3363 (br, N-H), 2983 (C-H), 1731 (C=O), 1614, 1591, 1491, 1037, 1240, 1106;

HRMS (ESI$^+$) calculated for $C_{15}H_{16}N_2NaO_2$ = 279.1104, mass found = 279.1094;

Chiral HPLC (Chiralpak ADH, 15 % IPA, 85 % hexane, 1.0 mL/min, λ = 222 nm, 20 μL injection) τ_R (major) = 6.9 min, τ_R (minor) = 7.8 min;

$[\alpha]_D^{20}$ = + 21 (c = 1.00, $CHCl_3$).

Ethyl 4-methyl-4,5-dihydro-1H-pyrrolo[3,2-c]quinoline-4-carboxylate, 102



Imine **101** (45 mg, 0.18 mmol) was dissolved in dichloromethane (1.8 mL) and scandium(III) triflate (9 mg, 0.02 mmol) was added. The reaction mixture was stirred at room temperature for 30 minutes and then concentrated under reduced pressure. Purification of the residue *via*

column chromatography eluting with dichloromethane afforded the title compound **102** as a yellow oil (42 mg, 93 %).

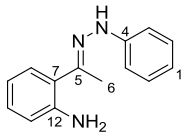
^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 8.36 (br s, 1H, pyrrole N*H*), 7.02 (dd, J = 7.9, 1.3 Hz, 1H, H_6), 6.98 (td, J = 7.6, 1.4 Hz, 1H, H_8), 6.70 (t, J = 2.7 Hz, 1H, H_2), 6.69-6.66 (m, 2H, H_7 and H_9), 6.29 (t, J = 2.5 Hz, 1H, H_1), 4.53 (br s, 1H, aniline N*H*), 4.15 (dq, J = 10.9, 7.2 Hz, 1H, H_{14}), 4.08 (dq, J = 11.0, 7.1 Hz, 1H, $H_{14'}$), 1.79 (s, 3H, H_{12}), 1.21 (t, J = 7.3 Hz, 3H, H_{15});

^{13}C NMR (126 MHz, $CDCl_3$) δ_C = 175.3 (Quat, C_{13}), 141.2 (Quat, C_{10}), 126.9 (CH, C_8), 125.0 (Quat, C_4), 118.8 (CH, $C_{2/6}$), 118.7 (CH, $C_{2/6}$), 118.2 (CH, $C_{7/9}$), 117.5 (Quat, C_3), 114.8 (Quat, C_5), 113.9 (CH, $C_{7/9}$), 106.8 (CH, C_1), 61.4 (CH_2, C_{14}), 59.8 (Quat, C_{11}), 28.4 (CH_3, C_{12}), 14.1 (CH_3, C_{15});

FTIR (neat) ν/cm^{-1} = 3376 (br), 2980, 1714, 1621, 1517, 1448, 1371, 1310, 1239, 1159, 1105, 1018;

HRMS (ESI$^+$) calculated for $C_{15}H_{16}N_2NaO_2$ = 279.1104, mass found = 279.1108.

2-(1-(2-Phenylhydrazono)ethyl)aniline, 106



This compound was prepared according to a literature procedure.[42a]

A solution of 2-acetylaniline (5.85 g, 43.3 mmol) in ethanol (300 mL) was stirred at room temperature. Phenylhydrazine (4.26 mL, 43.3 mmol) and glacial acetic acid (5.85 mL, 102 mmol) were added sequentially and the resulting stirred solution was heated to reflux for 3 hours. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue was purified by recrystallization from ethanol to afford the title compound **106** as a yellow solid (7.46 g, 77 %). The data matched that previously reported in the literature.[110]

Melting point 98-100 °C (ethanol) [lit. 104-106 °C];[110]

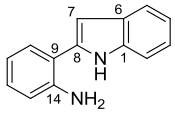
^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.42-7.38 (m, 1H, H_8), 7.37-7.31 (m, 2H, H_2), 7.28 (br s, 1H, N*H* hydrazine), 7.17-7.09 (m, 3H, H_3 and H_{10}), 6.95 (tt, J = 7.4, 1.1 Hz, 1H, H_1), 6.81-6.76 (m, 2H, H_9 and H_{11}), 5.86 (br s, 2H, NH_2 aniline), 2.33 (s, 3H, H_6);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 145.7 (Quat), 145.4 (Quat), 145.1 (Quat), 129.4 (CH, C_2), 128.7 (CH, C_{10}), 128.3 (CH, C_8), 121.1 (Quat, C_7), 120.3 (CH, C_1), 116.9 (CH, C_9), 116.8 (CH, C_{11}), 113.0 (CH, C_3), 13.8 (CH_3, C_6);

FTIR (neat) ν/cm^{-1} = 3454, 3332, 3054, 1601, 1585, 1491, 1445, 1316, 1251, 1161, 1135, 1074;

LRMS (ESI$^+$) 226 ([M + H]$^+$).

2-(1*H*-Indol-2-yl)aniline, 107



This compound was prepared according to a literature procedure.[42b]

Methanesulfonic acid (70 mL) was stirred and heated to 80 °C. Phosphorus pentoxide (9.45 g, 66.6 mmol) was added in one portion and the resulting suspension was stirred until a homogeneous solution was formed (c.a. 5 min). After this time, **106** (7.00 g, 31.1 mmol) was added portionwise over 15 minutes. The reaction mixture was stirred at 80 °C for a further 30 minutes and then cooled to room temperature an poured over a mixture of crushed ice (c.a. 500 g) and sodium hydroxide pellets (45.5 g). A precipitate was formed, which was isolated by vacuum filtration and washed with water (2 x 20 mL). The residue was purified *via* recrystallization from ethanol to afford the title compound **107** as a beige solid (3.75 g, 58 %). The data matched that previously reported in the literature.[42b]

Melting point 146-148 °C (ethanol) [lit. 146 °C];[42b]

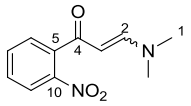
^{1}H NMR (400 MHz, d_6-DMSO) δ_H = 11.27 (s, 1H, N*H* indole), 7.56 (d, J = 7.8 Hz, 1H, H_{Ar}), 7.45-7.38 (m, 2H, H_{Ar}), 7.14-7.07 (m, 2H, H_{Ar}), 7.03 (t, J = 7.5 Hz, 1H, H_{Ar}), 6.87 (d, J = 8.1 Hz, 1H, H_{Ar}), 6.75 (m, 2H, H_7 and H_{Ar}), 5.22 (s, 2H, N*H* aniline);

^{13}C NMR (101 MHz, d_6-DMSO) δ_C = 146.1 (Quat, C_{Ar}), 136.8 (Quat, C_{Ar}), 136.6 (Quat, C_{Ar}), 129.3 (CH, C_{Ar}), 129.1 (Quat, C_{Ar}), 128.8 (CH, C_{Ar}), 121.5 (CH, C_{Ar}), 120.2 (CH, C_{Ar}), 119.5 (CH, C_{Ar}), 117.6 (Quat C_{Ar}), 117.1 (CH, C_{Ar}), 116.2 (CH, C_{Ar}), 111.6 (CH, C_{Ar}), 100.4 (CH, C_7);

FTIR (neat) ν/cm^{-1} = 3378, 3304, 3181, 1614, 1490, 1449, 1410, 1347, 1296, 1242, 1154;

LRMS (ESI$^+$) 209 ([M + H]$^+$).

1-(2-Aminophenyl)-3-(dimethylamino)prop-2-en-1-one, 109



This compound was prepared according to a literature procedure.[43]

A solution of *ortho*-nitroacetophenone (5.00 g, 30.3 mmol) and *N*,*N*-dimethylformamide dimethyl acetal (3.64 mL, 27.4 mmol) in *N*,*N*-dimethylformamide (13.5 mL) was heated to 100 °C for 2 hours and then cooled to room temperature and concentrated under reduced pressure. The resulting solid was washed with diethyl ether to afford the title compound **109** as a yellow solid (5.26 g, 87 %). The spectral data matched that previously reported in the literature.[111]

Melting point 118-120 °C (*N*,*N*-dimethylformamide) [lit. 124-127 °C];[112]

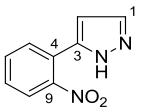
^{1}H NMR (400 MHz, $CDCl_3$)* δ_H = 7.94 (d, J = 6.6 Hz, 1H, H_{Ar}), 7.62 (dd, J = 7.5, 1.1 Hz, 1H, H_{Ar}), 7.53-7.54 (m, 2H, H_{Ar}), 5.28 (d, J = 12.5 Hz, 1H, H_3), 3.09 (s, 3H, H_1), 2.87 (s, 3H, $H_{1'}$);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 154.8, 147.3, 133.1 (CH, C_{Ar}), 129.4 (CH, C_{Ar}), 128.9 (CH, C_{Ar}), 124.2 (CH, C_{Ar}), 45.2 (CH_3, C_1), 37.3 (CH_3, $C_{1'}$);

FTIR (neat) ν/cm^{-1} = 2918, 1644, 1578, 1551, 1521, 1419, 1350, 1270, 1239;

LRMS (ESI$^+$) 221 ([M + H]$^+$).

5-(2-Nitrophenyl)-1*H*-pyrazole, 110



This compound was prepared according to a literature procedure.[43]

A stirred solution of **109** (5.21 g, 23.7 mmol) and hydrazine monohydrate (1.26 mL, 26.0 mmol) in ethanol (24 mL) was heated to reflux for 16 hours and then cooled to room temperature and concentrated under reduced pressure. Purification of the residue *via* column chromatography eluting with 3:7 ethyl acetate/petrol 40-60 afforded the title compound **110** as a brown solid (3.95 g, 88 %). The spectral data matched that previously reported in the literature.[113]

Melting point 60-62 ^{o}C (ethyl acetate/petrol 40-60) [lit. 75-78 ^{o}C];[113]

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 11.17 (br s, 1H, N*H*), 7.73 (dd, J = 8.1, 1.2 Hz, 1H, H_{Ar}), 7.70 (dd, J = 7.7, 1.3 Hz, 1H, H_{Ar}), 7.61-7.57 (m, 2H, H_1 and H_{Ar}), 7.48 (td, J = 7.7, 1.5 Hz, 1H, H_{Ar}), 6.49 (d, J = 2.4 Hz, 1H, H_2);

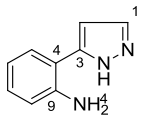
* In the ^{1}H spectrum the signal for H_2 was absent, which is consistent with the data previously reported in the literature. In the ^{13}C spectrum, several signals described in the literature were also absent (188.5, 138.5, 95.0). These peaks were however described by the authors as broad.

^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 149.2 (Quat, C_{Ar}), 146.1 (Quat, C_{Ar}), 132.0 (CH, C_{Ar}), 130.9 (CH, C_{Ar}), 130.7 (CH, C_1), 128.7 (CH, C_{Ar}), 126.9 (Quat, C_{Ar}), 123.6 (CH, C_{Ar}), 104.7 (CH, C_2);

FTIR (neat) ν/cm^{-1} =3175 (br), 2959, 1522, 1354;

LRMS (ESI$^-$) 188 ([M - H]$^-$).

2-(1*H*-Pyrazol-5-yl)aniline, 111



A solution of nitro compound **110** (1.00 g, 5.29 mmol) in anhydrous methanol (30 mL) was stirred at room temperature and Pd/C (100 mg, 10 wt. %) was added. The resulting stirred suspension was sparged with hydrogen for 30 minutes and then stirred under an atmosphere of hydrogen (balloon pressure) for 5 hours. The reaction mixture was filtered through a plug of celite, washing with dichloromethane and the filtrate was concentrated under reduced pressure to afford the title compound **111** as a pale purple solid (820 mg, 97 %) which was used without further purification in subsequent reactions. The spectral data matched that previously reported in the literature.[113]

Melting point 118-121 ^{o}C (dichloromethane) [lit. 124-126 ^{o}C];[113]

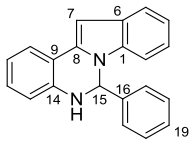
^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.51 (d, J = 2.4 Hz, 1H, H_1), 7.44 (dd, J = 8.1, 1.7 Hz, 1H, H_5), 7.05 (ddd, J = 8.0, 7.3, 1.5 Hz, 1H, H_7), 6.73-6.67 (m, 2H, H_6 and H_8), 6.56 (d, J = 2.4 Hz, 1H, H_2), 5.90 (br s, 2H, NH_2);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 151.2 (Quat, C_{Ar}), 144.6 (Quat, C_{Ar}), 130.0 (CH, C_1), 128.7 (CH, C_7), 128.5 (CH, C_5), 117.6 (CH, C_6), 116.6 (CH, C_8), 116.5 (Quat, C_{Ar}), 103.4 (CH, C_2);

FTIR (neat) ν/cm^{-1} = 3406, 3264, 3174 (br), 2964, 2918, 1719, 1607, 1529, 1505, 1470, 1445;

LRMS (ESI$^-$) 158 ([M - H]$^-$).

6-Phenyl-5,6-dihydroindolo[1,2-*c*]quinazoline, 113



Imine Formation:

Imine formation was carried out according to a literature procedure.[44]

A slurry of 2-(1*H*-indol-2-yl)aniline **107** (100 mg, 0.48 mmol), benzaldehyde (56 mg, 0.53 mmol), pyrrolidine (3 mg, 0.04 mmol) and oven dried 3 Å molecular sieves (408 mg) in anhydrous dichloromethane (4.8 mL) was stirred in a sealed vial at 60 ^{o}C for 16 hours. After this time, the reaction mixture was cooled to room temperature and filtered through a plug of Celite® washing with anhydrous dichloromethane. The filtrate was concentrated under reduced pressure to afford **112** as a yellow solid (137 mg) which was used without further purification in subsequent asymmetric and racemic cyclization reactions.

Asymmetric Cyclization: The crude imine **112** thus obtained (106 mg) was dissolved in toluene (3.6 mL) and *N*-benzylcinchoninium chloride (15 mg, 0.036 mmol) was added. Aqueous potassium hydroxide (50 % w/w, 0.20 mL, 3.6 mmol) was added and the biphasic reaction mixture was rapidly stirred at room temperature for 20 hours. After this time, water was added. The organic layer was separated and the aqueous layer was extracted with dichloromethane. The combined organic extracts were dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. Purification of the residue *via* column chromatography eluting with 1:1 dichloromethane/petrol 40-60 afforded the title compound **113** as a white solid (84 mg, 76 % from **107**, 63:37 e.r.).

Racemic Cyclization: The crude imine **112** thus obtained (31 mg) was dissolved in toluene (1.7 mL) and tetrabutylammonium bromide (5 mg, 0.02 mmol) was added. Aqueous potassium hydroxide (50 % w/w, 0.10 mL, 1.8 mmol) was added and the biphasic reaction mixture was rapidly stirred at room temperature for 45 minutes. After this time, water was added. The organic layer was separated and the aqueous layer was extracted with dichloromethane. The combined organic extracts were dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. Purification of the residue *via* column chromatography eluting with 1:1 dichloromethane/petrol 40-60 afforded the title compound *rac*-**113** as a white solid (24 mg, 74 % from **107**).

Melting point 208-210 ^{o}C (dichloromethane/petrol 40-60);

^{1}H NMR (400 MHz, d_6-DMSO) δ_H = 7.74 (dd, J = 7.1, 1.1 Hz, 1H, H_{10}), 7.61-7.56 (m, 1H, H_5), 7.40 (d, J = 2.0 Hz, 1H, N*H*), 7.37-7.32 (m, 1H, H_2), 7.25-7.16 (m, 3H, $H_{17/18}$ and H_{19}), 7.12-7.01 (m, 5H, H_3, H_4, H_{12} and $H_{17/18}$), 6.99 (d, J = 2.2 Hz, 1H, H_{15}), 6.98 (s, 1H, H_7), 6.82 (dd, J = 8.1, 0.7 Hz, 1H, H_{13}), 6.76 (td, J = 7.5, 0.7 Hz, 1H, H_{11});

^{13}C NMR (126 MHz, d_6-DMSO) δ_C = 142.4 (Quat), 140.5 (Quat), 135.2 (Quat), 133.9 (Quat), 129.4 (CH, C_{12}), 129.2 (Quat), 128.9 (CH, $C_{17/18}$), 128.5 (CH, C_{19}), 125.9 (CH, $C_{17/18}$), 124.4 (CH, C_{10}), 121.7 (CH, $C_{3/4}$), 120.5 (CH, $C_{3/4/5}$), 120.4 (CH, $C_{3/4/5}$), 118.6 (CH, C_{11}), 115.5 (CH, C_{13}), 115.2 (Quat), 110.6 (CH, C_2), 95.5 (CH, C_7), 66.7 (CH, C_{15});

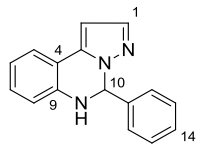
FTIR (neat) ν/cm^{-1} = 3397, 3049, 1609, 1584, 1547, 1486, 1455, 1317, 1258, 1069;

HRMS (ESI^{+}) calculated for $C_{21}H_{17}N_2$ = 297.1386, mass found = 297.1382;

Chiral HPLC (Chiralpak IC, 30 % IPA, 70 % hexane, 1.0 mL/min, λ = 350 nm, 20 μL injection) τ_R (minor) = 6.2 min, τ_R (major) = 16.5 min;

$[\alpha]_D^{20}$ = +100 (*c* = 1.00, $CHCl_3$).

5-Phenyl-5,6-dihydropyrazolo[1,5-c]quinazoline, 115



A slurry of aniline **111** (50 mg, 0.31 mmol), benzaldehyde (41.5 μL, 0.41 mmol) and oven dried anhydrous magnesium sulfate (189 mg, 1.57 mmol) in anhydrous toluene (10 mL) was stirred at room temperature for 16 hours. The reaction mixture was filtered through a plug of Celite® washing with anhydrous diethyl ether. The filtrate was concentrated under reduced pressure. Purification of the residue *via* column chromatography eluting with 1:4 ethyl acetate/petrol 40-60 afforded the title compound **115** as an off white solid (75 mg, 97 % yield).

Melting point 84-90 ^{o}C (ethyl acetate/petrol 40-60);

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.42 (d, J = 2.0 Hz, 1H, H_1), 7.40 (dd, J = 7.9, 1.3 Hz, 1H, H_5), 7.23 (s, 5H, H_{12}, H_{13} and H_{14}), 7.02 (ddd, J = 7.9, 7.5, 1.5 Hz, 1H, H_7), 6.78 (td, J = 7.5, 1.1 Hz, 1H, H_6), 6.57 (d, J = 7.8 Hz, 1H, H_8), 6.46 (d, J = 2.0 Hz, 1H, H_2), 6.37 (s, 1H, H_{10}), 4.58 (br s, 1H, N*H*);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 140.3 (CH, C_1), 139.6 (Quat, C_{Ar}), 139.2 (Quat, C_{Ar}), 137.5 (Quat, C_{Ar}), 129.4 (CH, $C_{7/14}$), 129.4 (CH, $C_{7/14}$), 128.9 (CH, $C_{12/13}$), 127.1 (CH, $C_{12/13}$), 124.2 (CH, C_5), 119.9 (CH, C_6), 115.0 (CH, C_8), 114.3 (Quat, C_{Ar}), 99.8 (CH, C_2), 72.6 (CH, C_{10});

FTIR (neat) ν/cm^{-1} = 3264, 3032, 1617, 1496, 1480, 1424, 1297, 1269;

HRMS (ESI^{+}) calculated for $C_{16}H_{14}N_3$ = 248.1182, mass found = 248.1175.

Table 2.3 – Asymmetric conditions for one-pot imine formation and *N*1-cyclization

Entry 1: A slurry of aniline **111** (10 mg, 0.063 mmol), benzaldehyde (7.0 μL, 0.069 mmol) and oven dried anhydrous magnesium sulfate (38 mg, 0.31 mmol) in d_8-toluene (1 mL) was stirred at room temperature for 3 hours. The reaction mixture was filtered through a small plug of Celite®. Analysis of the filtrate by ^{1}H NMR indicated the presence of a 64:36 ratio of **115**:**111**.

Entry 2: A solution of aniline **111** (10 mg, 0.063 mmol) and benzaldehyde (7.0 μL, 0.069 mmol) in d_8-toluene (1 mL) was stirred at room temperature for 3 hours. The reaction mixture was filtered through a small plug of Celite®. Analysis of the filtrate by ^{1}H NMR indicated the presence of a 23:77 ratio of **115**:**111**.

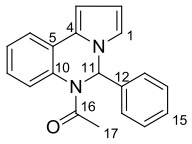
Entry 3: A solution of aniline **111** (10 mg, 0.063 mmol), benzaldehyde (7.0 μL, 0.069 mmol) and cinchonidine (2 mg, 0.006 mmol) in d_8-toluene (1 mL) was stirred at room temperature for 3 hours. The reaction mixture was filtered through a small plug of Celite®. Analysis of the filtrate by ^{1}H NMR indicated the presence of a <5:95 ratio of **115**:**111**.

Entries 4-6: A slurry of scandium(III) triflate (31 mg, 0.063 mmol), PyBox (23 mg, 0.063 mmol) and 3Å molecular sieves (100 mg) in *the appropriate solvent* (3 mL) was stirred at room temperature for 2 hours. A solution of aniline **111** (100 mg, 0.63 mmol) in *the appropriate solvent* (2.5 mL) was added followed by a solution of benzaldehyde (76 μL, 0.69 mmol) in *the appropriate solvent* (0.8 mL). The reaction mixture was stirred at room temperature for *the appropriate time* and then concentrated under reduced pressure. Purification of the residue *via* column chromatography afforded **115**.

Entries 7-8: A solution of aniline **111** (10 mg, 0.063 mmol), benzaldehyde (14 μL, 0.12 mmol) and *the appropriate catalyst* (0.003 mmol) in dichloromethane (1 mL) was stirred at room temperature for 1 hour and then concentrated under reduced pressure. The reaction mixture was filtered through a plug of Celite® washing with anhydrous diethyl ether. The filtrate was

concentrated under reduced pressure. ^{1}H NMR of the residue indicated the presence of a >95:5 ratio of **115**:**111**. An analytical HPLC sample of **115** was obtained by preparative TLC (3:7 ethyl acetate/petrol 40-60).

1-(5-Phenylpyrrolo[1,2-*c*]quinazolin-6(5*H*)-yl)ethanone, 120



Asymmetric: Asymmetric cyclization product **52** (50 mg, 0.20 mmol, 86:14 e.r.) was dissolved in a mixture of acetic anhydride (1.0 mL) and pyridine (1 mL). The resulting stirred solution was heated to 60 ^{o}C in a sealed vial for 3 hours. After this time, the solution was cooled to room temperature, diluted with diethyl ether and washed three times with saturated aqueous copper sulfate and then with brine. The resulting organic phase was dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. Purification of the residue *via* column chromatography eluting with 1:4 diethyl ether/petrol 40-60 afforded the title compound **120** as a white solid (58 mg, 99 %, 85:15 e.r.).

Racemic: Racemic cyclization product *rac*-**52** (100 mg, 0.41 mmol) was dissolved in a mixture of acetic anhydride (2.0 mL) and pyridine (2.0 mL). The resulting stirred solution was heated to 60 ^{o}C in a sealed vial for 3 hours. After this time, the solution was cooled to room temperature, diluted with diethyl ether and washed three times with saturated aqueous copper sulfate and then with brine. The resulting organic phase was dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. Purification of the residue *via* column chromatography eluting with 1:4 diethyl ether/petrol 40-60 afforded the title compound *rac*-**120** as a white solid (113 mg, 97 %).

Melting point = 148-149 ^{o}C (diethyl ether/petrol 40-60);

^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 7.97 (s, 1H, H_{11}), 7.56 (d, J = 7.6 Hz, 1H, H_6), 7.19-7.12 (m, 4H, H_7, H_{14} and H_{15}), 7.07-7.01 (m, 2H, H_8 and H_9), 6.94 (dd, J = 2.7, 1.4 Hz, 1H, H_1), 6.81-6.77 (m, 2H, H_{13}), 6.66 (dd, J = 3.8, 1.3 Hz, 1H, H_3), 6.36 (dd, J = 2.5, 3.4 Hz, 1H, H_2), 2.28 (s, 3H, H_{17});

^{13}C NMR (126 MHz, $CDCl_3$) δ_C = 170.5 (Quat, C_{16}), 138.2 (Quat, C_{12}), 131.0 (Quat, C_{10}), 128.4 (CH, C_{14}), 128.2 (CH, C_{15}), 127.1 (Quat, C_4), 126.7 (CH, C_7), 125.8 (CH, $C_{8/9}$), 125.7 (CH, C_{13}), 125.5 (CH, $C_{8/9}$), 124.8 (Quat, C_5), 123.0 (CH, C_6), 120.8 (CH, C_1), 109.6 (CH, C_2), 104.5 (CH, C_3), 65.9 (CH, C_{11}), 22.6 (CH_3, C_{17});

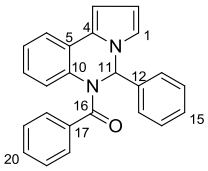
FTIR (neat) ν/cm^{-1} = 3063, 1666, 1488, 1452, 1369, 1265, 1238;

HRMS (ESI^+) calculated for $C_{19}H_{16}N_2NaO$ = 311.1155, mass found = 311.1163;

Chiral HPLC (Chiralpak IA, 15 % IPA, 85 % hexane, 1.0 mL/min, λ = 304 nm, 20 μL injection) τ_R (major) = 8.4 min, τ_R (minor) = 9.8 min;

$[\alpha]_D^{20}$ = -34 (*c* = 0.51, $CHCl_3$).

Phenyl(5-phenylpyrrolo[1,2-*c*]quinazolin-6(5*H*)-yl)methanone, 121



Asymmetric: Asymmetric cyclization product **52** (51 mg, 0.21 mmol, 86:14 e.r.) was dissolved in dichloromethane (2.0 mL). Pyridine (82 μL, 1.0 mmol) and benzoyl chloride (31 μL, 0.27 mmol) were added. The resulting solution was stirred at room temperature for 16 hours. After this time, the solution was diluted with dichloromethane and washed with 1 M HCl and then with brine. The resulting organic phase was dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. Purification of the residue *via* column

chromatography eluting with 7:93 diethyl ether/petrol 40-60 afforded the title compound **121** as a white solid (73 mg, quant., 86:14 e.r.).

Racemic: Racemic cyclization product *rac*-**52** (39 mg, 0.16 mmol) was dissolved in dichloromethane (1.6 mL). Pyridine (63 μL, 0.78 mmol) and benzoyl chloride (24 μL, 0.21 mmol) were added. The resulting solution was stirred at room temperature for 16 hours. After this time, the solution was diluted with dichloromethane and washed with 1 M HCl and then with brine. The resulting organic phase was dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. Purification of the residue *via* column chromatography eluting with 7:93 diethyl ether/petrol 40-60 afforded the title compound *rac*-**121** as a white solid (59 mg, quant.).

Melting point = 167-168 ^{o}C (diethyl ether/petrol 40-60);

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.81 (s, 1H, H_{11}), 7.46 (dd, J = 7.8, 1.2, 1H, H_6), 7.33-7.25 (m, 3H, H_{18} and H_{20}), 7.19-7.13 (m, 2H, H_{19}), 7.13-7.06 (m, 3H, H_{14} and H_{15}), 6.93 (td, J = 7.6, 0.9 Hz, 1H, H_7), 6.90-6.83 (m, 3H, H_1 and H_{13}), 6.63 (dd, J = 3.7, 1.2 Hz, 1H, H_3), 6.57 (t, 7.4 Hz, 1H, H_8), 6.34-6.25 (m, 2H, H_2 and H_9);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 169.5 (Quat, C_{16}), 138.3 (Quat, C_{12}), 134.3 (Quat, C_{17}), 131.5 (Quat, C_{10}), 131.0 (CH, C_{20}), 129.4 (CH, C_{18}), 128.5 (CH, C_{14}), 128.4 (CH, C_{15}), 128.1 (CH, C_{19}), 127.3 (Quat, C_4), 126.3 (CH, C_9), 125.9(2) (CH, C_7), 125.8(9) (CH, C_{13}), 125.3 (CH, C_8), 123.6 (Quat, C_5), 122.7 (CH, C_6), 120.5 (CH, C_1), 109.9 (CH, C_2), 104.6 (CH, C_3), 67.9 (CH, C_{11});

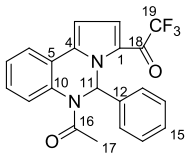
FTIR (neat) ν/cm^{-1} = 3062, 1649, 1577, 1488, 1451, 1365, 1332, 1271, 1237;

HRMS (ESI^{+}) calculated for $C_{24}H_{18}N_2NaO$ = 373.1311, mass found = 373.1313;

Chiral HPLC (Chiralpak IA, 50 % IPA, 50 % hexane, 1.0 mL/min, λ = 214 nm, 20 μL injection) τ_R (major) = 15.3 min, τ_R (minor) = 37.2 min;

$[\alpha]_D^{20}$ = -189 (*c* = 1.00, $CHCl_3$).

1-(6-Acetyl-5-phenyl-5,6-dihydropyrrolo[1,2-*c*]quinazolin-3-yl)-2,2,2-trifluoroethanone, 123*



Asymmetric: Asymmetric acylation product **120** (54 mg, 0.19 mmol, 85:15 e.r.) was dissolved in anhydrous diethyl ether (2.3 mL). Pyridine (30 μL, 0.37 mmol) and trifluoroacetic anhydride (29 μL, 0.21 mmol) were added. The resulting solution was stirred at room temperature for 2 hours. After this time, TLC (1:1 diethyl ether/petrol 40-60) indicated that a mixture of starting material (R_f = 0.50) and product (R_f = 0.25) was present. Pyridine (30 μL, 0.37 mmol) and trifluoroacetic anhydride (29 μL, 0.21 mmol) were added and the resulting solution was stirred at room temperature for a further 2 hours and then diluted with diethyl ether. The organic phase was separated and the aqueous layer was extracted twice with dichloromethane. The combined organic extracts were dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. Purification of the residue *via* column chromatography eluting with 2:3 diethyl ether/petrol 40-60 afforded the title compound **123** as a white solid (69 mg, 96 %, 86:14 e.r.).

Racemic: Racemic acylation product *rac*-**120** (72 mg, 0.25 mmol) was dissolved in anhydrous diethyl ether (2.5 mL). Pyridine (40 μL, 0.50 mmol) and trifluoroacetic anhydride (39 μL, 0.28 mmol) were added. The resulting stirred solution was stirred at room temperature for 2 hours. After this time, TLC (1:1 diethyl ether/petrol 40-60) indicated that a mixture of starting material (R_f = 0.50) and product (R_f = 0.25) was present. Pyridine (40 μL, 0.50 mmol) and trifluoroacetic anhydride (39 μL, 0.28 mmol) were added and the resulting solution was

* This structure was assigned using homo- and heteronuclear nOe experiments. The NOESY and HOESY spectra are shown below.

stirred at room temperature for a further 2 hours and then diluted with diethyl ether. The organic phase was separated and the aqueous layer was extracted twice with dichloromethane. The combined organic extracts were dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. Purification of the residue *via* column chromatography eluting with 2:3 diethyl ether/petrol 40-60 afforded the title compound *rac*-**123** as a white solid (90 mg, 94 %).

Melting point = 95-98 ^{o}C (diethyl ether/petrol 40-60);

^{1}H NMR (500 MHz, d_6-DMSO, 353 K) δ_H = 8.90 (s, 1H, H_{11}), 7.90 (dd, J = 7.6, 1.6 Hz, 1H, H_6), 7.56-7.51 (m, 2H, H_2 and H_9), 7.40 (td, J = 7.7, 1.5 Hz, 1H, H_8), 7.34 (td, J = 7.6, 1.3 Hz, 1H, H_7), 7.27-7.20 (m, 3H, H_{14} and H_{15}), 7.16 (d, 4.7 Hz, 1H, H_3), 6.83-6.79 (m, 2H, H_{13}), 2.33 (s, 3H, H_{17});

^{1}H NMR (500 MHz, d_6-DMSO, 298 K) δ_H = 8.95 (br s, 1H, H_{11}), 7.92 (d, J = 7.6 Hz, 1H, H_6), 7.59 (d, J = 7.9 Hz, 1H, H_9), 7.58-7.55 (m, 1H, H_2), 7.40 (td, J = 7.7, 1.5 Hz, 1H, H_8), 7.33 (t, J = 7.4 Hz, 1H, H_7), 7.33-7.19 (m, 4H, H_3, H_{15} and H_{14}), 6.78 (br d, J = 7.3 Hz, 2H, H_{13}), 2.29 (br s, 3H, H_{17});

^{13}C NMR (126 MHz, d_6-DMSO, 298 K) δ_C = 170.7 (Quat, C_{16}), 168.7 (q, J = 35.3 Hz, Quat, C_{18}), 138.8 (Quat, C_4), 136.8 (Quat, C_{12}), 133.7 (Quat, C_{10}), 130.6 (CH, C_8), 129.2 (CH, C_{14}), 128.9 (CH, C_{15}), 127.3 (CH, C_7), 126.3 (CH, C_9), 125.9 (CH, C_6), 125.7 (CH, C_{13}), 125.3 (q, J = 3.9 Hz, CH, C_2), 124.3 (Quat, C_1), 121.4 (Quat, C_5), 117.2 (q, J = 290.6 Hz, Quat, C_{19}), 109.1 (CH, C_3), 64.1 (CH, C_{11}), 22.7 (CH_3, C_{17});

^{19}F NMR (470 MHz, d_6-DMSO, 298 K) δ_F = -70.5 (s);

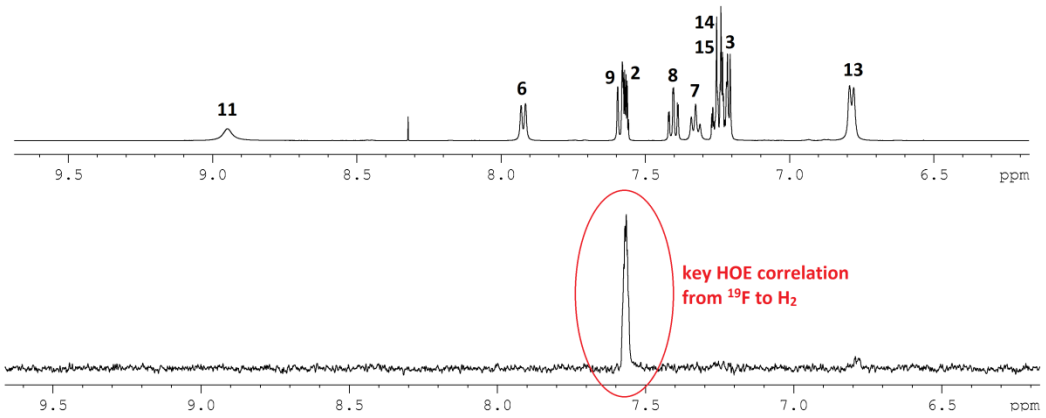
FTIR (neat) ν/cm^{-1} = 3011, 1659, 1497, 1451, 1414, 1368, 1258, 1239, 1195, 1145, 1063;

HRMS (ESI^{+}) calculated for $C_{21}H_{15}F_3N_2NaO_2$ = 407.0978, mass found = 407.0981;

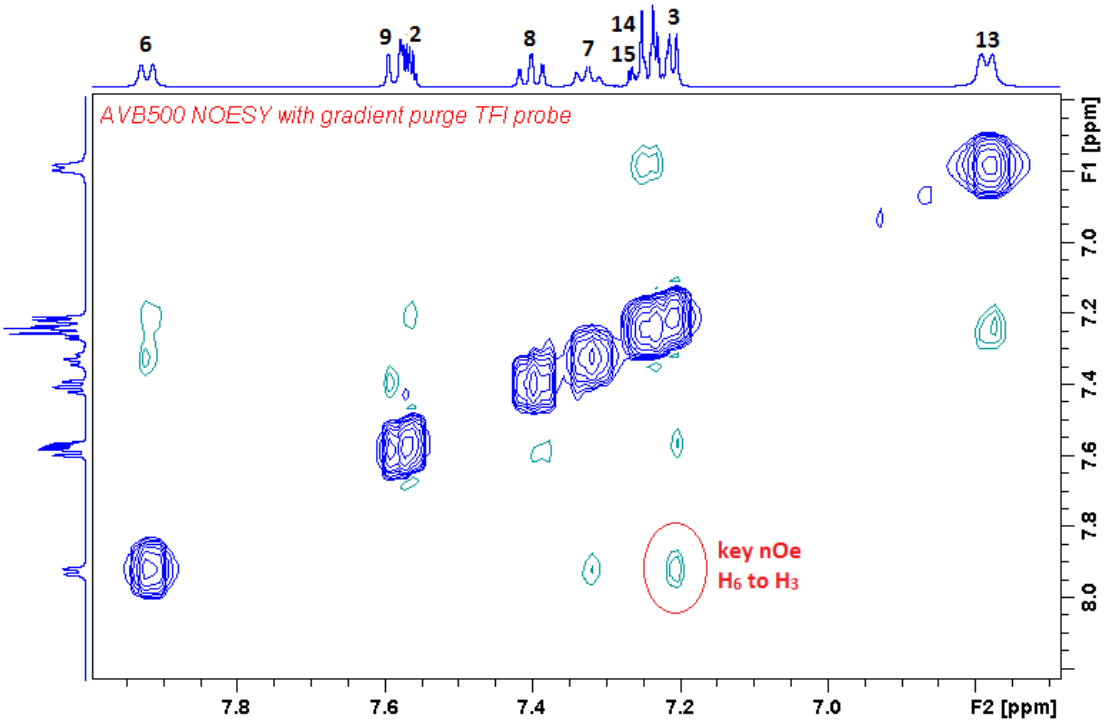
Chiral HPLC (Chiralpak IC, 25 % IPA, 75 % hexane, 1.0 mL/min, λ = 352 nm, 20 μL injection) τ_R (minor) = 7.1 min, τ_R (major) = 13.1 min;

$[\alpha]_D^{20}$ = -296 (*c* = 1.00, $CHCl_3$).

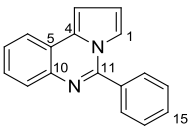
^{1}H and HOESY spectrum of **123** (298 K, key ^{19}F-^{1}H correlation in red):



NOESY spectrum of **123** (298 K, key ^{1}H-^{1}H correlation in red):



5-Phenylpyrrolo[1,2-*c*]quinazoline, 124



Cyclization product *rac*-**52** (50 mg, 0.20 mmol) was dissolved in dichloromethane (2.0 mL) and stirred at room temperature. 2,3-Dichloro-5,6-dicyano-*p*-benzoquinone (51 mg, 0.22 mmol) was added in one portion. The resulting solution was stirred at room temperature for 1 hour and then diluted with dichloromethane. Water was added and the organic layer was separated. The aqueous layer was extracted twice with dichloromethane and the combined organic extracts were dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. Purification of the residue *via* column chromatography eluting with 7:93 diethyl ether/petrol 40-60 afforded the title compound **124** as a dark yellow oil (49 mg, 99 %).

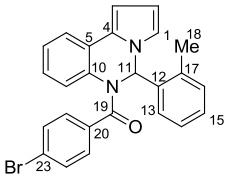
^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 8.01-7.98 (m, 1H, H_6), 7.89-7.84 (m, 3H, H_9 and H_{13}), 7.59-7.56 (m, 3H, H_{14} and H_{15}), 7.51-7.44 (m, 2H, H_7 and H_8), 7.39 (dd, J = 3.0, 1.3 Hz, 1H, H_1), 7.01 (dd, J = 3.7, 1.2 Hz, 1H, H_3), 6.77 (dd, J = 3.8, 3.2 Hz, 1H, H_2);

^{13}C NMR (126 MHz, $CDCl_3$) δ_C = 147.7 (Quat, C_{11}), 138.2 (Quat, C_{10}), 134.3 (Quat, C_{12}), 130.7 (Quat, C_4), 130.6 (CH, C_{15}), 129.0 (CH, C_{14}), 128.6 (CH, C_{13}), 128.3 (CH, C_9), 127.5 (CH, $C_{7/8}$), 127.3 (CH, $C_{7/8}$), 121.6 (CH, C_6), 121.0 (Quat, C_5), 114.8 (CH, C_1), 114.0 (CH, C_2), 101.1 (CH, C_3);

FTIR (neat) ν/cm^{-1} = 3059, 1611, 1539, 1479, 1446, 1358, 1153;

HRMS (ESI$^+$) calculated for $C_{17}H_{13}N_2$ = 245.1073, mass found = 245.1073.

(4-Bromophenyl)(5-phenylpyrrolo[1,2-c]quinazolin-6(5H)-yl)methanone, 125



Asymmetric: Asymmetric cyclization product **72** (113 mg, 0.43 mmol, 96:4 e.r.) was dissolved in dichloromethane (4.3 mL). Pyridine (170 μL, 2.2 mmol) and 4-bromobenzoyl chloride (124 mg, 0.56 mmol) were added and the resulting solution was stirred at room temperature for 19 hours. A further portion of 4-bromobenzoyl chloride (20 mg, 0.09 mmol) was added and the resulting mixture was stirred for 5 hours at room temperature. After this time, the solution was diluted with dichloromethane and washed with saturated aqueous copper sulfate and then with brine. The organic phase was dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. Purification of the residue *via* column chromatography eluting with 6:94 diethyl ether/petrol 40-60 afforded the title compound **125** as a white solid (175 mg, 91 %, 86:14 e.r.). Recrystallization of this material from boiling petrol 60-80 afforded **125** as a white solid (132 mg, 97:3 e.r.).

Racemic: Racemic cyclization product *rac*-**72** (100 mg, 0.38 mmol) was dissolved in dichloromethane (3.8 mL). Pyridine (150 μL, 1.9 mmol) and 4-bromobenzoyl chloride (110 mg, 0.50 mmol) were added and the resulting solution was stirred at room temperature for 22 hours. After this time, the solution was diluted with dichloromethane and washed with saturated aqueous copper sulfate and then with brine. The organic phase was dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. Purification of the residue *via* column chromatography eluting with 6:94 diethyl ether/petrol 40-60 afforded the title compound *rac*-**125** as a white solid (162 mg, 95 %).

Melting point = 96-98 ^{o}C (petrol 60-80);

^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 7.75 (s, 1H, H_{11}), 7.51 (dd, J = 7.9, 1.2 Hz, 1H, H_6), 7.25 (d, J = 8.4 Hz, 2H, H_{22}), 7.03 (d, J = 7.4 Hz, 1H, H_{16}), 7.02 (td, J = 7.6, 1.2 Hz, 1H, H_7), 6.97 (td, J = 7.5, 1.1 Hz, 1H, H_{15}), 6.93 (d, J = 8.6 Hz, 2H, H_{21}), 6.84 (dd, J = 2.6, 1.4 Hz, 1H, H_1), 6.73 (t, J = 7.3 Hz, 1H, H_{14}), 6.68 (dd, J = 3.7, 1.3 Hz, 1H, H_3), 6.60 (td, J = 7.7, 1.3 Hz, 1H, H_8), 6.31 (dd, J = 3.7, 2.7 Hz, 1H, H_2), 6.26 (d, J = 7.9 Hz, 1H, H_9), 5.81 (d, J = 7.8 Hz, 1H, H_{13}), 2.55 (s, 3H, H_{18});

^{13}C NMR (126 MHz, $CDCl_3$) δ_C = 168.1 (Quat, C_{19}), 135.8 (Quat, C_{17}), 135.2 (Quat, C_{12}), 133.8 (Quat, C_{20}), 131.1 (CH, C_{22}), 131.0 (Quat, C_{10}), 130.8 (CH, C_{16}), 130.2 (CH, C_{21}), 128.6 (CH, C_{15}), 127.6 (Quat, C_4), 127.0 (CH, C_7), 126.7 (CH, C_9), 126.3 (CH, C_{13}), 126 (CH, C_{14}), 125.5 (CH, C_8), 125.2 (Quat, C_5), 124.7 (Quat, C_{23}), 122.7 (CH, C_6), 120.6 (CH, C_1), 110.0 (CH, C_2), 104.9 (CH, C_3), 66.2 (CH, C_{11}), 19.8 (CH_3, C_{18});

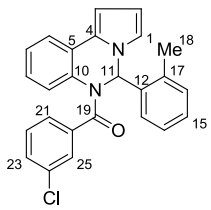
FTIR (neat) ν/cm^{-1} = 3051, 1653, 1608, 1486, 1358, 1326, 1298, 1264, 1180;

HRMS (ESI$^+$) calculated for $C_{25}H_{19}BrN_2NaO$ = 465.0573, mass found = 465.0577;

Chiral HPLC (Chiralpak AS, 5 % IPA, 95 % hexane, 1.0 mL/min, λ = 222 nm, 20 μL injection) τ_R (major) = 6.6 min, τ_R (minor) = 8.5 min;

$[\alpha]_D^{20}$ = -291 (*c* = 1.00, $CHCl_3$).

(3-Chlorophenyl)(5-(*o*-tolyl)pyrrolo[1,2-c]quinazolin-6(5*H*)-yl)methanone, 126



Asymmetric cyclization product **72** (20 mg, 0.077 mmol, 96:4 e.r.) was dissolved in dichloromethane (2 mL). Pyridine (31 μL, 0.39 mmol) and 3-chlorobenzoyl chloride (27 mg, 0.15 mmol) were added and the resulting solution was stirred at room temperature for

20 hours. After this time, the solution was diluted with dichloromethane and washed with saturated aqueous copper sulfate and then with brine. The organic phase was dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. Purification of the residue *via* column chromatography eluting with 1:19 diethyl ether/petrol 40-60 afforded the title compound **126** as a beige solid (30 mg, 98 %).

Melting point = 174-176 ^{o}C (diethyl ether/petrol 40-60);

^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 7.96 (s, 1H, H_{11}), 7.52 (dd, J = 8.0, 1.3 Hz, 1H, H_6), 7.21 (ddd, J = 8.0, 2.0, 1.0 Hz, 1H, $H_{21/23}$), 7.18-7.16 (m, 1H, H_{25}), 7.07-7.96 (m, 4H, H_7, H_{15}, H_{16} and H_{22}), 6.86 dd, J = 2.7, 1.4 Hz, 1H, H_1), 6.82 (d, J = 7.6 Hz, 1H, $H_{21/23}$), 6.75 (t, J = 7.4 Hz, 1H, H_{14}), 6.69 (dd, J = 3.8, 1.3 Hz, 1H, H_3), 6.61 (t, J = 7.4 Hz, 1H, H_8), 6.34 (dd, J = 3.6, 2.7 Hz, 1H, H_2), 6.27 (br d, J = 6.5 Hz, 1H, H_9), 5.80 (d, J = 7.9 Hz, 1H, H_{13}), 2.55 (s, 3H, H_{18});

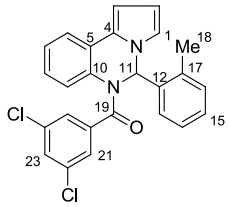
^{13}C NMR (121 MHz, $CDCl_3$) δ_C = 167.6 (Quat, C_{19}), 136.6 (Quat, C_{Ar}), 135.8 (Quat, C_{Ar}), 135.1 (Quat, C_{Ar}), 134.1 (Quat, C_{Ar}), 130.8 (CH, C_{Ar}), 130.8 (Quat, C_{Ar}), 130.3 (CH, C_{Ar}), 129.1 (CH, C_{Ar}), 128.7 (CH, C_{Ar}), 128.6 (CH, C_{Ar}), 127.6 (Quat, C_{Ar}), 127.1 (CH, C_7), 126.7 (CH, C_9), 126.4 (CH, C_{Ar}), 126.2 (CH, C_{13}), 126.0 (CH, C_{14}), 125.4 (CH, C_8), 125.2 (Quat, C_5), 122.7 (CH, C_6), 120.6 (CH, C_1), 110.0 (CH, C_2), 105.0 (CH, C_3), 66.1 (CH, C_{11}), 19.8 (CH_3, C_{18});

FTIR (neat) ν/cm^{-1} = 3068, 1658, 1569, 1487, 1360, 1325, 1296, 1263;

HRMS (ESI^{+}) calculated for $C_{25}H_{19}ON_2ClNa$ = 421.1078, mass found = 421.1078;

$[\alpha]_D^{20}$ = -251 (*c* = 0.50, $CHCl_3$).

(3,5-Dichlorophenyl)(5-(*o*-tolyl)pyrrolo[1,2-c]quinazolin-6(5H)-yl)methanone, 127



Asymmetric cyclization product **72** (20 mg, 0.077 mmol, 96:4 e.r.) was dissolved in dichloromethane (2 mL). Pyridine (31 μL, 0.39 mmol) and 3,5-dichlorobenzoyl chloride (32 mg, 0.15 mmol) were added and the resulting solution was stirred at room temperature for 20 hours. After this time, the solution was diluted with dichloromethane and washed with saturated aqueous copper sulfate and then with brine. The organic phase was dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. Purification of the residue *via* column chromatography eluting with 1:19 diethyl ether/petrol 40-60 afforded the title compound **127** as a white solid (34 mg, quant).

Melting point = 196-199 ^{o}C (diethyl ether/petrol 40-60);

^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 7.93 (s, 1H, H_{11}), 7.54 (dd, J = 8.0, 1.0 Hz, 1H, H_6), 7.22 (t, 1.9 Hz, 1H, H_{23}), 7.10-7.03 (m, 2H, H_7 and H_{16}), 7.00 (t, 7.1 Hz, 1H, H_{15}), 6.92 (d, J = 1.7 Hz, 2H, H_{21}), 6.85 (dd, J = 2.7, 1.3 Hz, 1H, H_1), 6.75 (t, J = 7.4 Hz, 1H, H_{14}), 6.71 (dd, J = 3.7, 1.4 Hz, 1H, H_3), 6.65 (t, J = 7.3 Hz, 1H, H_8), 6.33 (dd, J = 3.5, 2.8 Hz, 1H, H_2), 6.28 (br d, J = 6.6 Hz, 1H, H_9), 5.79 (d, J = 8.0 Hz, 1H, H_{13}), 2.53 (s, 3H, H_{18});

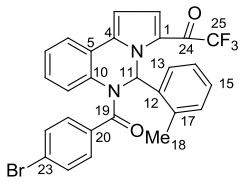
^{13}C NMR (121 MHz, $CDCl_3$) δ_C =166.2 (Quat, C_{19}), 137.6 (Quat, C_{Ar}), 135.8 (Quat, C_{Ar}), 134.9 (Quat, C_{Ar}), 134.7 (Quat, C_{22}), 130.9 (CH, C_{16}), 130.3 (Quat, C_{Ar}), 130.2 (CH, C_{23}), 128.7 (CH, C_{15}), 127.5 (CH, C_7), 127.5 (Quat, C_{Ar}), 127.0 (CH, C_{21}), 126.6 (CH, C_9), 126.2 (CH, C_{13}), 126.1 (CH, C_{14}), 125.5 (CH, C_8), 125.3 (Quat, C_5), 122.9 (CH, C_6), 120.7 (CH, C_1), 110.1 (CH, C_2), 105.2 (CH, C_3), 66.2 (CH, C_{11}), 19.8 (CH_3, C_{18});

FTIR (neat) ν/cm^{-1} = 3073, 1658, 1564, 1487, 1360, 1324, 1296, 1264, 1047;

HRMS (ESI$^+$) calculated for $C_{25}H_{18}ON_2Cl_2Na$ = 455.0688, mass found = 455.0686;

$[\alpha]_D^{20}$ = -251 (*c* = 0.50, $CHCl_3$).

1-(6-(4-Bromobenzoyl)-5-(o-tolyl)-5,6-dihydropyrrolo[1,2-c]quinazolin-3-yl)-2,2,2-trifluoroethanone, 128



Asymmetric: Asymmetric acylated product **125** (50 mg, 0.11 mmol, 97:3 e.r.) was dissolved in anhydrous diethyl ether (1.3 mL). Pyridine (18 μL, 0.23 mmol) and trifluoroacetic anhydride (18 μL, 0.12 mmol) were added. The resulting solution was stirred at room temperature for 1.5 hours. A further portion of pyridine (18 μL, 0.23 mmol) and trifluoroacetic anhydride (18 μL, 0.12 mmol) were added and the resulting solution was stirred at room temperature for a further 2 hours and then diluted with diethyl ether. The organic phase was separated and the aqueous layer was extracted twice with dichloromethane. The combined organic extracts were dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. Purification of the residue *via* column chromatography eluting with 1:9 diethyl ether/petrol 30-40 afforded the title compound **128** as a white solid (57 mg, 94 %, 97:3 e.r.).

Racemic: Racemic acylation product *rac*-**125** (50 mg, 0.11 mmol, 97:3 e.r.) was dissolved in anhydrous diethyl ether (1.3 mL). Pyridine (18 μL, 0.23 mmol) and trifluoroacetic anhydride (18 μL, 0.12 mmol) were added. The resulting solution was stirred at room temperature for 1.5 hours. A further portion of pyridine (18 μL, 0.23 mmol) and trifluoroacetic anhydride (18 μL, 0.12 mmol) were added and the resulting solution was stirred at room temperature for a further 2 hours and then diluted with diethyl ether. The organic phase was separated and

the aqueous layer was extracted twice with dichloromethane. The combined organic extracts were dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. Purification of the residue *via* column chromatography eluting with 1:4 diethyl ether/petrol 40-60 afforded the title compound *rac*-**128** as a white solid (38 mg, 63 %).

Melting point = 94-97 ^{o}C (diethyl ether/petrol 30-40);

^{1}H NMR (500 MHz, DMSO-d_6) δ_H = 9.07 (s, 1H, H_{11}), 8.04 (dd, J = 7.9, 1.1 Hz, 1H, H_6), 7.64 (m, 1H, H_2), 7.50 (d, J = 8.5 Hz, 2H, H_{22}), 7.37 (d, J = 4.7 Hz, 1H, H_3), 7.30 (td, J = 7.6, 0.7 Hz, 1H, H_7), 7.24 (d, J = 7.6 Hz, 1H, H_{16}), 7.13 (t, J = 7.5 Hz, 1H, H_{15}), 7.07 (d, J = 8.5 Hz, 2H, H_{21}), 7.04 (t, J = 7.6 Hz, 1H, H_8), 6.86 (t, J = 7.5 Hz, 1H, H_{14}), 6.62 (d, J = 7.3 Hz, 1H, H_9), 5.81 (d, J = 7.9 Hz, 1H, H_{13}), 2.66 (s, 3H, H_{18});

^{13}C NMR (126 MHz, DMSO-d_6) δ_C = 168.9 (q, J = 35.0 Hz, Quat, C_{24}), 168.3 (Quat, C_{19}), 139.3 (Quat, C_4), 136.8 (Quat, C_{17}), 133.9 (Quat, C_{20}), 133.4 (Quat, C_{12}), 133.0 (Quat, C_{10}), 131.8 (CH, C_{16}), 131.6 (CH, C_{22}), 130.5 (CH, C_{21}), 130.0 (CH, C_8), 129.4 (CH, C_{15}), 128.0 (CH, C_7), 127.4 (CH, C_9), 126.5 (CH, C_{14}), 125.9 (CH, C_6), 125.7 (q, J = 3.8 Hz, CH, C_2), 125.4 (CH, C_{13}), 124.4 (Quat, C_{23}), 123.8 (Quat, C_1), 122.5 (Quat, C_5), 117.1 (q, J = 290.2 Hz, Quat, C_{25}), 109.4 (CH, C_3), 64.5 (CH, C_{11}), 19.9 (CH_3, C_{18});

^{19}F NMR (470 MHz, $CDCl_3$) δ_F = -70.6 (s);

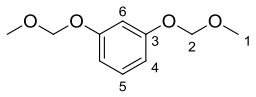
FTIR (neat) ν/cm^{-1} = 3023, 1664, 1323, 1238, 1190, 1147, 1124, 1084;

HRMS (FI^{+}) calculated for $C_{17}H_{18}N_2O_2F_3Br$ = 538.0504, mass found = 538.0509;

Chiral HPLC (Chiralpak IC, 15 % IPA, 85 % hexane, 1.0 mL/min, λ = 222 nm, 20 μL injection) τ_R (minor) = 5.0 min, τ_R (major) = 12.3 min;

$[\alpha]_D^{20}$ = -771 (*c* = 1.00, $CHCl_3$).

1,3-Bis(methoxymethoxy)benzene, 176



This compound was prepared according to a literature procedure.[114]

A stirred suspension of sodium hydride (60 % w/w dispersion in mineral oil, 1.67 g, 41.8 mmol) in dimethylformamide (30 mL) was cooled to 0 ^{o}C. A solution of resorcinol (2.00 g, 18.2 mmol) in dimethylformamide (30 mL) was added dropwise. Chloromethyl methyl ether (3.0 mL, 39.5 mmol) was added and the resulting suspension was warmed to room temperature and stirred for 4 hours. The solution was carefully acidified with 1 M HCl and extracted four times with ethyl acetate. The combined organic extracts were washed six times with 1 M HCl and brine, dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. Purification of the residue *via* column chromatography eluting with 7:93 ethyl acetate/petrol 40-60 afforded the title compound **176** as a colourless oil (2.72 g, 76 %). The spectral data matched that previously reported in the literature.[114]

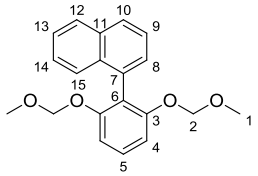
^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 7.20 (t, J = 8.2 Hz, 1H, H_5), 6.76 (t, J = 2.2 Hz, 1H, H_6), 6.72 (dd, J = 8.4, 2.4 Hz, 2H, H_4), 5.17 (s, 4H, H_2), 3.49 (s, 6H, H_1);

^{13}C NMR (121 MHz, $CDCl_3$) δ_C = 158.3 (Quat, C_3), 130.0 (CH, C_5), 109.6 (CH, C_4), 105.0 (CH, C_6), 94.4 (CH_2, C_2), 56.0 (CH_3, C_1);

FTIR (neat) ν/cm^{-1} = 2956, 2827, 1592, 1488, 1314, 1138, 1074, 1006;

LRMS (ESI^{+}) 407.1 ([M+H]$^{+}$).

1-(2,6-Bis(methoxymethoxy)phenyl)naphthalene, 179



ortho-Lithiation/boronic acid formation:[71] A stirred solution of **176** (2.61 g, 13.2 mmol) in diethyl ether (50 mL) was cooled to 0 ^{o}C. *n*-Butyllithium (1.6 M in hexanes, 9.9 mL, 16 mmol) was added dropwise and the resulting solution was warmed to room temperature and stirred for 3 hours. The solution was cooled to 0 ^{o}C and trimethyl borate (2.20 mL, 19.7 mmol) was added. The resulting solution was warmed to room temperature and stirred for 1 hour. The solution was cooled to 0 ^{o}C and carefully acidified with 2 M HCl (50 mL). The resulting biphasic mixture was allowed to warm to room temperature and stirred for 1 hour. After this time an off white precipitate had formed, which was collected by vacuum filtration, washed with water (3 x 10 mL) and dried under high vacuum for 16 hours to afford boronic acid **177** as an off white solid (1.06 g) which was used in the next step without further purification.

Suzuki Coupling: A schlenk tube was charged with the above crude boronic acid **177** (1.06 g), 1-iodonaphthalene (855 mg, 3.36 mmol), tetrakis(triphenylphosphane)palladium(0) (584 mg, 0.51 mmol) and potassium phosphate (2.15 g, 10.1 mmol) and the atmosphere was purged with argon three times. A degassed mixture of 3:1 dimethoxyethane/water was added and the solution was heated to 95 ^{o}C for 20 hours. After this time the reaction mixture was cooled to room temperature and diethyl ether and water were added. The organic layer was separated and the aqueous layer was extracted twice with diethyl ether. The combined organic extracts were dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. Purification of the residue *via* column chromatography eluting with 1:9 ethyl acetate/petrol 40-60 afforded the title compound **179** as a white solid (1.01 g, 93 % based on 1-iodonaphthalene).

Melting point: 82-84 ^{o}C (ethyl acetate/petrol 40-60);

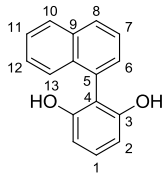
^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 7.89 (t, J = 8.5 Hz, 2H, H_{Ar}), 7.58-7.54 (m, 2H, H_{Ar}), 7.48-7.44 (m, 1H, H_{Ar}), 7.42-7.35 (m, 3H, H_5 and H_{Ar}), 6.98 (d, J = 8.5 Hz, 2H, H_4), 4.95 (d, J = 12.9 Hz, 2H, H_2), 4.96 (d, J = 12.9 Hz, 2H, $H_{2'}$), 3.15 (s, 6H, H_1);

^{13}C NMR (121 MHz, $CDCl_3$) δ_C = 156.0 (Quat, C_3), 133.5 (Quat, C_{Ar}), 132.8 (Quat, C_{Ar}), 132.6 (Quat, C_{Ar}), 129.2 (CH, C_{Ar}), 128.1 (CH, C_{Ar}), 127.9 (CH, C_{Ar}), 127.4 (CH, C_{Ar}), 126.1 (CH, C_{Ar}), 125.5 (CH, C_{Ar}), 125.4 (CH, C_{Ar}), 125.3 (CH, C_{Ar}), 120.5 (Quat, C_6), 109.0 (CH, C_4), 94.5 (CH_2, C_2), 55.9 (CH_3, C_1);

FTIR (neat) ν/cm^{-1} = 2955, 1600, 1583, 1463, 1440, 1399, 1310, 1245, 1204, 1152, 1037;

HRMS (ESI^{+}) calculated for $C_{20}H_{20}NaO_4$ = 347.1254; mass found = 347.1248.

2-(Naphthalen-1-yl)benzene-1,3-diol, 180



This compound was prepared according to a modified literature procedure.[71]

A stirred solution of **179** (902 mg, 2.78 mmol) in a mixture of THF (10.5 mL) and methanol (14 mL) was cooled to 0 ^{o}C. 2 M aqueous HCl (6.95 mL, 13.9 mmol) was added. The resulting mixture was allowed to warm to room temperature and then heated to 50 ^{o}C for 6 hours. The solution was cooled to room temperature and saturated aqueous sodium bicarbonate and ethyl acetate were added. The organic layer was separated and the aqueous layer was extracted twice with ethyl acetate. The combined organic extracts were dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. Purification of the

residue *via* column chromatography eluting with 1:4 ethyl acetate/petrol 40-60 afforded the title compound **180** as a white solid (449 mg, 68 %).

Melting point: 151-152 ^{o}C (ethyl acetate/petrol 40-60);

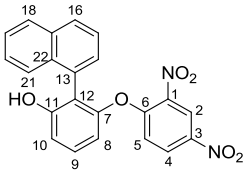
^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 7.99-7.92 (m, 2H, H_{Ar}), 7.66-7.47 (m, 5H, H_{Ar}), 7.26 (t, J = 8.2 Hz, 1H, H_1), 6.67 (d, J = 8.2 Hz, 2H, H_2), 4.66 (s, 2H, O*H*);

^{13}C NMR (121 MHz, $CDCl_3$) δ_C = 154.0 (Quat, C_3), 134.3 (Quat, C_{Ar}), 132.3 (Quat, C_{Ar}), 130.1 (CH, C_{Ar}), 130.0 (CH, C_{Ar}), 129.8 (CH, C_{Ar}), 128.6 (CH, C_{Ar}), 127.6 (Quat, C_{Ar}), 127.4 (CH, C_{Ar}), 127.0 (CH, C_{Ar}), 126.1 (CH, C_{Ar}), 125.2 (CH, C_{Ar}), 113.1 (Quat, C_4), 107.7 (CH, C_2);

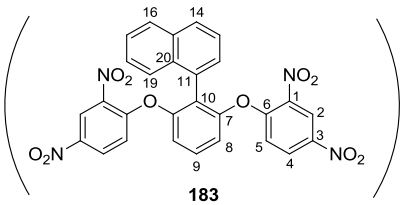
FTIR (neat) ν/cm^{-1} = 3300-3600, 3058, 1623, 1586, 1506, 1150, 1004;

HRMS (ESI$^-$) calculated for $C_{16}H_{11}O_2$ = 235.0765; mass found = 235.0760.

3-(2,4-Dinitrophenoxy)-2-(naphthalen-1-yl)phenol, 182



182



183

Asymmetric: To a solution of **180** (30 mg, 0.13 mmol), 2,4-dinitrofluorobenzene (25 mg, 0.13 mmol) and *N*-benzylcinchoninium chloride (5 mg, 0.01 mmol) in toluene (1.3 mL) was added potassium carbonate (88 mg, 0.64 mmol). The resulting suspension was stirred rapidly at room temperature for 16 hours. After this time, 1 M HCl and dichloromethane were added. The organic layer was separated and the aqueous layer was extracted twice with dichloromethane. The combined organic extracts were dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. Purification of the residue *via* column chromatography eluting with a gradient from 3:17 ethyl acetate/petrol 40-60 to 1:4

ethyl acetate/petrol 40-60 afforded the title compound **182** as a yellow oil (12 mg, 23 %, 51:49 e.r.) along with diarylated by-product **183** as a yellow oil (16 mg, 22 %).

Racemic: To a solution of **180** (30 mg, 0.13 mmol), 2,4-dinitrofluorobenzene (25 mg, 0.13 mmol) and tetrabutylammonium bromide (5 mg, 0.01 mmol) in toluene (1.3 mL) was added potassium carbonate (88 mg, 0.64 mmol). The resulting suspension was stirred rapidly at room temperature for 16 hours. After this time, 1 M HCl and dichloromethane were added. The organic layer was separated and the aqueous layer was extracted twice with dichloromethane. The combined organic extracts were dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. Purification of the residue *via* column chromatography eluting with a gradient from 3:17 ethyl acetate/petrol 40-60 to 1:4 ethyl acetate/petrol 40-60 afforded the title compound *rac*-**182** as a yellow oil (6 mg, 12 %) along with diarylated by-product **183** as a yellow oil (35 mg, 48 %).

Data for **182**

^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 8.42 (d, J = 2.8 Hz, 1H, H_2), 8.00 (dd, J = 9.3, 2.7 Hz, 1H, H_4), 7.83 (t, 7.4 Hz, 2H, H_{Ar}), 7.55-7.35 (m, 6H, H_{Ar}), 7.10 (dd, J = 8.5, 0.9 Hz, 1H, H_{10}), 6.98-7.10 (m, 2H, H_5 and H_8), 7.10 (s, 1H, O*H*);

^{13}C NMR (121 MHz, $CDCl_3$) δ_C = 155.6 (Quat, $C_{6/7}$), 155.4 (Quat, $C_{6/7}$), 152.1 (Quat, C_{11}), 140.8 (Quat, C_3), 138.3 (Quat, C_1), 133.7 (Quat, C_{Ar}), 131.1 (Quat, C_{Ar}), 130.6 (CH, C_{Ar}), 129.9 (CH, C_{Ar}), 129.3 (CH, C_{Ar}), 128.6 (CH, C_{Ar}), 128.1 (CH, C_4), 127.1 (CH, C_{Ar}), 126.8 (Quat, C_{Ar}), 126.7 (CH, C_{Ar}), 125.6 (CH, C_{Ar}), 124.7 (CH, C_{Ar}), 121.5 (CH, C_2), 119.3 (Quat, C_{12}), 118.5 (CH, C_5), 114.1 (CH, C_{10}), 113.3 (CH, C_8);

FTIR (neat) ν/cm^{-1} =3507 (br), 3109, 1606, 1535, 1462, 1345, 1268, 1001;

HRMS (ESI^-) calculated for $C_{22}H_{13}N_2O_6$ = 401.0779; mass found = 401.0781.

Data for **183**

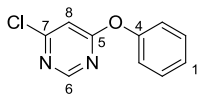
^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 8.43 (d, J = 2.8 Hz, 2H, H_2), 8.02 (dd, J = 9.1, 2.8 Hz, 2H, H_4), 7.72 (t, J = 8.4 Hz, 1H, H_9), 7.69-7.62 (m, 2H, H_{Ar}), 7.52-7.48 (m, 1H, H_{Ar}), 7.45-7.40 (m, 2H, H_{Ar}), 7.37 (d, J = 8.2 Hz, 2H, H_8), 7.27-7.24 (m, 1H, H_{Ar}), 7.21 (t, J = 7.6 Hz, 1H, H_{Ar}), 6.93 (d, J = 9.1 Hz, 2H, H_5);

^{13}C NMR (121 MHz, $CDCl_3$) δ_C = 154.7 (Quat, C_6), 153.6 (Quat, C_7), 141.4 (Quat, C_3), 138.6 (Quat, C_1), 133.0 (Quat, C_{Ar}), 131.1 (CH, C_9), 130.3 (Quat, C_{Ar}), 129.7 (CH, C_{Ar}), 128.7 (CH, C_{Ar}), 128.4 (CH, C_{Ar}), 128.2 (CH, C_4), 126.8 (CH, C_{Ar}), 126.7 (Quat, C_{Ar}), 126.5 (CH, C_{Ar}), 126.1 (Quat, C_{Ar}), 124.9 (CH, C_{Ar}), 124.6 (CH, C_{Ar}), 121.6 (CH, C_2), 119.5 (CH, C_8), 118.9 (CH, C_5);

FTIR (neat) ν/cm^{-1} = 3108, 1607, 1572, 1532, 1480, 1451, 1343, 1260, 1243, 1148, 1068;

HRMS (EI^+) calculated for $C_{28}H_{16}N_4O_{10}$ = 568.0867, mass found = 568.0793.

4-Chloro-6-phenoxypyrimidine, 195



To a stirred suspension of 4,6-dichloropyrimidine **194** (50 mg, 0.34 mmol), phenol (33 mg, 0.35 mmol) and tetrabutylammonium bromide (11 mg, 0.034 mmol) in toluene (3.4 mL) was added cesium hydroxide monohydrate (282 mg, 1.68 mmol). The resulting suspension was stirred rapidly at room temperature for 16 hours. After this time, 1 M HCl and dichloromethane were added. The organic layer was separated and the aqueous layer was extracted twice with dichloromethane. The combined organic extracts were dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. Purification of the residue *via* column chromatography eluting with 1:19 ethyl acetate/petrol 40-60

afforded the title compound **195** as a colourless oil (24 mg, 35 %). The spectral data matched that previously reported in the literature[115]

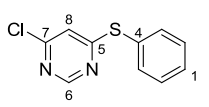
^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 8.60 (s, 1H, H_6), 7.46 (t, J = 7.9 Hz, 2H, H_2), 7.31 (t, J = 7.4 Hz, 1H, H_1), 7.15 (d, J = 7.6 Hz, 2H, H_3), 6.92 (d, J = 0.6 Hz, 1H, H_8);

^{13}C NMR (126 MHz, $CDCl_3$) δ_C = 170.4 (Quat), 162.0 (Quat), 158.6 (CH, C_6), 151.9 (Quat), 130.0 (CH, C_2), 126.3 (CH, C_1), 121.4 (CH, C_3), 107.8 (CH, C_8);

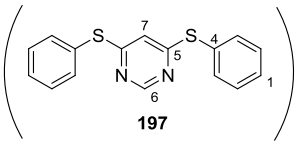
FTIR (neat) ν/cm^{-1} = 3059, 1595, 1552, 1489, 1442, 1353, 1258, 1192, 1161, 1086, 1024;

LRMS (ESI$^+$) 207 ([M+H]$^+$).

4-Chloro-6-(phenylthio)pyrimidine, 196



196



197

To a stirred suspension of 4,6-dichloropyrimidine **194** (100 mg, 0.67 mmol), thiophenol (1.0 M in toluene, 68 μL, 0.67 mmol) and tetrabutylammonium bromide (22 mg, 0.068 mmol) in toluene (6.0 mL) was added 50 % aqueous potassium hydroxide (0.19 mL, 3.4 mmol). The resulting biphasic mixture was stirred rapidly at room temperature for 1 hour. After this time, 1 M HCl and dichloromethane were added. The organic layer was separated and the aqueous layer was extracted twice with dichloromethane. The combined organic extracts were dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. Purification of the residue *via* column chromatography eluting with 1:19 ethyl acetate/petrol 40-60 afforded the title compound **196** as a colourless oil (130 mg, 85 %) along with by-product **197** resulting from double addition as a colourless oil (10 mg, 5 %).

Data for **196**

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 8.67 (d, J = 1.0 Hz, 1H, H_6), 7.61-7.57 (m, 2H, H_3), 7.55-7.47 (m, 3H, H_1 and H_2), 6.72 (d, J = 1.0 Hz, 1H, H_8);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 174.8 (Quat, C_5), 160.8 (Quat, C_7), 157.9 (CH, C_6), 135.8 (CH, C_3), 130.8 (CH, C_1), 130.3 (CH, C_2), 126.8 (Quat, C_4), 116.6 (CH, C_8);

FTIR (neat) ν/cm^{-1} = 3057, 1537, 1506, 1424, 1286, 1188, 1167, 1082;

HRMS (ESI^+) calculated for $C_{10}H_7ClN_2NaS$ = 244.9911, mass found = 244.9916.

Data for **197**

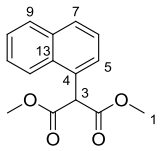
^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 8.62 (s, 1H, H_6), 7.43-7.37 (m, 6H, H_1 and H_3), 7.34 (t, J = 7.4 Hz, 4H, H_2), 6.05 (s, 1H, H_7);

^{13}C NMR (126 MHz, $CDCl_3$) δ_C = 172.3 (Quat, C_5), 156.7 (CH, C_6), 135.6 (CH, C_3), 130.1 (CH, C_1) 129.8 (CH, C_2), 127.3 (Quat, C_4), 112.0 (CH, C_7);

FTIR (neat) ν/cm^{-1} = 3060, 1536, 1495, 1475, 1455, 1280;

HRMS (ESI^+) calculated for $C_{16}H_{12}N_2NaS_2$ = 319.0334, mass found = 319.0325.

Dimethyl 2-(naphthalen-1-yl)malonate, 199



This compound was prepared in analogy to a literature procedure.[109]

A stirred solution of 1-naphthaleneacetic acid (10.0 g, 53.7 mmol) in methanol (130 mL) was cooled to 0 ^{o}C. Thionyl chloride (4.70 mL, 64.7 mmol) was added and the resulting solution was

warmed to room temperature and stirred for 3 hours. After this time, the reaction mixture was concentrated to dryness under reduced pressure. The residue was redissolved in ethyl acetate and washed successively with brine (x 2), 2 M aqueous sodium carbonate, brine and then dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to afford the crude methyl ester (10.8 g) which was used without purification in the next step.

A stirred suspension of sodium hydride (60 % w/w in mineral oil, 5.39 g, 135 mmol) in THF (80 mL) was heated to 40 ^{o}C. A solution of the crude methyl ester obtained above (10.8 g) in THF (30 mL) was added dropwise *via* cannula. The resulting stirred suspension was stirred at 40 ^{o}C for 5 minutes and then cooled to room temperature. Dimethyl carbonate (18.2 mL, 216 mmol) was added and the reaction mixture was stirred at room temperature for 24 hours and then cooled to 0 ^{o}C and quenched by dropwise addition of 25 % aqueous HCl (16 mL) [care – mixture foams and evolves hydrogen gas] and then diluted with water (50 mL). The volatile organics were removed under reduced pressure and the remaining aqueous suspension was extracted three times with ethyl acetate. The combined organic extracts were washed successively with 1 M HCl and brine, dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. Purification of the residue *via* recrystallization from boiling petrol 60-80/ethyl acetate afforded the title compound **199** as a white solid (11.0 g, 79 % over 2 steps).

Melting point: 86-88 ^{o}C (petrol 60-80/ethyl acetate);

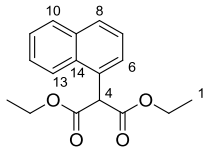
^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 7.97 (d, J = 8.3 Hz, 1H, H_{Ar}), 7.91-7.85 (m, 2H, H_{Ar}), 7.60-7.47 (m, 4H, H_{Ar}), 5.48 (s, 1H, H_3), 3.78 (s, 6H, H_1);

^{13}C NMR (121 MHz, $CDCl_3$) δ_C = 168.9 (Quat, C_2), 134.0 (Quat, C_{Ar}), 131.6 (Quat, C_{Ar}), 129.1 (CH, C_{Ar}), 129.1 (CH, C_{Ar}), 129.0 (Quat, C_{Ar}), 127.2 (CH, C_{Ar}), 126.9 (CH, C_{Ar}), 125.9 (CH, C_{Ar}), 125.5 (CH, C_{Ar}), 122.8 (CH, C_{Ar}), 54.1 (CH, C_3), 53.0 (CH, C_1);

FTIR (neat) ν/cm^{-1} = 3014, 2959, 1734, 1734, 1433, 1316, 1292, 1262, 1192, 1157;

HRMS (ESI^+) calculated for $C_{15}H_{14}NaO_4$ = 281.0784; mass found = 281.0797.

Diethyl 2-(naphthalen-1-yl)malonate, 202



This compound was prepared according to a modified literature procedure.[109]

A stirred solution of 1-naphthaleneacetic acid (20.0 g, 107 mmol) in ethanol (130 mL) was cooled to 0 ^oC. Thionyl chloride (9.3 mL, 129 mmol) was added and the resulting solution was warmed to room temperature and stirred for 4 hours. After this time, the reaction mixture was concentrated to dryness under reduced pressure. The residue was redissolved in ethyl acetate and washed successively with brine (x 2), 2 M aqueous sodium carbonate, brine and then dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to afford the crude ethyl ester (24.2 g) which was used without purification in the next step.

A stirred suspension of sodium hydride (60 % w/w in mineral oil, 10.8 g, 269 mmol) in THF (160 mL) was heated to 40 ^oC. A solution of the crude ethyl ester obtained above (24.2 g) in THF (60 mL) was added dropwise *via* cannula. The resulting stirred suspension was stirred at 40 ^oC for 5 minutes and then cooled to room temperature. Diethyl carbonate (52 mL, 430 mmol) was added and the reaction mixture was stirred at room temperature for 20 hours and then cooled to 0 ^oC and quenched by dropwise addition of 25 % aqueous HCl (34 mL) [care

– mixture foams and evolves hydrogen gas] and then diluted with water (50 mL). The volatile organics were removed under reduced pressure and the remaining aqueous suspension was extracted three times with ethyl acetate. The combined organic extracts were washed successively with 1 M HCl and brine, dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. Purification of the residue *via* column chromatography eluting with 1:19 ethyl acetate/petrol 40-60 afforded the title compound **202** as a white solid (22.9 g, 74 % over 2 steps). The spectral data matched that previously reported in the literature.[86]

Melting point: 59-61 ^{o}C (petrol 60-80/ethyl acetate), [lit. 61-62 ^{o}C];[86]

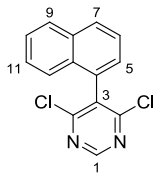
^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.99 (d, J = 8.3 Hz, 1H, H_{Ar}), 7.91-7.83 (m, 2H, H_{Ar}), 7.63-7.48 (m, 4H, H_{Ar}), 5.46 (s, 1H, H_4), 4.28 (dq, J = 11.1, 7.1 Hz, 2H, H_{2A}), 4.26 (dq, J = 11.0, 7.0 Hz, 2H, H_{2B}), 1.27 (t, J = 7.2 Hz, 6H, H_1);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 168.5 (Quat, C_3), 134 (Quat, C_{Ar}), 131.7 (Quat, C_{Ar}), 129.4 (Quat, C_{Ar}), 129.0 (CH, C_{Ar}), 128.9 (CH, C_{Ar}), 127.1 (CH, C_{Ar}), 126.7 (CH, C_{Ar}), 125.8 (CH, C_{Ar}), 125.4 (CH, C_{Ar}), 122.9 (CH, C_{Ar}), 61.9 (CH_2, C_2), 54.5 (CH, C_4), 14.1 (CH_3, C_1);

FTIR (neat) ν/cm^{-1} = 2982, 1730, 1306, 1258, 1196, 1175, 1142, 1034;

LRMS (ESI^{+}) 287 ([M + H]$^{+}$).

4,6-Dichloro-5-(naphthalen-1-yl)pyrimidine, 201



According to **General Procedure D**. Pyrimidine formation with metallic sodium (4.02 g, 175 mmol), methanol (90 mL), formamidine acetate salt (7.27 g, 69.9 mmol), THF (55 mL), **202**

(10.0 g, 34.9 mmol), THF (55 mL), methanol (90 mL) at 80 °C for 24 hours. Crude aryl pyrimidine product was obtained as a white solid (7.31 g). Chlorination with crude aryl pyrimidine (7.31 g, 30.7 mmol), phosphorus (V) oxychloride (86 mL), *N*,*N*-dimethylaniline (8.6 mL, 67.5 mmol) at 130 °C for 3 hours. Purification *via* column chromatography eluting with 1:19 ethyl acetate/petrol 40-60 followed by recrystallization from petrol 60-80/ethyl acetate afforded the title compound **201** as white needles (5.77 g, 60 % over 2 steps).

Melting point: 144-146 °C (ethyl acetate/petrol 60-80);

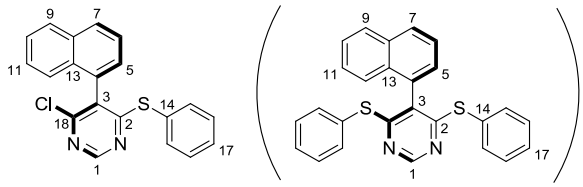
^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 8.92 (s, 1H, H_1), 8.01 (d, J = 8.3 Hz, 1H, H_7), 7.96 (d, J = 8.1 Hz, 1H, H_9), 7.60 (dd, J = 8.2, 7.2 Hz, 1H, H_6), 7.56 (ddd, J = 8.1, 7.1, 1.1 Hz, 1H, H_{10}), 7.49 (ddd, J = 8.3, 6.8, 1.5 Hz, 1H, H_{11}), 7.39 (dd, J = 7.0, 1.1 Hz, 1H, H_5), 7.31 (d, J = 8.6 Hz, 1H, H_{12});

^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 162.5 (Quat, C_2), 157.4 (CH, C_1), 133.6 (Quat, C_8), 132.8 (Quat, C_3), 130.4 (Quat, C_4 and C_{13}), 130.1 (CH, C_7), 128.9 (CH, C_9), 127.4 (CH, C_5), 127.3 (CH, C_{11}), 126.6 (CH, C_{10}), 125.4 (CH, C_6), 124.0 (CH, C_{12});

FTIR (neat) ν/cm^{-1} = 3044, 1546, 1508, 1401, 1377, 1351, 1262, 1231;

HRMS (FI$^+$) calculated for $C_{14}H_8Cl_2N_2$ = 274.0065, mass found = 274.0068.

(*R*)-4-Chloro-5-(naphthalen-1-yl)-6-(phenylthio)pyrimidine, 203



Asymmetric: According to **General Procedure E** with **201** (50 mg, 0.18 mmol), carbon tetrachloride (1.8 mL), *N*-benzylquininium chloride (8 mg, 0.018 mmol), thiophenol (20.3 μL, 0.20 mmol), 50 % w/w aqueous potassium carbonate (0.12 mL, 0.90 mmol) at room

temperature for 48 hours. Purification *via* column chromatography eluting with 1:19 ethyl acetate/petrol 40-60 afforded the title compound **203** as a white solid (59 mg, 93 %, 97:3 e.r.) along with by-product **204** as a white solid (4.5 mg, 6 %).

Racemic: According to **General Procedure F** with **201** (36 mg, 0.13 mmol), toluene (1.3 mL), tetrabutylammonium bromide (4 mg, 0.013 mmol), thiophenol (14.8 μL, 0.14 mmol), 50 % w/w aqueous potassium hydroxide (36 μL, 0.65 mmol) at room temperature for 1 hour. Purification *via* column chromatography eluting with 1:19 ethyl acetate/petrol 40-60 afforded the title compound *rac*-**203** as a white solid (38 mg, 83 %) along with by-product **204** as a white solid (2.8 mg, 5 %).

Data for **203**

Melting point: 140-142 ^{o}C (ethyl acetate/petrol 40-60);

^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 8.72 (s, 1H, H_1), 8.05 (d, J = 8.2 Hz, 1H, H_7), 8.00 (d, J = 7.9 Hz, 1H, H_9), 7.66 (dd, J = 6.8, 8.6 Hz, 1H, H_6), 7.62-7.56 (m, 1H, H_{10}), 7.57-7.51 (m, 2H, H_5 and H_{11}), 7.49-7.39 (m, 6H, H_{12}, H_{15}, H_{16} and H_{17});

^{13}C NMR (126 MHz, $CDCl_3$) δ_C = 173.2 (Quat, C_2), 159.7 (Quat, C_{18}), 157.5 (CH, C_1), 135.9 (CH, C_{15}), 134.3 (Quat, C_8), 131.0 (Quat, C_{Ar}), 130.9 (Quat, C_{Ar}), 130.5 (CH, C_7), 130.1 (CH, C_{17}), 129.7 (CH, C_{16}), 129.5 (Quat, C_{Ar}), 129.3 (CH, C_9), 128.5 (CH, C_5), 128.5 (Quat, C_{Ar}), 127.6 (CH, C_{11}), 127.0 (CH, C_{10}), 126.1 (CH, C_6), 124.6 (CH, C_{12});

FTIR (neat) ν/cm^{-1} = 3059, 1536, 1501, 1397, 1345, 1231;

HRMS (ESI^{+}) calculated for $C_{20}H_{13}ClN_2NaS$ = 371.0380, mass found = 371.0376.

Chiral HPLC (Chiralpak ADH, 20 % IPA, 80 % hexane, 1.0 mL/min, λ = 219 nm, 20 μL injection) τ_R (minor) = 8.1 min, τ_R (major) = 10.3 min;

$[\alpha]_D^{20}$ = 0 (*c* = 1.00, $CHCl_3$).

Data for **204**

Melting point: 208-210 °C (ethyl acetate/petrol 40-60);

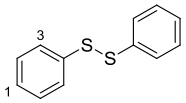
^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 8.61 (s, 1H, H_1), 8.07 (d, J = 8.1 Hz, 1H, H_7), 8.01 (d, J = 7.1 Hz, 1H, H_9), 7.70 (dd, J = 7.8, 7.3 Hz, 1H, H_6), 7.66-7.56 (m, 4H, H_5, H_{10}, H_{11} and H_{12}), 7.50-7.45 (m, 4H, H_{15}), 7.42-7.36 (m, 6H, H_{16} and H_{17});

^{13}C NMR (121 MHz, $CDCl_3$) δ_C = 168.2 (Quat, C_2), 157 (CH, C_1), 135.4 (CH, C_{15}), 134.1 (Quat, C_{Ar}), 130.8 (Quat, C_{Ar}), 130.7 (Quat, C_{Ar}), 130.1 (CH, C_7), 129.3 (CH, C_{17}), 129.1 (CH, C_{16}), 128.9 (Quat, C_{14}), 128.8 (CH, C_{Ar}), 128.8 (CH, C_{Ar}), 127.1 (CH, C_{11}), 126.8 (Quat, C_{Ar}), 126.6 (CH, C_{10}), 125.9 (CH, C_6), 124.4 (CH, C_{12});

FTIR (neat) ν/cm^{-1} = 3057, 1507, 1397, 1339;

HRMS (ESI$^+$) calculated for $C_{26}H_{18}N_2NaS_2$ = 445.0804, mass found = 445.0825.

1,2-Diphenyldisulfane



If the reaction was carried out without purging the atmosphere with nitrogen, traces of this compound < 1 mg were isolated from the asymmetric S_NAr reaction. The spectral data matched that previously reported in the literature.[116]

Melting point: 54-55 °C (ethyl acetate/petrol 40-60), [lit. 51-52 °C][117];

^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 7.44-7.40 (m, 4H, H_3), 7.25-7.20 (m, 4H, H_2), 7.17-7.13 (m, 2H, H_1);

^{13}C NMR (126 MHz, $CDCl_3$) δ_C = 137.2 (Quat, C_4), 129.2 (CH, C_{Ar}), 127.6 (CH, C_{Ar}), 127.3 (CH, C_1);

FTIR (neat) ν/cm^{-1} = 3070, 1577, 1475, 1437.

Table 3.1 – Initial base optimization

Entries 1-5: According to **General Procedure E** with **201** (10 mg, 0.036 mmol), toluene (0.36 mL), *N*-benzylcinchonidinium chloride (1.5 mg, 0.0036 mmol), thiophenol (4.3 μL, 0.20 mmol) and *the appropriate base* at room temperature for 48 hours. An analytical HPLC sample of **203** was obtained by preparative TLC (1:4 ethyl acetate/petrol 40-60).

Table 3.2 – Catalyst optimization

Entries 1-13: According to **General Procedure E** with **201** (10 mg, 0.036 mmol), toluene (0.36 mL), *the appropriate phase-transfer catalyst* (0.0036 mmol), thiophenol (4.3 μL, 0.036 mmol) and 50 % w/w aqueous potassium carbonate (50 μL, 0.36 mmol) at room temperature for 48 hours. An analytical HPLC sample of **203** was obtained by preparative TLC (1:4 ethyl acetate/petrol 40-60).

Table 3.3 – Base optimization

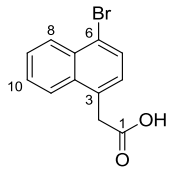
Entries 1-7: According to **General Procedure E** with **201** (20 mg, 0.072 mmol), *the appropriate solvent* (0.73 mL), *N*-benzylquininium chloride (3 mg, 0.007 mmol), thiophenol (8.6 μL, 0.073 mmol) and *the appropriate base* (0.36 mmol) at room temperature for 24 hours. An analytical HPLC sample of **203** was obtained by preparative TLC (1:4 ethyl acetate/petrol 40-60).

Figure 203 - Thermal stability of 203

A solution of **203** (5 mg, 0.014 mmol, 97:3 e.r.) in DMSO (0.5 mL) was heated to 100 ^{o}C (oil bath temperature) for 20 hours. The solution was cooled to room temperature and diluted

with ethyl acetate. An analytical HPLC sample of **203** (97:3 e.r.) was obtained by prepaprative TLC (1:4 ethyl acetate/petrol 40-60).

2-(4-Bromonaphthalen-1-yl)acetic acid, 214



This compound was prepared according to a literature procedure.[118]

To a stirred room temperature solution of 1-naphthaleneacetic acid (10.0 g, 53.7 mmol) in glacial acetic acid (30 mL) was added bromine (2.75 mL, 53.7 mmol). The resulting solution was heated to 60 ^{o}C for 2 hours. After this time, stirring was stopped and the solution was allowed to cool to room temperature and then left to stand for 6 hours, after which time a crystalline solid had formed. The solid was obtained by vacuum filtration and was washed with aqueous acetic acid (10 % v/v, 25 mL). The resulting solid was dried under high vacuum to afford the title compound **214** as a white solid (5.11 g, 36 %), which was contaminated by c.a. 10 % of an inseparable regioisomeric impurity. The spectral data matched that previously reported in the literature.[118]

Melting point: 147-150 ^{o}C (acetic acid);

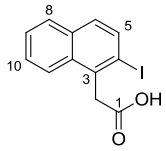
^{1}H NMR (400 MHz, d_6-DMSO) δ_H = 12.51 (s, 1H, COO*H*), 8.20-8.18 (m, 1H, H_{Ar}), 8.05-8.02 (m, 1H, H_{Ar}), 7.85 (d, J = 7.7 Hz, 1H, H_5), 7.73-7.66 (m, 2H, H_9 and H_{10}), 7.39 (d, J = 7.6 Hz, 1H, H_4), 4.08 (s, 2H, H_2);

^{13}C NMR (101 MHz, d_6-DMSO) δ_C = 172.8 (Quat, C_1), 133.7 (Quat, C_{Ar}), 132.9 (Quat, C_{Ar}), 131.7 (Quat, C_{Ar}), 130.1 (CH, C_5), 129.2 (CH, C_4), 128.1 (CH, C_{Ar}), 127.7 (CH, C_{Ar}), 127.4 (CH, C_{Ar}), 125.4 (CH, C_{Ar}), 121.5 (Quat, C_6), 38.7 (CH_2, C_2);

FTIR (neat) ν/cm^{-1} = 3300-2800 (br), 1697, 1597, 1567, 1507, 1410, 1381, 1316, 1240, 1219, 1197, 1160, 1113, 1025;

LRMS (ESI^-) 263 & 265 ($[M - H]^-$).

2-(2-Iodonaphthalen-1-yl)acetic acid, 215



This compound was prepared by modification of a literature procedure.[119]

A solution of 1-naphthaleneacetic acid (3.13 g, 16.8 mmol), palladium acetate (189 mg, 0.84 mmol), (diacetoxyiodo)benzene (4.05 g, 12.6 mmol) and iodine (3.20 g, 12.6 mmol) in anhydrous dimethylformamide (100 mL) was heated to 70 ^oC for 24 hours in the dark. After this time, the reaction mixture was cooled to room temperature and palladium acetate (189 mg, 0.84 mmol), (diacetoxyiodo)benzene (4.05 g, 12.6 mmol) and iodine (3.20 g, 12.6 mmol) were added and the reaction mixture was heated to 70 ^oC for a further 24 hours in the dark. After this time, the reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue was purified by column chromatography eluting with a gradient from petrol 40-60 to 3:7 ethyl acetate/petrol 40-60. The resulting solid was further purified by recrystallization from petrol 60-80/ethyl acetate, affording the title compound **215** as a yellow solid (1.29 g, 25 %). The spectral data matched that previously reported in the literature.[119]

Melting point: 178-180 ^oC (petrol 60-80/ethyl acetate);

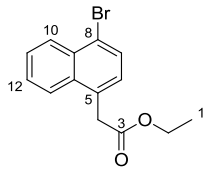
^1H NMR (400 MHz, d_6-acetone) δ_H = 12.0-10.0 (br s, 1H, COO*H*), 8.15-8.10 (m, 1H, H_{Ar}), 7.97-7.92 (m, 2H, H_{Ar}), 7.65-7.55 (m, 3H, H_{Ar}), 4.44 (s, 2H, H_2);

^{13}C NMR (101 MHz, d_6-acetone) δ_C = 170.6 (Quat, C_1), 135.9 (CH, C_{Ar}), 135.0 (Quat, C_{Ar}), 133.3 (Quat, C_{Ar}), 133.0 (Quat, C_{Ar}), 129.2 (CH, C_{Ar}), 128.6 (CH, C_{Ar}), 127.3 (CH, C_{Ar}), 126.3 (CH, C_{Ar}), 124.7 (CH, C_{Ar}), 100.8 (Quat, C_4), 43.0 (CH_2, C_2);

FTIR (neat) ν/cm^{-1} = 3400-2800 (br), 1692, 1452, 1327, 1232;

LRMS (ESI$^+$) 335 ([M + Na]$^+$).

Ethyl 2-(4-bromonaphthalen-1-yl)acetate, 216



A stirred solution of **214** (5.11 g, 19.4 mmol) in ethanol (23 mL) was cooled to 0 ^{o}C. Thionyl chloride (1.7 mL, 23.2 mmol) was added and the resulting solution was warmed to room temperature and stirred for 3 hours. After this time, the reaction mixture was concentrated to dryness under reduced pressure. The residue was redissolved in ethyl acetate and washed successively with brine (x 2), 2 M aqueous sodium carbonate, brine and then dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. Purification of the residue *via* column chromatography eluting with 2.5:97.5 ethyl acetate/petrol 40-60 to afford the title compound **216** as a gummy solid (4.76 g, 84 %) which was contaminated by c.a. 10 % of an inseparable regioisomeric impurity.

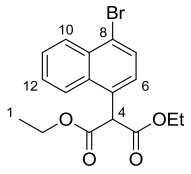
^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 8.21-8.17 (m, 1H, H_{Ar}), 7.91-7.86 (m, 1H, H_{Ar}), 7.64 (d, J = 7.7 Hz, 1H, H_{Ar}), 7.53-7.45 (m, 2H, H_{Ar}), 7.15 (d, J = 7.5 Hz, 1H, H_{Ar}), 4.05 (q, J = 7.1 Hz, 2H, H_2), 3.92 (s, 2H, H_4), 1.12 (t, J = 7.2 Hz, 3H, H_1);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 171.1 (Quat, C_3), 133.3 (Quat, C_{Ar}), 132.2 (Quat, C_{Ar}), 130.9 (Quat, C_{Ar}), 129.6 (CH, C_{Ar}), 128.4 (CH, C_{Ar}), 128.0 (CH, C_{Ar}), 127.2 (CH, C_{Ar}), 127.2 (CH, C_{Ar}), 124.4 (CH, C_{Ar}), 122.7 (Quat, C_8), 61.1 (CH_2, C_2), 39.1 (CH_2, C_4), 14.2 (CH_3, C_1);

FTIR (neat) ν/cm^{-1} = 2981, 1729, 1379, 1367, 1315, 1253, 1171, 1150, 1024;

HRMS (ESI^+) calculated for $C_{14}H_{13}BrNaO_2$ = 314.9991, mass found = 314.9988

Diethyl 2-(4-bromonaphthalen-1-yl)malonate, 217



A stirred suspension of sodium hydride (60 % w/w in mineral oil, 1.62 g, 40.6 mmol) in THF (24 mL) was heated to 40 °C. A solution of **216** (4.76 g, 16.2 mmol) in THF (9 mL) was added dropwise *via* cannula. The resulting suspension was stirred at 40 °C for 5 minutes and then cooled to room temperature. Diethyl carbonate (7.8 mL, 65 mmol) was added and the reaction mixture was stirred at room temperature for 24 hours and then cooled to 0 °C and quenched by dropwise addition of 25 % aqueous HCl (5.2 mL) [care – mixture foams and evolves hydrogen gas] and then diluted with water (10 mL). The volatile organics were removed under reduced pressure and the remaining aqueous suspension was extracted three times with ethyl acetate. The combined organic extracts were washed successively with 1 M HCl and brine, dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. Purification of the residue *via* column chromatography eluting with 7:93 ethyl acetate/petrol 40-60 afforded the title compound **217** as a yellow oil (5.70 g, 96 %) which was contaminated by c.a. 10 % of an inseparable regioisomeric impurity.

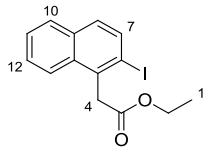
^1H NMR (400 MHz, $CDCl_3$) δ_H = 8.26-8.19 (m, 1H, H_{Ar}), 7.90-7.84 (m, 1H, H_{Ar}), 7.71 (d, J = 7.8 Hz, 1H, H_{Ar}), 7.56-7.47 (m, 2H, H_{Ar}), 7.34 (d, J = 7.9 Hz, 1H, H_{Ar}), 5.30 (s, 1H, H_4), 4.22-4.10 (m, 4H, H_2), 1.16 (t, J = 7.1 Hz, 6H, H_1);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 168.1 (Quat, C_3), 132.9 (Quat, C_{Ar}), 132.3 (Quat, C_{Ar}), 129.6 (CH, C_{Ar}), 129.5 (Quat, C_{Ar}), 128.3 (CH, C_{Ar}), 127.5 (2 x CH, C_{Ar}), 127.3 (CH, C_{Ar}), 123.8 (Quat, C_8), 123.4 (CH, C_{Ar}), 62.1 (CH_2, C_2), 54.3 (CH, C_4), 14.0 (CH_3, C_1);

FTIR (neat) ν/cm^{-1} = 2982, 1730, 1302, 1256, 1233, 1193, 1175, 1143, 1034;

HRMS (ESI^+) calculated for $C_{17}H_{17}BrNaO_4$ = 387.0202, mass found = 387.0199.

Ethyl 2-(2-iodonaphthalen-1-yl)acetate, 218



A stirred solution of **215** (1.23 g, 3.94 mmol) in ethanol (10 mL) was cooled to 0 ^oC. Thionyl chloride (0.85 mL, 11.7 mmol) was added and the resulting solution was warmed to room temperature and stirred for 8 hours. A further portion of thionyl chloride (0.86 mL, 11.8 mmol) was added and the resulting solution was stirred at room temperature for 16 hours and then concentrated to dryness under reduced pressure. The residue was redissolved in ethyl acetate and washed successively with brine (x 2), 2M aqueous sodium carbonate, brine and then dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. Purification of the residue *via* column chromatography eluting with 3:97 ethyl acetate/petrol 40-60 to afford the title compound **218** as a pale yellow solid (1.20 g, 90 %).

Melting point: 40-41 ^oC (petrol 40-60/ethyl acetate);

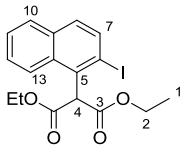
^1H NMR (400 MHz, $CDCl_3$) δ_H = 7.88-7.83 (m, 1H, H_{Ar}), 7.79 (d, J = 8.6 Hz, 1H, H_{Ar}), 7.73-7.68 (m, 1H, H_{Ar}), 7.45-7.39 (m, 2H, H_{11} and H_{12}), 7.37 (d, J = 8.9 Hz, 1H, H_{Ar}), 4.27 (s, 2H, H_4), 4.08 (q, J = 7.2 Hz, 2H, H_2), 1.15 (t, J = 7.1 Hz, 3H, H_1);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 170.3 (Quat, C_3), 136.1 (CH, C_{Ar}), 134.3 (Quat, C_{Ar}), 133.2 (Quat, C_{Ar}), 132.9 (Quat, C_{Ar}), 129.2 (CH, C_{Ar}), 128.7 (CH, C_{Ar}), 127.3 (CH, C_{Ar}), 126.2 (CH, C_{Ar}), 124.3 (CH, C_{Ar}), 101.4 (Quat, C_6), 61.1 (CH_2, C_2), 43.8 (CH_2, C_4), 14.2 (CH_3, C_1);

FTIR (neat) ν/cm^{-1} = 2980, 1727, 1580, 1505, 1323, 1248, 1194, 1171, 1027;

HRMS (ESI$^+$) calculated for $C_{14}H_{13}INaO_2$ = 362.9852, mass found = 362.9853.

Diethyl 2-(2-iodonaphthalen-1-yl)malonate, 219



A stirred suspension of sodium hydride (60 % w/w in mineral oil, 317mg, 7.93 mmol) in THF (5 mL) was heated to 40 ^{o}C. A solution of **218** (1.08 g, 3.17 mmol) in THF (2 mL) was added dropwise *via* cannula. The resulting suspension was stirred at 40 ^{o}C for 5 minutes and then cooled to room temperature. Diethyl carbonate (1.54 mL, 12.7 mmol) was added and the reaction mixture was stirred at room temperature for 18 hours. After this time, only starting material could be detected by TLC (5 % ethyl acetate/petrol 40-60). Ethyl chloroformate (1.22 mL, 12.8 mmol) was added and the reaction mixture was stirred at room temperature for 24 hours and 1 M HCl and ethyl acetate were added. The organic layer was separated and the aqueous layer was extracted twice with ethyl acetate. The combined organic extracts were washed successively with 1M HCl and brine, dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. Purification of the residue *via* column chromatography eluting with 1:19 ethyl acetate/petrol 40-60 afforded the title compound **219** as a yellow solid (294 mg, 22 %).

Melting point: 87-88 ^{o}C (petrol 40-60/ethyl acetate);

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 8.08-8.01 (m, 1H, H_{Ar}), 7.91 (d, J = 8.8 Hz, 1H, H_{Ar}), 7.82-7.77 (m, 1H, H_{Ar}), 7.52-7.45 (m, 3H, H_{Ar}), 5.75 (s, 1H, H_4), 4.24 (dq, J = 10.8, 7.1 Hz, 2H, H_{2A}), 4.21 (dq, J = 10.9, 7.0 Hz, 2H, H_{2B}), 1.20 (t, J = 7.1 Hz, 6H, H_1);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 167.9 (Quat, C_3), 136.1 (CH, C_{Ar}), 133.8 (Quat, C_{Ar}), 133.7 (Quat, C_{Ar}), 132.5 (Quat, C_{Ar}), 130.4 (CH, C_{Ar}), 128.6 (CH, C_{Ar}), 126.9 (CH, C_{Ar}), 126.3 (CH, C_{Ar}), 125.9 (CH, C_{Ar}), 103.2 (Quat, C_{Ar}), 62.9 (CH, C_4), 62.0 (CH_2, C_2), 14.0 (CH_3, C_1);

FTIR (neat) ν/cm^{-1} = 2983, 1731, 1303, 1225, 1151, 1070, 1034;

HRMS (ESI^+) calculated for $C_{17}H_{17}INaO_4$ = 435.0064, mass found = 435.0064.

Scheme 3.34a – Palladium catalysed coupling

This reaction was carried out according to a literature procedure.[120]

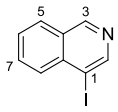
An oven dried schlenk tube was charged sequentially with freshly distilled diethyl malonate (405 μL, 2.65 mmol), anhydrous THF (7.2 mL), sodium hydride (60 % w/w in mineral oil, 110 mg, 2.75 mmol) and the resulting mixture was stirred at room temperature for 10 minutes. 1-Naphthyl bromide (338 mL, 2.41 mmol) was added followed by tri-*tert*-butylphosphonium tetrafluoroborate (28 mg, 0.09 mmol) and $Pd(dba)_2$ (28 mg, 0.048 mmol) and the resulting mixture was heated to 70 ^{o}C for 20 hours and then cooled to room temperature and concentrated under reduced pressure. Purification of the residue *via* column chromatography eluting with 7:93 ethyl acetate/petrol 40-60 returned the starting material **220** (323 mg, 65 %) along with a small quantity of product **202** which could not be separated from diethyl malonate.

Scheme 3.34b - Copper catalysed coupling

According to **General Procedure C** with copper (I) iodide (67 mg, 0.35 mmol), 2-picolinic acid (43 mg, 0.35 mmol), cesium carbonate (3.42 g, 10.5 mmol), 1,4-dioxane (3.5 mL),

diethylmalonate (1.10 mL, 7.00 mmol) and 2-iodonaphthalene (511 μL, 3.50 mmol) at room temperature for 20 hours. TLC and crude ^{1}H NMR indicated only a trace of starting material **178** to be present along with product **202** which could not be separated from diethyl malonate.

4-Iodoisoquinoline, 221



This compound was prepared by analogy to a literature procedure.[121]

An oven dried Schlenk tube was charged sequentially with copper (I) iodide (458 mg, 2.40 mmol), sodium iodide (7.20 g, 48.1 mmol) and 4-bromoisoquinoline (5.00 g, 24.0 mmol). The atmosphere was purged with argon three times and anhydrous 1,4-dioxane (24 mL) and *N*,*N'*-dimethylethylenediamine (0.52 mL, 4.81 mmol) were added. The resulting stirred solution was heated to 110 ^{o}C for 21 hours and then cooled to room temperature. Aqueous ammonium hydroxide (28 % NH_3, 120 mL) and water (500 mL) were added. The resulting mixture was extracted three times with dichloromethane. The combined organic extracts were dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. Purification of the residue *via* column chromatography eluting with petrol 40-60 afforded a 1:0.23 inseparable mixture of the title compound **221** with the starting aryl bromide (5.40 g, 91 % brsm) as a white solid. The spectral data matched that previously reported in the literature.[122]

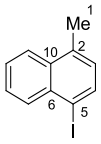
^{1}H NMR (400 MHz, $CDCl_3$) δ_H = Data quoted is for aryl iodide (peaks from the aryl bromide are excluded for clarity) 9.11 (s, 1H, H_{Ar}), 8.29 (s, 1H, H_{Ar}), 7.98-7.91 (m, 1H, H_{Ar}), 7.86 (d, J = 8.4 Hz, 1H, H_{Ar}), 7.78-7.73 (m, 1H, H_{Ar}), 7.66-7.60 (m, 1H, H_{Ar});

^{13}C NMR (101 MHz, $CDCl_3$) δ_C = Data quoted is for aryl iodide (peaks from the aryl bromide are excluded for clarity) 152.6 (CH, C_{Ar}), 151 (CH, C_{Ar}), 137.1 (Quat, C_{Ar}), 132 (CH, C_{Ar}), 130.7 (CH, C_{Ar}), 129.7 (Quat, C_{Ar}), 128.3 (CH, C_{Ar}), 128.1 (CH, C_{Ar}), 96.8 (Quat, C_1);

FTIR (neat) ν/cm^{-1} = 3022, 1616, 1570, 1559, 1486, 1446, 1373, 1306, 1249, 1226, 1216, 1163, 1141, 1090, 1019;

LRMS (ESI+) 256 ($[M + H]^+$).

1-Iodo-4-methylnaphthalene, 222



This compound was prepared by analogy to a literature procedure.[121]

An oven dried Schlenk tube was charged sequentially with copper (I) iodide (441 mg, 2.32 mmol) and sodium iodide (6.94 g, 46.3 mmol). The atmosphere was purged with argon three times and anhydrous 1,4-dioxane (23 mL), *N*,*N'*-dimethylethylenediamine (0.50 mL, 4.63 mmol) and 1-bromo-4-methylnaphthalene (5.12 g, 23.2 mmol) were added. The resulting stirred solution was heated to 110 ^oC for 24 hours and then cooled to room temperature. Aqueous ammonium hydroxide (28 % NH_3, 120 mL) and water (500 mL) were added. The resulting mixture was extracted three times with dichloromethane. The combined organic extracts were dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. Purification of the residue *via* column chromatography eluting with petrol 40-60 afforded a 1:0.76 inseparable mixture of the title compound **222** with the starting aryl bromide as a pale yellow oil (5.46 g, 95 % brsm). The spectral data matched that previously reported in the literature.[123]

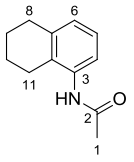
^{1}H NMR (400 MHz, $CDCl_3$) δ_H = Data quoted is for aryl iodide (peaks from the aryl bromide are excluded for clarity) 8.15-8.12 (m, 1H, H_{Ar}), 7.98 (d, J = 7.3 Hz, 1H, H_{Ar}), 7.96-7.92 (m, 1H, H_{Ar}), 7.64-7.54 (m, 2H, H_{Ar}), 7.04 (dd, J = 7.6, 0.7 Hz, 1H, H_{Ar}), 2.67 (s, 3H, H_1);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C = Data quoted is for aryl iodide (peaks from the aryl bromide are excluded for clarity) 137.2 (CH, C_{Ar}), 135.5 (Quat, C_{Ar}), 134.1 (Quat, C_{Ar}), 133.5 (Quat, C_{Ar}), 132.8 (CH, C_{Ar}), 127.8 (CH, C_{Ar}), 127.4 (CH, C_{Ar}), 126.6 (CH, C_{Ar}), 124.7 (CH, C_{Ar}), 97.1 (Quat, C_5), 19.3 (CH_3, C_1);

FTIR (neat) ν/cm^{-1} = 3067, 2944, 1593, 1561, 1506, 1440, 1416, 1379, 1258, 1228, 1198, 1161, 1110, 1029;

HRMS (FI+) calculated for $C_{11}H_9I$ = 267.9749; mass found = 267.9752.

_N_-(5,6,7,8-Tetrahydronaphthalen-1-yl)acetamide, 226



Boron trifluoride diethyl etherate (5.00 mL, 40.7 mmol) was stirred at 0 °C and a solution of 5,6,7,8-tetrahydro-1-naphthylamine (4.00 g, 27.2 mmol) in dichloromethane (54 mL) was added over 5 minutes. A solution of *tert*-butyl nitrite (90 %, 4.30 mL, 32.6 mmol) in dichloromethane (27 mL) was added over 30 minutes. The resulting suspension was stirred at -15 °C for 20 minutes and then warmed to 0 °C and stirred for a further 30 minutes. The suspension was then warmed to room temperature and concentrated to dryness under reduced pressure. The residue was suspended in acetonitrile (96 mL). At this point a significant exothermic reaction was observed which caused the solvent to boil. The reaction was cooled to 0 °C and the resulting solution was added to a stirred suspension of sodium iodide (4.89 g, 32.6 mmol) and iodine (690 mg, 2.72 mmol) in acetonitrile (177 mL). The reaction mixture was

warmed to room temperature and stirred for 1 hour and then saturated aqueous sodium sulfite and dichloromethane were added. The organic layer was separated and the aqueous layer was extracted twice with dichloromethane. The combined organic extracts were dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. Purification of the residue *via* column chromatography eluting with 1:1 ethyl acetate/petrol 40-60 afforded the title compound **226** as a white solid (3.05 g, 59 %). The spectral data matched that previously reported in the literature.[124]

Melting point: 139-140 ^{o}C (petrol 40-60/ethyl acetate) [lit. 145-146 ^{o}C];[125]

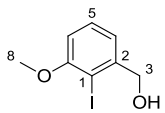
^{1}H NMR (400 MHz, $CDCl_3$)* δ_H = 7.42 (d, J = 7.8 Hz, 1H, H_4), 7.05 (t, J = 7.7 Hz, 1H, H_5), 6.89 (d, J = 7.6 Hz, 1H, H_6), 2.74 (t, J = 6.0 Hz, 2H, H_8), 2.55 (t, J = 6.1 Hz, 2H, H_{11}), 2.13 (s, 3H, H_1), 1.83-1.67 (m, 4H, H_9 and H_{10});

^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 168.8 (Quat, C_2), 138.0 (Quat, C_{Ar}), 135.3 (Quat, C_{Ar}), 129.5 (Quat, C_{Ar}), 126.6 (CH, C_6), 125.6 (CH, C_5), 121.6 (CH, C_4), 29.8 (CH_2, C_8), 24.6 (CH_2, C_{11}), 24.0 (CH_3, C_1), 22.8 (CH_2, $C_{9/10}$), 22.6 (CH_2, $C_{9/10}$);

FTIR (neat) ν/cm^{-1} = 3287 (br), 2933, 1653, 1538, 1467, 1371, 1303, 1283;

LRMS (ESI^{+}) 190 ([M + H]$^{+}$).

(2-Iodo-3-methoxyphenyl)methanol, 230



This compound was prepared according to a modified literature procedure.[71]

A stirred solution of *m*-anisaldehyde (5.00 g, 36.7 mmol) in diethyl ether (122 mL) was cooled to 0 ^{o}C and lithium aluminium hydride (1.39 g, 36.7 mmol) was added portionwise. The

* The broad singlet corresponding to the amide N*H* was not observed

reaction mixture was stirred at 0 °C for 30 minutes. After this time, water (1.39 mL) was added dropwise followed by sequential dropwise addition of 15 % aqueous sodium hydroxide (1.39 mL) and water (4.17 mL). The resulting granular suspension was warmed to room temperature and stirred rapidly for 1 hour. Magnesium sulfate was added and the suspension was filtered through a pad of Celite®, washing with diethyl ether. The filtrate was concentrated under reduced pressure to afford the crude alcohol **229** (5.06 g) which was used without further purification in the next step.

A stirred solution of crude alcohol **229** thus obtained (5.06 g) in a mixture of diethyl ether (61 mL) and hexane (183 mL) was cooled to 0 °C. *n*-Butyllithium (2.5 M in hexanes, 32.3 mL, 80.7 mmol) was added dropwise and the resulting solution was warmed to room temperature and stirred for 4 hours and then cooled to 0 °C. A solution of iodine (14.0 g, 55.1 mmol) in THF (61 mL) was added. The resulting mixture was warmed to room temperature and stirred for 30 minutes and 10 % aqueous sodium thiosulfate was added. The organic layer was separated and the aqueous layer was extracted with ethyl acetate three times. The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. Purification of the residue *via* column chromatography eluting with 3:17 ethyl acetate/petrol 40-60 followed by recrystallization from hexane/ethyl acetate afforded the title compound **230** as a white solid (4.25 g, 44 % over 2 steps). The spectral data matched that previously reported in the literature.[126]

Melting point: 85-87 °C (hexane/ethyl acetate) [lit. 90 °C];[126]

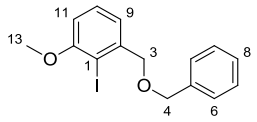
^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.30 (t, J = 7.9 Hz, 1H, H_5), 7.07 (d, J = 7.6 Hz, 1H, H_4), 6.75 (d, J = 8.1 Hz, 1H, H_6), 4.68 (d, J = 6.1 Hz, 2H, H_3), 3.89 (s, 3H, H_8), 2.38 (t, J = 6.4 Hz, 1H, O*H*).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 157.9 (Quat, C_7), 144.6 (Quat, C_2), 129.4 (CH, C_5), 120.9 (CH, C_4), 110.1 (CH, C_6), 89.4 (Quat, C_1), 69.7 (CH_2, C_3), 56.6 (CH_3, C_8);

FTIR (neat) ν/cm^{-1} = 3300, 2836, 1587, 1567, 1467, 1428, 1287, 1267, 1187, 1041, 1011;

LRMS (ESI^+) 287 ($[M + Na]^+$).

1-((Benzyloxy)methyl)-2-iodo-3-methoxybenzene, 231



A suspension of sodium hydride (60 % w/w in mineral oil, 666 mg, 16.7 mmol) in THF (30 mL) was cooled to 0 ^oC. A solution of **230** (4.00 g, 15.1 mmol) in THF (20 mL) was added dropwise and the resulting suspension was stirred for 5 minutes at 0 ^oC. Benzyl bromide (1.98 mL, 16.7 mmol) was added dropwise and the reaction mixture was warmed to room temperature and stirred for 2 hours. After this time further sodium hydride (60 % w/w in mineral oil, 333 mg, 8.40 mmol) and benzyl bromide (0.99 mL, 8.40 mmol) were added and the reaction mixture was stirred at room temperature for 1 hour and then cooled to 0 ^oC. Saturated aqueous ammonium chloride was added followed by ethyl acetate. The organic layer was separated and the aqueous layer was extracted twice with ethyl acetate. The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. Purification of the residue *via* column chromatography eluting with 1:19 ethyl acetate/petrol 40-60 afforded the title compound **231** as a white solid (4.40 g, 82 %).

Melting point: 57-58 ^oC (petrol 40-60/ethyl acetate);

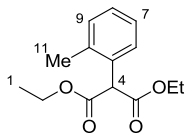
^1H NMR (400 MHz, $CDCl_3$) δ_H = 7.43 (d, J = 7.5 Hz, 2H, H_6), 7.38 (t, J = 7.3 Hz, 2H, H_7), 7.34-7.29 (m, 2H, H_8 and H_{10}), 7.16 (t, J = 7.6 Hz, 1H, H_9), 6.77 (d, J = 8.3 Hz, 1H, H_{11}), 4.66 (s, 2H, H_4), 4.62 (s, 2H, H_3), 3.90 (s, 3H, H_{13});

^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 157.9 (Quat, C_{12}), 142.5 (Quat, C_{Ar}), 138.2 (Quat, C_{Ar}), 129.1 (CH, C_{Ar}), 128.5 (CH, C_7), 127.8 (CH, C_6), 127.7 (CH, C_{Ar}), 121.2 (CH, C_9), 110.0 (CH, C_{11}), 89.9 (Quat, C_1), 76.5 (CH_2, C_3), 72.8 (CH_2, C_4), 56.6 (CH_3, C_{13});

FTIR (neat) ν/cm^{-1} = 2837, 1568, 1466, 1428, 1351, 1269, 1110, 1062, 1014;

HRMS (ESI$^+$) calculated for $C_{15}H_{16}O_2I$ = 355.0190, mass found = 355.0193.

Diethyl 2-(*o*-tolyl)malonate, 232



According to **General Procedure C** with copper (I) iodide (262 mg, 1.38 mmol), 2-picolinic acid (169 mg, 1.38 mmol), cesium carbonate (13.4 g, 41.3 mmol), 1,4-dioxane (14 mL), diethylmalonate (4.2 mL, 27.5 mmol) and 2-iodotoluene (1.75 mL, 13.8 mmol) at 50 ^{o}C for 20 hours. Purification *via* column chromatography eluting twice with 3:97 ethyl acetate/petrol 40-60 to afford the title compound **232** as a colourless oil (3.33 g, 97 %). The spectral data matched that previously reported in the literature.[86]

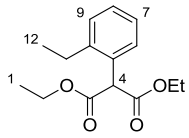
^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.43-7.37 (m, 1H, H_{Ar}), 7.25-7.17 (m, 3H, H_{Ar}), 4.88 (s, 1H, H_4), 4.25 (dq, J = 10.8, 7.2 Hz, 2H, H_{2A}), 4.22 (dq, J = 10.8, 7.1 Hz, 2H, H_{2B}), 2.35 (s, 3H, H_{11}), 1.27 (t, J = 7.1 Hz, 6H, H_1);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 168.4 (Quat, C_3), 136.5 (Quat, C_{Ar}), 131.7 (Quat, C_{Ar}), 130.5 (CH, C_{Ar}), 128.9 (CH, C_{Ar}), 128.1 (CH, C_{Ar}), 126.3 (CH, C_{Ar}), 61.7 (CH_2, C_2), 54.4 (CH, C_4), 19.8 (CH_3, C_{11}), 14.0 (CH_3, C_1);

FTIR (neat) ν/cm^{-1} = 2982, 1731, 1464, 1367, 1301, 1263, 1210, 1144, 1096, 1031;

LRMS (ESI$^+$) 251 ([M + H]$^+$).

Diethyl 2-(2-ethylphenyl)malonate, 233



According to **General Procedure C** with copper (I) iodide (262 mg, 1.38 mmol), 2-picolinic acid (169 mg, 1.38 mmol), cesium carbonate (13.4 g, 41.3 mmol), 1,4-dioxane (14 mL), diethylmalonate (4.2 mL, 27.5 mmol) and 1-ethyl-2-iodobenzene (1.97 mL, 13.8 mmol) at 50 ^{o}C for 20 hours. Purification *via* column chromatography eluting with 1:19 ethyl acetate/petrol 40-60 and then with 2.5:97.5 ethyl acetate/toluene to afford the title compound **233** as a colourless oil (3.40 g, 94 %).

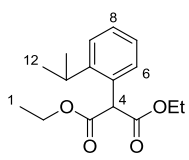
^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.39-7.34 (m, 1H, H_{Ar}), 7.22-7.11 (m, 3H, H_{Ar}), 4.84 (s, 1H, H_4), 4.16 (dq, J = 10.9, 7.1 Hz, 2H, H_{2A}), 4.12 (dq, J = 10.9, 7.1 Hz, 2H, H_{2B}), 2.60 (q, J = 7.6 Hz, 2H, H_{11}), 1.18 (t, J = 7.2 Hz, 6H, H_1), 1.14 (t, J = 7.7 Hz, 3H, H_{12});

^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 168.6 (Quat, C_3), 142.4 (Quat, C_{Ar}), 130.9 (Quat, C_{Ar}), 129.2 (CH, C_{Ar}), 128.9 (CH, C_{Ar}), 128.3 (CH, C_{Ar}), 126.3 (CH, C_{Ar}), 61.8 (CH_2, C_2), 53.5 (CH, C_4), 26.3 (CH_3, C_{11}), 15.3 (CH_3, C_{12}), 14.0 (CH_3, C_1);

FTIR (neat) ν/cm^{-1} = 2977, 1732, 1447, 1367, 1302, 1208, 1143, 1031;

HRMS (ESI^{+}) calculated for $C_{15}H_{21}O_4$ = 265.1434, mass found = 265.1432.

Diethyl 2-(2-isopropylphenyl)malonate, 234



According to **General Procedure C** with copper (I) iodide (262 mg, 1.38 mmol), 2-picolinic acid (169 mg, 1.38 mmol), cesium carbonate (13.4 g, 41.3 mmol), 1,4-dioxane (14 mL),

diethylmalonate (4.2 mL, 27.5 mmol) and 1-iodo-2-isopropylbenzene (2.20 mL, 13.8 mmol) at 50 ^{o}C for 20 hours. Purification was achieved *via* column chromatography eluting with 1:49 ethyl acetate/toluene and then twice with 1:19 ethyl acetate/petrol 40-60 to afford the title compound **234** as a colourless oil (2.96 g, 77 %). The spectral data matched that previously reported in the literature.[127]

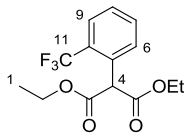
^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.43-7.37 (m, 1H, H_{Ar}), 7.33-7.28 (m, 2H, H_{Ar}), 7.24-7.18 (m, 1H, H_{Ar}), 5.01 (s, 1H, H_4), 4.25 (dq, J = 10.5, 7.0 Hz, 2H, H_{2A}), 4.20 (dq, J = 10.5, 7.0 Hz, 2H, H_{2B}), 3.12 (sept, J = 6.8 Hz, 1H, H_{11}), 1.26 (t, J = 7.2 Hz, 6H, H_1), 1.25 (d, J = 6.8 Hz, 6H, H_{12}).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 168.7 (Quat, C_3), 146.8 (Quat, C_{Ar}), 130.2 (Quat, C_{Ar}), 129.3 (CH, C_{Ar}), 128.4 (CH, C_{Ar}), 126.0 (CH, C_{Ar}), 125.5 (CH, C_{Ar}), 61.8 (CH_2, C_2), 53.5 (CH, C_4), 29.3 (CH, C_{11}), 23.7 (CH_3, C_{12}), 14.0 (CH_3, C_1).

FTIR (neat) ν/cm^{-1} = 2966, 1732, 1492, 1447, 1367, 1301, 1208, 1141, 1032;

LRMS (ESI^{+}) 279 ([M + H]$^{+}$).

Diethyl 2-(2-(trifluoromethyl)phenyl)malonate, 235



According to **General Procedure C** with copper (I) iodide (262 mg, 1.38 mmol), 2-picolinic acid (169 mg, 1.38 mmol), cesium carbonate (13.4 g, 41.3 mmol), 1,4-dioxane (14 mL), diethylmalonate (4.2 mL, 27.5 mmol) and 2-iodobenzotrifluoride (1.93 mL, 13.8 mmol) at 50 ^{o}C for 20 hours. Purification *via* column chromatography eluting with 1:49 ethyl acetate/toluene to afford the title compound **235** as a colourless oil (3.56 g, 85 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.67 (d, J = 8.3 Hz, 2H, H_6 and H_9), 7.60 (t, J = 7.6 Hz, 1H, H_{Ar}), 7.44 (t, J = 7.7 Hz, 1H, H_{Ar}), 5.09 (s, 1H, H_4), 4.24 (dq, J = 10.9, 7.1 Hz, 2H, H_{2A}), 4.21 (dq, J = 10.9, 7.1 Hz, 2H, H_{2B}), 1.25 (t, J = 7.1 Hz, 6H, H_1);

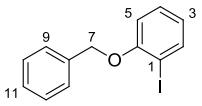
^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 167.7 (Quat, C_3), 132.0 (CH, C_{Ar}), 131.3 (Quat, C_{Ar}), 131.1 (CH, C_6), 128.9 (q, J = 29.9 Hz, Quat, C_{10}), 128.2 (CH, C_{Ar}), 125.9 (q, J = 5.6 Hz, CH, C_9), 124.1 (q, J = 274.2 Hz, Quat, C_{11}), 62.1 (CH_2, C_2), 53.6 (q, J = 2.3 Hz, CH, C_4), 13.9 (CH_3, C_1);

^{19}F NMR (376 MHz, $CDCl_3$) δ_F = -58.9;

FTIR (neat) ν/cm^{-1} = 2986, 1754, 1736, 1313, 1220, 1195, 1155, 1110, 1063, 1036;

HRMS (ESI^+) calculated for $C_{14}H_{15}O_4F_3Na$ = 327.0815, mass found = 327.0806.

1-(Benzyloxy)-2-iodobenzene, 349



This compound was prepared according to a literature procedure.[128]

To a solution of 2-iodophenol (5.2 g, 23.6 mmol) in acetone (120 mL) was added potassium carbonate (29.4 g, 213 mmol) and benzyl bromide (14.0 mL, 118 mmol). The resulting suspension was heated to reflux for 18 hours and then cooled to room temperature, filtered and washed with acetone. The filtrate was concentrated under reduced pressure. Purification of the residue *via* column chromatography eluting with a gradient from petrol 40-60 to 7:93 ethyl acetate/petrol 40-60 afforded the title compound **349** as a colourless oil (6.92 g, 94 %). The spectral data matched that previously reported in the literature.[129]

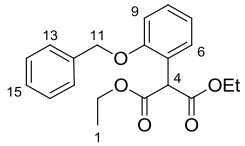
^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.83 (dd, J = 7.8, 1.5 Hz, 1H, H_2), 7.53 (d, J = 7.4 Hz, 2H, H_9), 7.44-7.39 (m, 2H, H_{10}), 7.37-7.32 (m, 1H, H_{11}), 7.31-7.26 (m, 1H, H_4), 6.88 (dd, J = 8.2, 1.3 Hz, 1H, H_5), 6.75 (td, J = 7.6, 1.2 Hz, 1H, H_3), 5.17 (s, 2H, H_7);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 157.2 (Quat, C_6), 139.6 (CH, C_2), 136.6 (Quat, C_8), 129.5 (CH, C_4), 128.6 (CH, C_{10}), 127.9 (CH, C_{11}), 127.0 (CH, C_9), 122.9 (CH, C_3), 112.8 (CH, C_5), 86.9 (Quat, C_1), 70.9 (CH_2, C_7);

FTIR (neat) ν/cm^{-1} = 3062, 1583, 1471, 1453, 1438, 1275, 1245, 1079, 1050;

LRMS (ESI$^+$) 333 ([M + Na]$^+$).

Diethyl 2-(2-(benzyloxy)phenyl)malonate, 236



According to **General Procedure C** with copper (I) iodide (262 mg, 1.38 mmol), 2-picolinic acid (169 mg, 1.38 mmol), cesium carbonate (13.4 g, 41.3 mmol), 1,4-dioxane (14 mL), diethylmalonate (4.2 mL, 27.5 mmol) and **349** (4.27 g, 13.8 mmol) at 50 ^{o}C for 20 hours. Purification *via* column chromatography eluting with 1:19 ethyl acetate/petrol 40-60 to afford the title compound **236** as a white solid (4.40 g, 93 %). The spectral data matched that previously reported in the literature.[130]

Melting point: 59-60 ^{o}C (petrol 40-60/ethyl acetate);

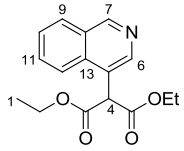
^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.44-7.27 (m, 7H, H_{Ar}), 7.01 (td, J = 7.5, 1.1 Hz, 1H, H_7), 6.96 (dd = 8.2, 1.1 Hz, 1H, H_9), 5.20 (s, 1H, H_4), 5.10 (s, 2H, H_{11}), 4.23 (dq, J = 10.8, 7.2 Hz, 2H, H_{2A}), 4.20 (dq, J = 10.6, 7.2 Hz, 2H, H_{2B}), 1.25 (t, J = 7.1 Hz, 6H, H_1);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 168.6 (Quat, C_3), 156.1 (Quat, C_{10}), 136.9 (Quat, C_{12}), 129.5 (CH, C_{Ar}), 129.3 (CH, C_{Ar}), 128.5 (CH, C_{Ar}), 127.9 (CH, C_{Ar}), 127.2 (CH, C_{Ar}), 122.4 (Quat, C_5), 121.0 (CH, C_7), 112.0 (CH, C_9), 70.2 (CH_2, C_{11}), 61.6 (CH_2, C_2), 51.7 (CH, C_4), 14.1 (CH_3, C_1);

FTIR (neat) ν/cm^{-1} = 2982, 1751, 1731, 1602, 1495, 1453, 1297, 1244, 1222, 1026;

LRMS (ESI$^+$) 365 ([M + Na]$^+$).

Diethyl 2-(isoquinolin-4-yl)malonate, 237



According to **General Procedure C** with copper (I) iodide (410 mg, 2.16 mmol), 2-picolinic acid (285 mg, 2.16 mmol), cesium carbonate (21.1 g, 64.7 mmol), 1,4-dioxane (21.6 mL), diethylmalonate (6.55 mL, 43.1 mmol) and a 1:0.23 mixture of aryl iodide **221** and 4-bromoisoquinoline (5.27 g) at room temperature for 16 hours, then 50 ^{o}C for 3 hours. Purification *via* column chromatography eluting with 3:7 ethyl acetate/petrol 40-60 afforded the title compound **237** was obtained as a pale yellow solid (4.60 g, 75 %).

Melting point: 74-77 ^{o}C (ethyl acetate/petrol 40-60);

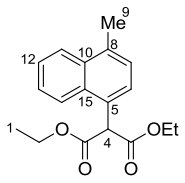
^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 9.21 (s, 1H, H_{Ar}), 8.54 (s, 1H, H_{Ar}), 8.01-7.94 (m, 2H, H_{Ar}), 7.76-7.70 (m, 1H, H_{Ar}), 7.61 (t, J = 7.1 Hz, 1H, H_{Ar}), 5.23 (s, 1H, H_4), 4.26 (dq, J = 10.8, 7.1 Hz, 2H, H_{2A}), 4.22 (dq, J = 10.8, 7.2 Hz, 2H, H_{2B}), 1.23 (t, J = 7.1 Hz, 6H, H_1);

^{13}C NMR (101 MHz, $CDCl_3$) δC = 167.8 (Quat, C_3), 153.3 (CH, C_{Ar}), 144.0 (CH, C_{Ar}), 134.3 (Quat, C_{Ar}), 131.0 (CH, C_{Ar}), 128.6 (Quat, C_{Ar}), 128.5 (CH, C_{Ar}), 127.3 (CH, C_{Ar}), 123.4 (Quat, C_{Ar}), 122.7 (CH, C_{Ar}), 62.2 (CH_2, C_2), 53.4 (CH, C_4), 14.0 (CH_3, C_1);

FTIR (neat) ν/cm^{-1} = 2982, 1729, 1306, 1255, 1226, 1198, 1175, 1146, 1030;

HRMS (ESI+) calculated for $C_{16}H_{18}NO_4$ = 288.1230; mass found = 288.1230.

Diethyl 2-(4-methylnaphthalen-1-yl)malonate, 238



According to **General Procedure C** with copper (I) iodide (396 mg, 2.08 mmol), 2-picolinic acid (256 mg, 2.08 mmol), cesium carbonate (20.3 g, 62.4 mmol), 1,4-dioxane (20.8 mL), diethylmalonate (6.32 mL, 41.6 mmol) and a 1:0.76 mixture of aryl iodide **222** and 1-bromo-4-methylnaphthalene (5.08 g) at room temperature for 16 hours, then 50 ^{o}C for 3 hours. Purification was achieved initially *via* column chromatography eluting with 1:9 ethyl acetate/petrol 40-60 followed by column chromatography eluting with 1:49 ethyl acetate/toluene. The title compound **238** was obtained as a white solid (2.81 g, 43 % from 1-bromo-4-methylnaphthalene).

Melting point: 48-50 ^{o}C (toluene/ethyl acetate);

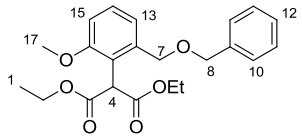
^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.97-7.92 (m, 1H, H_{Ar}), 7.90-7.85 (m, 1H, H_{Ar}), 7.48-7.41 (m, 2H, H_{Ar}), 7.36 (d, J = 7.3 Hz, 1H, H_6), 7.24 (d, J = 7.3 Hz, 1H, H_7), 5.32 (s, 1H, H_4), 4.15 (qd, J = 7.1, 0.9 Hz, 4H, H_2), 2.60 (s, 3H, H_9), 1.56 (t, J = 7.1 Hz, 6H, H_1);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 168.7 (Quat, C_3), 135.2 (Quat, C_{Ar}), 133.1 (Quat, C_{Ar}), 131.7 (Quat, C_{Ar}), 127.6 (Quat, C_{Ar}) ,126.8 (CH, C_6) ,126.3 (CH, C_7 and C_{Ar}), 125.7 (CH, C_{Ar}), 125.1 (CH, C_{Ar}), 123.4 (CH, C_{Ar}), 61.9 (CH_2, C_2), 54.5 (CH, C_4), 19.6 (CH_3, C_9), 14.1 (CH_3, C_1);

FTIR (neat) ν/cm^{-1} = 2981, 1730, 1304, 1249, 1221, 1194, 1174, 1141, 1095, 1032;

HRMS (ESI+) calculated for $C_{18}H_{20}NaO_4$ = 323.1254; mass found = 323.1248.

Diethyl 2-(2-((benzyloxy)methyl)-6-methoxyphenyl)malonate, 239



According to **General Procedure C** with copper (I) iodide (227 mg, 1.19 mmol), 2-picolinic acid (146 mg, 1.19 mmol), cesium carbonate (11.6 g, 35.7 mmol), 1,4-dioxane (12 mL), diethylmalonate (3.61 mL, 23.8 mmol) and **231** (4.22 g, 11.9 mmol) at 50 ^{o}C for 20 hours. Purification *via* column chromatography eluting with 1:9 ethyl acetate/petrol 40-60 to afforded the title compound **239** as a colourless oil (3.17 g, 69 %).

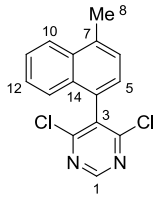
^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.26-7.16 (m, 6H, H_{Ar}), 6.86 (d, J = 7.8 Hz, 2H, H_{13} and H_{15}), 4.98 (s, 1H, H_4), 4.48 (s, 2H, $H_{7/8}$), 4.35 (s, 2H, $H_{7/8}$), 4.08 (dq, J = 10.8, 7.1 Hz, 2H, H_{2A}), 4.01 (dq, J = 10.8, 7.1 Hz, 2H, H_{2B}), 3.73 (s, 3H, H_{17}), 1.12 (t, J = 7.2 Hz, 6H, H_1);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 168.6 (Quat, C_3), 158.4 (Quat, C_{16}), 138.0 (Quat, C_{Ar}), 137.8 (Quat, C_{Ar}), 128.9 (CH, C_{Ar}), 128.3 (CH, C_{Ar}), 127.9 (CH, C_{Ar}), 127.6 (CH, C_{Ar}), 123.1 (Quat, C_5), 122.5 (CH, C_{13}), 112.1 (CH, C_{15}), 71.8 (CH_2, $C_{7/8}$), 71.0 (CH_2, $C_{7/8}$), 61.2 (CH_2, C_2), 56.1 (CH_3, C_{17}), 50.6 (CH, C_4), 14.1 (CH_3, C_1);

FTIR (neat) ν/cm^{-1} = 2981, 1733, 1588, 1474, 1366, 1301, 1272, 1147, 1066, 1037;

HRMS (ESI^+) calculated for $C_{22}H_{27}O_6$ = 387.1802, mass found = 387.1803.

4,6-Dichloro-5-(4-methylnaphthalen-1-yl)pyrimidine, 241



According to **General Procedure D**. Pyrimidine formation with metallic sodium (812 mg, 35.3 mmol), methanol (18 mL), formamidine acetate salt (1.47 g, 14.1 mmol), THF (11 mL), **238** (2.12 g, 7.05 mmol), THF (11 mL), methanol (18 mL) at 80 ^{o}C for 24 hours. Crude aryl pyrimidine product was obtained as a white solid (1.54 g). Chlorination with crude aryl pyrimidine (1.00 g, 3.96 mmol), phosphorus (V) oxychloride (11.0 mL), *N*,*N*-dimethylaniline (1.11 mL, 8.72 mmol) at 130 ^{o}C for 3 hours. Purification *via* column chromatography eluting with 1:19 ethyl acetate/petrol 40-60 followed by recrystallization from petrol 60-80/ethyl acetate afforded the title compound **241** as a white solid (584 mg, 44 % over 2 steps).

Melting point: 110-112 ^{o}C (petrol 60-80/ethyl acetate);

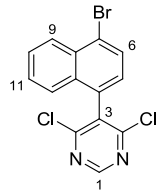
^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 8.90 (s, 1H, H_1), 8.13 (d, J = 8.3 Hz, 1H, H_{10}), 7.60 (ddd, J = 8.1, 7.2, 1.2 Hz, 1H, H_{11}), 7.49 (ddd, J = 8.3, 6.9, 1.3 Hz, 1H, H_{12}), 7.45 (d, J = 7.2 Hz, 1H, H_6), 7.30 (d, J = 8.2 Hz, 1H, H_{13}), 7.29 (d, J = 7.1 Hz, 1H, H_5), 2.79 (s, 3H, H_8);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 162.7 (Quat, C_2), 157.2 (CH, C_1), 136.9 (Quat, C_{Ar}), 133.1 (Quat, C_{Ar}), 132.8 (Quat, C_{Ar}), 130.4 (Quat, C_{Ar}), 128.7 (Quat, C_{Ar}), 127.1 (CH, C_5), 126.9 (CH, C_{12}), 126.4 (CH, C_{11}), 126.2 (CH, C_6), 125.0 (CH, C_{10}), 124.6 (CH, C_{13}), 19.7 (CH_3, C_8);

FTIR (neat) ν/cm^{-1} = 3077, 1591, 1546, 1457, 1440, 1423, 1263;

HRMS (ESI^{+}) calculated for $C_{15}H_{10}Cl_2N_2Na$ = 311.0113, mass found = 311.0116.

5-(4-Bromonaphthalen-1-yl)-4,6-dichloropyrimidine, 243



According to **General Procedure D**. Pyrimidine formation with metallic sodium (945 mg, 41.1 mmol), methanol (21 mL), formamidine acetate salt (1.71 g, 16.4 mmol), THF (13 mL), **217** (3.00 g, 8.21 mmol), THF (13 mL), methanol (21 mL) at 80 ^{o}C for 20 hours. The resulting crude white solid was recrystallized from ethanol to afford the corresponding aryl pyrimidine an impure white solid (938 mg). Chlorination with recrystallized aryl pyrimidine (818 mg, 2.58 mmol), phosphorus (V) oxychloride (7.2 mL), *N*,*N*-dimethylaniline (0.72 mL, 5.68 mmol) at 130 ^{o}C for 2 hours. Purification *via* column chromatography eluting with 1:19 ethyl acetate/petrol 40-60 followed by recrystallization from petrol 60-80/ethyl acetate afforded the title compound **243** as a white solid (530 mg, 21 % over 2 steps) which was contaminated by c.a. 5 % of an inseparable regioisomeric impurity.

Melting point: 135-138 ^{o}C (petrol 60-80/ethyl acetate);

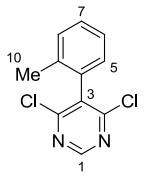
^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 8.84 (s, 1H, H_1), 8.30 (d, J = 8.6 Hz, 1H, H_9), 7.84 (d, J = 7.6 Hz, 1H, $H_{5/6}$), 7.59 (d, J = 7.5 Hz, 1H, H_{10}), 7.46 (d, J = 7.5 Hz, 1H, H_{11}), 7.20 (d, J = 8.3 Hz, 1H, H_{12}), 7.17 (d, J = 7.6 Hz, 1H, $H_{5/6}$);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 162.4 (Quat, C_2), 157.6 (CH, C_1), 132.3 (Quat, C_{Ar}), 132.1 (Quat, C_{Ar}), 131.5 (Quat, C_{Ar}), 130.4 (Quat, C_{Ar}), 129.7 (CH, $C_{5/6}$), 128.2 (CH, C_9), 128.1 (CH, C_{11}), 128.1 (CH, C_{10}), 127.7 (CH, $C_{5/6}$), 125.2 (Quat, C_7), 124.5 (CH, C_{12});

FTIR (neat) ν/cm^{-1} = 3048, 1588, 1545, 1399, 1378, 1353, 1225;

HRMS (FI^{+}) calculated for $C_{14}H_7Cl_2N_2Br$ = 351.9170, mass found = 351.9174.

4,6-Dichloro-5-(*o*-tolyl)pyrimidine, 245



According to **General Procedure** D. Pyrimidine formation with metallic sodium (919 mg, 40.0 mmol), methanol (20 mL), formamidine acetate salt (1.66 g, 16.0 mmol), THF (12 mL), **232** (2.00 g, 8.00 mmol), THF (12 mL), methanol (20 mL) at 80 ^{o}C for 24 hours. Crude aryl pyrimidine product was obtained as a white solid (652 mg). *n.b*. The crude solid was not washed with water. Chlorination with crude aryl pyrimidine (583 mg, 2.88 mmol), phosphorus (V) oxychloride (8.0 mL), *N*,*N*-dimethylaniline (0.80 mL, 6.3 mmol) at 130 ^{o}C for 3 hours. Purification *via* column chromatography eluting with 1:24 ethyl acetate/petrol 40-60 afforded the title compound **245** as a white solid (568 mg, 33 % over 2 steps).

Melting point: 83-84 ^{o}C (ethyl acetate/petrol 40-60);

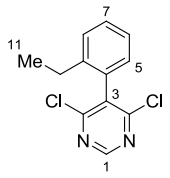
^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 8.81 (s, 1H, H_1), 7.40 (td, J = 7.7, 1.3 Hz, 1H, H_7), 7.36-7.29 (m, 2H H_6 and H_8), 7.10 (dd, J = 7.8, 1.2 Hz, 1H, H_5), 2.11 (s, 3H, H_{10});

^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 161.8 (Quat, C_2), 157.1 (CH, C_1), 136.0 (Quat, C_{Ar}), 133.8 (Quat, C_{Ar}), 132.6 (Quat, C_{Ar}), 130.5 (CH, C_8), 129.7 (CH, C_7), 128.7 (CH, C_5), 126.4 (CH, C_6), 19.4 (CH_3, C_{10});

FTIR (neat) ν/cm^{-1} = 3070, 1540, 1509, 1399, 1379, 1361, 1230, 1036;

HRMS (ESI^{+}) calculated for $C_{11}H_9N_2Cl_2$ = 239.0137, mass found = 239.0135.

4,6-Dichloro-5-(2-ethylphenyl)pyrimidine, 246



According to **General Procedure D**. Pyrimidine formation with metallic sodium (919 mg, 40.0 mmol), methanol (20 mL), formamidine acetate salt (1.66 g, 16.0 mmol), THF (12 mL), **233** (2.11 g, 8.00 mmol), THF (12 mL), methanol (20 mL) at 80 ^{o}C for 24 hours. Crude aryl pyrimidine product was obtained as a white solid (1.12 g). *n.b*. The crude solid was not washed with water. Chlorination with crude aryl pyrimidine (1.09 g, 5.04 mmol), phosphorus (V) oxychloride (14.1 mL), *N*,*N*-dimethylaniline (1.41 mL, 11.1 mmol) at 130 ^{o}C for 3 hours. Purification *via* column chromatography eluting with 1:24 ethyl acetate/petrol 40-60 afforded the title compound **246** as a white solid (1.23 g, 63 % over 2 steps).

Melting point: 60-62 ^{o}C (ethyl acetate/petrol 40-60);

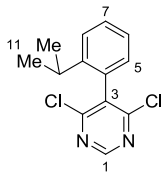
^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 8.81 (s, 1H, H_1), 7.46 (dd, J = 7.5, 1.3 Hz, 1H, H_7), 7.40 (dd, J = 7.8, 1.0 Hz, 1H, H_8), 7.33 (td, J = 7.5, 1.2 Hz, 1H, H_6), 7.08 (dd, J = 7.7, 1.1 Hz, 1H, H_5), 2.39 (q, J = 7.6 Hz, 2H, H_{10}), 1.14 (t, J = 7.6 Hz, 3H, H_{11});

^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 162.0 (Quat, C_2), 157.0 (CH, C_1), 141.8 (Quat, C_{Ar}), 133.8 (Quat, C_{Ar}), 132.0 (Quat, C_{Ar}), 129.9 (CH, C_7), 128.9 (CH, C_5), 128.8 (CH, C_8), 126.4 (CH, C_6), 26.2 (CH_2, C_{10}), 14.6 (CH_3, C_{11});

FTIR (neat) ν/cm^{-1} = 2967, 1541, 1507, 1450, 1399, 1378, 1360, 1225, 997;

HRMS (ESI^{+}) calculated for $C_{12}H_{11}N_2Cl_2$ = 253.0294, mass found = 253.0293.

4,6-Dichloro-5-(2-isopropylphenyl)pyrimidine, 247



According to **General Procedure D**. Pyrimidine formation with metallic sodium (1.22 g, 53.1 mmol), methanol (27 mL), formamidine acetate salt (2.21 g, 21.3 mmol), THF (16 mL), **234** (2.96 g, 10.6 mmol), THF (16 mL), methanol (27 mL) at 80 ^{o}C for 24 hours. Crude aryl pyrimidine product was obtained as a white solid (1.41 g). *n.b*. The crude solid was not washed with water. Chlorination with crude aryl pyrimidine (1.41 g, 6.12 mmol), phosphorus (V) oxychloride (17.1 mL), *N*,*N*-dimethylaniline (1.71 mL, 13.5 mmol) at 130 ^{o}C for 3 hours. Purification *via* column chromatography eluting with 3:97 ethyl acetate/petrol 40-60 followed by recrystallization from petrol 60-80 afforded the title compound **247** as a white solid (508 mg, 18 % over 2 steps).

Melting point: 80-82 ^{o}C (ethyl acetate/petrol 40-60);

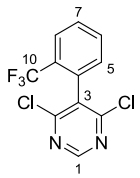
^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 8.81 (s, 1H, H_1), 7.52-7.44 (m, 2H, H_{Ar}), 7.31 (ddd, J = 7.6, 6.7, 1.8 Hz, 1H, H_{Ar}), 7.05 (dd, J = 7.6, 0.9, 1H, H_{Ar}), 2.46 (sept, J = 6.8 Hz, 1H, H_{10}), 1.19 (d, J = 6.8 Hz, 6H, H_{11});

^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 162.0 (Quat, C_2), 156.9 (CH, C_1), 146.7 (Quat, C_{Ar}), 134.0 (Quat, C_{Ar}), 131.3 (Quat, C_{Ar}), 130.1 (CH, C_{Ar}), 128.8 (CH, C_{Ar}), 126.4 (CH, C_{Ar}), 126.1 (CH, C_{Ar}), 31.2 (CH, C_{10}), 23.9 (CH_3, C_{11});

FTIR (neat) ν/cm^{-1} = 2964, 1545, 1507, 1399, 1378, 1361, 1223;

HRMS (ESI^{+}) calculated for $C_{13}H_{12}N_2Cl_2Na$ = 289.0270, mass found = 289.0266.

4,6-Dichloro-5-(2-(trifluoromethyl)phenyl)pyrimidine, 248



According to **General Procedure D**. Pyrimidine formation with metallic sodium (919 mg, 40.0 mmol), methanol (20 mL), formamidine acetate salt (1.66 g, 16.0 mmol), THF (12 mL), **235** (2.43 g, 8.00 mmol), THF (12 mL), methanol (20 mL) at 80 ^{o}C for 24 hours. Crude aryl pyrimidine product was obtained as a white solid (1.04 g). *n.b*. The crude solid was not washed with water. Chlorination with crude aryl pyrimidine (974 mg, 3.80 mmol), phosphorus (V) oxychloride (10.6 mL), *N*,*N*-dimethylaniline (1.06 mL, 8.36 mmol) at 130 ^{o}C for 3 hours. Purification *via* column chromatography eluting with 1:19 ethyl acetate/petrol 40-60 followed by recrystallization from petrol 60-80 afforded the title compound **248** as a white solid (534 mg, 19 % over 2 steps).

Melting point: 108-110 ^{o}C (petrol 60-80);

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 8.76 (s, 1H, H_1), 7.77 (d, J = 7.8 Hz, 1H, H_8), 7.65 (t, J = 7.5 Hz, 1H, H_6), 7.58 (t, J = 7.6 Hz, 1H, H_7), 7.21 (d, J = 7.4 Hz, 1H, H_5);

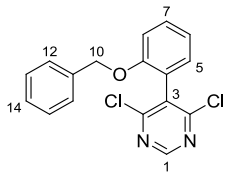
^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 161.6 (Quat, C_2), 157.6 (CH, C_1), 132.6 (CH, C_6), 131.8 (Quat, C_3), 131.2 (q, J = 2.1 Hz, Quat, C_4), 130.6 (CH, C_5), 130.0 (CH, C_7), 128.6 (q, J = 31.0 Hz, Quat, C_9), 126.9 (q, J = 4.8 Hz, CH, C_8), 123.4 (q, J = 273.9 Hz, Quat, C_{10});

^{19}F NMR (376 MHz, $CDCl_3$) δ_F = -61.1;

FTIR (neat) ν/cm^{-1} = 1551, 1512, 1450, 1380, 1313, 1164, 1129, 1109, 1067;

HRMS (ESI^{+}) calculated for $C_{11}H_6N_2Cl_2F_3$ = 292.9855, mass found = 292.9850.

5-(2-(Benzyloxy)phenyl)-4,6-dichloropyrimidine, 249



According to **General Procedure D**. Pyrimidine formation with metallic sodium (919 mg, 40.0 mmol), methanol (20 mL), formamidine acetate salt (1.66 g, 16.0 mmol), THF (12 mL), **236** (2.59 g, 8.00 mmol), THF (12 mL), methanol (20 mL) at 80 ^{o}C for 24 hours. Crude aryl pyrimidine product was obtained as a white solid (2.04 g). *n.b*. The crude solid was only washed once with water. Chlorination with crude aryl pyrimidine (2.01 g, 6.83 mmol), phosphorus (V) oxychloride (19.0 mL), *N*,*N*-dimethylaniline (1.90 mL, 15.0 mmol) at 110 ^{o}C for 3 hours. Purification *via* column chromatography eluting with 1:19 ethyl acetate/petrol 40-60 afforded the title compound **249** as a pale yellow oil (550 mg, 22 % over 2 steps).

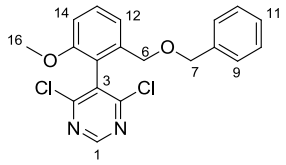
^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 8.68 (s, 1H, H_1), 7.36 (ddd, J = 8.4, 7.5, 1.8 Hz, 1H, H_7), 7.26-7.16 (m, 5H, H_{12}, H_{13} and H_{14}), 7.12 (dd, J = 7.6-1.7 Hz, 1H, H_5), 7.04-6.96 (m, 2H, H_6 and H_8), 5.01 (s, 2H, H_{10});

^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 162.1 (Quat, C_2), 156.8 (CH, C_1), 155.6 (Quat, C_{Ar}), 136.4 (Quat, C_{Ar}), 131.5 (Quat, C_{Ar}), 131.2 (CH, C_7), 130.3 (CH, C_5), 128.6 (CH, $C_{12/13}$), 128.0 (CH, C_{14}), 127.0 (CH, $C_{12/13}$), 122.3 (Quat, C_4), 121.1 (CH, C_6), 112.7 (CH, C_8), 70.4 (CH_2, C_{10});

FTIR (neat) ν/cm^{-1} = 3034, 1546, 1509, 1449, 1399, 1361, 1227, 1014;

HRMS (ESI^{+}) calculated for $C_{17}H_{13}ON_2Cl_2$ = 331.0399, mass found = 331.0394.

5-(2-((Benzyloxy)methyl)-6-methoxyphenyl)-4,6-dichloropyrimidine, 251



According to a modification of **General Procedure D**. Pyrimidine formation with metallic sodium (274 mg, 11.9 mmol), methanol (6 mL), formamidine acetate salt (495 mg, 4.76 mmol), THF (4 mL), **239** (919 mg, 2.38 mmol), THF (4 mL), methanol (6 mL) at 80 ^{o}C for 48 hours. Upon acidification with aqueous 1 M HCl, no solid precipitated and an emulsion was formed. This was concentrated under reduced pressure and dried under high vacuum to afford a viscous oily residue which was used without further purification in the chlorination step. Chlorination with crude aryl pyrimidine, phosphorus (V) oxychloride (10.0 mL), *N*,*N*-dimethylaniline (1.51 mL, 11.9 mmol) at 110 ^{o}C for 3 hours. Purification *via* column chromatography eluting with 3:97 ethyl acetate/petrol 40-60 afforded the title compound **251** as a colourless oil (111 mg, 12 % over 2 steps).

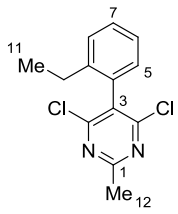
^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 8.66 (s, 1H, H_1), 7.40 (t, J = 7.9 Hz, 1H, H_{13}), 7.26-7.15 (m, 3H, H_{10} and H_{11}), 7.14-7.08 (m, 3H, H_9 and H_{12}), 6.90 (d, J = 8.3 Hz, 1H, H_{14}), 4.30 (s, 2H, H_7), 4.20 (s, 2H, H_6), 3.68 (s, 3H, H_{16});

^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 162.3 (Quat, C_2), 156.9 (CH, C_1), 156.5 (Quat, C_{Ar}), 137.7 (Quat, C_{Ar}), 137.6 (Quat, C_{Ar}), 130.9 (CH, C_{13}), 130.2 (Quat, C_{Ar}), 128.4 (CH, C_{10}), 127.8 (CH, C_9 and C_{11}), 121.3 (CH, C_{12}), 121.2 (Quat, C_4), 110.7 (CH, C_{14}), 72.6 (CH_2, C_7), 69.8 (CH_2, C_6), 56.0 (CH_3, C_{16});

FTIR (neat) ν/cm^{-1} = 2840, 1586, 1548, 1509, 1471, 1439, 1400, 1365, 1297, 1268, 1226, 1066;

HRMS (ESI^{+}) calculated for $C_{19}H_{16}O_2N_2Cl_2Na$ = 397.0481, mass found = 397.0475.

4,6-Dichloro-5-(2-ethylphenyl)-2-methylpyrimidine, 350



A stirred solution of **246** (500 mg, 1.98 mmol) in THF (20 mL) was cooled to -78 ^{o}C and methyl lithium (1.6 M in hexanes, 1.4 mL, 2.17 mmol) was added. The resulting solution was stirred at -78 ^{o}C for 10 minutes. After this time, water (5.0 mL) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (493 mg, 2.17 mmol) were sequentially added and the mixture was allowed to warm to room temperature and stirred for 5 minutes. 1 M Aqueous sodium hydroxide and dichloromethane were added. The organic layer was separated and the aqueous layer was extracted twice with dichloromethane. The combined organic extracts were dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. Purification of the residue *via* column chromatography eluting with 1:24 ethyl acetate/petrol 40-60 afforded the title compound **350** as a white solid (446 mg, 84 %).

Melting point 72-74 ^{o}C (ethyl acetate/petrol 40-60);

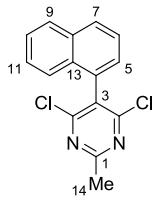
^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.44 (td, J = 7.5, 1.3 Hz, 1H, H_7), 7.38 (dd, J = 7.4, 1.0 Hz, 1H, H_8), 7.31 (td, J = 7.4, 1.2 Hz, 1H, H_6), 7.06 (dd, J = 7.6, 1.2 Hz, 1H, H_5), 2.76 (s, 3H, H_{12}), 2.39 (q, J = 2.39 Hz, 2H, H_{10}), 1.23 (t, J = 7.6 Hz, 3H, H_{11});

^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 167.8 (Quat, C_{Ar}), 161.5 (Quat, C_{Ar}), 142.1 (Quat, C_{Ar}), 132.2 (Quat, C_{Ar}), 130.1 (Quat, C_{Ar}), 129.7 (CH, C_7), 129.2 (CH, C_5), 128.7 (CH, C_8), 126.3 (CH, C_6), 26.2 (CH_3, C_{10}), 25.5 (CH_2, C_{12}), 14.6 (CH_3, C_{11});

FTIR (neat) ν/cm^{-1} = 2969, 1557, 1494, 1450, 1411, 1295;

HRMS (ESI^{+}) calculated for $C_{13}H_{13}N_2Cl_2$ = 267.0450, mass found = 267.0447.

4,6-Dichloro-2-methyl-5-(naphthalen-1-yl)pyrimidine, 252



According to **General Procedure D**. Pyrimidine formation with metallic sodium (1.11 g, 48.4 mmol), methanol (25 mL), acetamidine hydrochloride (1.83 g, 19.4 mmol), THF (15 mL), **199** (2.5 g, 9.68 mmol), THF (15 mL), methanol (25 mL) at 80 ^{o}C for 48 hours. Crude aryl pyrimidine product was obtained as a white solid (1.95 g). Chlorination with crude aryl pyrimidine (1.95 g, 7.73 mmol), phosphorus (V) oxychloride (22 mL), *N*,*N*-dimethylaniline (2.20 mL, 17.0 mmol) at 130 ^{o}C for 2 hours. Purification *via* column chromatography eluting with 1:19 ethyl acetate/petrol 40-60 followed by recrystallization from petrol 60-80/ethyl acetate afforded the title compound **252** as a white solid (474 mg, 17 % over 2 steps).

Melting point: 154-157 ^{o}C (ethyl acetate/petrol 60-80);

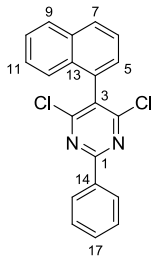
^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 8.00 (d, J = 8.2 Hz, 1H, H_7), 7.96 (d, J = 8.2 Hz, 1H, H_9), 7.60 (t, J = 7.7 Hz, 1H, H_6), 7.58-7.54 (m, 1H, H_{10}), 7.51-7.47 (m, 1H, H_{11}), 7.39 (dd, J = 7.3, 0.9 Hz, 1H, H_5), 7.34 (d, J = 8.5 Hz, 1H, H_{12}), 2.84 (s, 3H, H_{14});

^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 168.2 (Quat, C_1), 162.0 (Quat, C_2), 133.6 (Quat, C_{Ar}), 130.6 (Quat, C_{Ar}), 130.5 (Quat, C_{Ar}), 129.8 (CH, C_7), 129.1 (Quat, C_{Ar}), 128.8 (CH, C_9), 127.6 (CH, C_5), 127.1 (CH, C_{11}), 126.5 (CH, C_{10}), 125.4 (CH, C_6), 124.1 (CH, C_{12}), 25.5 (CH_3, C_{14});

FTIR (neat) ν/cm^{-1} = 3043, 1595, 1557, 1494, 1417, 1391, 1299;

HRMS (ESI^{+}) calculated for $C_{15}H_{10}Cl_2N_2Na$ = 311.0113, mass found = 311.0099.

4,6-Dichloro-5-(naphthalen-1-yl)-2-phenylpyrimidine, 253



According to **General Procedure D**. Pyrimidine formation with metallic sodium (1.34 g, 58.1 mmol), methanol (30 mL), benzamidine hydrochloride (3.64 g, 23.3 mmol), THF (18 mL), **199** (3.00 g, 11.6 mmol), THF (18 mL), methanol (30 mL) at 80 ^{o}C for 48 hours. Crude aryl pyrimidine product was obtained as a white solid (686 mg). Chlorination with crude aryl pyrimidine (686 mg, 2.18 mmol), phosphorus (V) oxychloride (6.1 mL), *N*,*N*-dimethylaniline (0.61 mL, 4.8 mmol) at 130 ^{o}C for 2 hours. Purification *via* column chromatography eluting with 1:19 ethyl acetate/petrol 40-60 afforded the title compound **253** as a gummy solid (70 mg, 2 % over 2 steps).

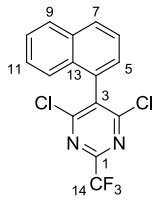
^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 8.56-8.52 (m, 2H, H_{15}), 8.01 (d, J = 8.2 Hz, 1H, H_7), 7.97 (d, J = 8.0 Hz, 1H, H_9), 7.64-7.52 (m, 5H, H_6, H_{10}, H_{16} and H_{17}), 7.51-7.47 (m, 1H, H_{11}), 7.44 (dd, J = 7.1, 1.1 Hz, 1H, H_5), 7.42 (d, J = 8.2 Hz, 1H, H_{12});

^{13}C NMR (121 MHz, $CDCl_3$) δ_C = 164.3 (Quat, C_{Ar}), 162.5 (Quat, C_{Ar}), 134.9 (Quat, C_{Ar}), 133.6 (Quat, C_{Ar}), 132.2 (CH, C_{17}), 130.9 (Quat, C_{Ar}), 130.7 (Quat, C_{Ar}), 129.8 (CH, C_7), 129.5 (Quat, C_{Ar}), 128.9 (CH, $C_{9/15/16}$), 128.8 (CH, $C_{9/15/16}$), 128.8 (CH, $C_{9/15/16}$), 127.7 (CH, C_5), 127.1 (CH, C_{11}), 126.5 (CH, C_{10}), 125.4 (CH, C_6), 124.3 (CH, C_{12});

FTIR (neat) ν/cm^{-1} = 3058, 1553, 1488, 1414, 1383, 1321;

HRMS (FI^{+}) calculated for $C_{20}H_{12}N_2Cl_2$ = 350.0378, mass found = 350.0382.

4,6-Dichloro-5-(naphthalen-1-yl)-2-(trifluoromethyl)pyrimidine, 254



According to **General Procedure D**. Pyrimidine formation with metallic sodium (804 mg, 35.0 mmol), methanol (17 mL), trifluoroacetamidine (1.57 g, 14.0 mmol), THF (11 mL), **202** (2.00 g, 6.99 mmol), THF (11 mL), methanol (17 mL) at 80 ^{o}C for 70 hours. Crude aryl pyrimidine product was obtained as a white solid (1.42 g). Chlorination with crude aryl pyrimidine (1.37 g, 4.47 mmol), phosphorus (V) oxychloride (12.5 mL), *N*,*N*-dimethylaniline (1.25 mL, 9.84 mmol) at 130 ^{o}C for 2 hours. Purification *via* column chromatography eluting with 3:47 ethyl acetate/petrol 40-60 followed by recrystallization from petrol 60-80 afforded the title compound **254** as a white solid (482 mg, 21 % over 2 steps).

Melting point: 129-130 ^{o}C (petrol 60-80);

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.96 (d, J = 8.3 Hz, 1H, H_7), 7.89 (d, J = 8.1 Hz, 1H, H_9), 7.56-7.47 (m, 2H, H_6 and H_{10}), 7.45-7.40 (m, 1H, H_{11}), 7.31 (dd, J = 7.1, 1.2 Hz, 1H, H_5), 7.71 (d, J = 8.6 Hz, 1H, H_{12});

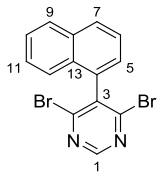
^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 163.9 (Quat, C_2), 155.5 (q, J = 39.2 Hz, Quat, C_1), 135.3 (Quat, C_{Ar}), 133.7 (Quat, C_{Ar}), 130.6 (CH, C_7), 130 (Quat, C_{Ar}), 129.3 (Quat, C_{Ar}), 129.0 (CH, C_9), 127.6 (CH, C_{11}), 127.3 (CH, C_5), 126.8 (CH, C_{10}), 125.5 (CH, C_6), 123.6 (CH, C_{12}), 118.5 (q, J = 276.3 Hz, Quat, C_{14});

^{19}F NMR (376 MHz, $CDCl_3$) δ_F = -70.2;

FTIR (neat) ν/cm^{-1} = 3059, 1549, 1316, 1303, 1211, 1153;

HRMS (FI^+) calculated for $C_{15}H_7N_2F_3Cl_2$ = 341.9938, mass found = 341.9928.

4,6-Dibromo-5-(naphthalen-1-yl)pyrimidine, 256



To a stirred room temperature suspension of sodium methoxide, prepared *in situ* by the portionwise addition of metallic sodium (4.02 g, 175 mmol) to anhydrous methanol (90 mL), was added formamidine acetate salt (7.27 g, 69.9 mmol) in a single portion. The resulting suspension was stirred at room temperature for 30 minutes and then diluted with THF (55 mL). A solution of **202** (10.0 g, 34.9 mmol) in a mixture of THF (55 mL) and methanol (90 mL) was added. The reaction mixture was stirred at 80 ^{o}C for 24 hours and then cooled to room temperature and concentrated to dryness under reduced pressure. The residue was suspended in water (c.a. 20 mL), acidified with 1 M HCl and cooled to 0 ^{o}C for 30 minutes. A solid was formed, which was isolated by vacuum filtration and washed five times with water and then dried under high vacuum to afford the corresponding aryl pyrimidine as a white solid (7.31 g).

A mixture of crude aryl pyrimidine (2.00 g, 8.40 mmol) and phosphorus (V) oxybromide (3.13 g, 10.9 mmol) was heated to 200 ^{o}C for 1 hour in a sealed tube. After this time, the reaction mixture was cooled to room temperature and the plug of solid which had formed was dissolved with dichloromethane and carefully added to an ice cold solution of saturated aqueous sodium carbonate. The organic layer was separated and the aqueous layer was extracted twice with dichloromethane. The combined organic extracts were dried over anhydrous magnesium sulfate and concentrated under reduced pressure. Purification of the residue *via* column chromatography eluting with 1:9 ethyl acetate/petrol 40-60 followed by recrystallization from petrol 60-80/ethyl acetate afforded the title compound **256** as a white solid (935 mg, 27 % over 2 steps).

Melting point: 167-170 ^{o}C (ethyl acetate/petrol 60-80);

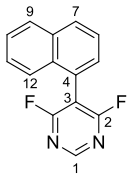
^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 8.79 (s, 1H, H_1), 8.02 (d, J = 8.3 Hz, 1H, H_7), 7.96 (d, J = 8.3 Hz, 1H, H_9), 7.63-7.54 (m, 2H, H_6 and H_{10}), 7.53-7.48 (m, 1H, H_{11}), 7.38 (dd, J = 7.1, 1.0 Hz, 1H, H_5), 7.32 (d, J = 8.5 Hz, 1H, H_{12});

^{13}C NMR (126 MHz, $CDCl_3$) δ_C = 157.3 (CH, C_1), 154.8 (Quat, C_2), 138.5 (Quat, C_{Ar}), 133.8 (Quat, C_{Ar}), 133.6 (Quat, C_{Ar}), 130.2 (Quat, C_{Ar}), 130.0 (CH, C_7), 128.8 (CH, C_9), 127.3 (CH, $C_{5/11}$), 127.3 (CH, $C_{5/11}$), 126.6 (CH, C_{10}), 125.5 (CH, C_6), 124.1 (CH, C_{12});

FTIR (neat) ν/cm^{-1} = 3050, 1591, 1535, 1388, 1346, 1261, 1215, 1142, 1015;

HRMS (ESI^{+}) calculated for $C_{14}H_8Br_2N_2Na$ = 384.8946, mass found = 384.8953.

4,6-Difluoro-5-(naphthalen-1-yl)pyrimidine, 257



A mixture of potassium fluoride (211 mg, 3.64 mmol) and 18-crown-6 (38 mg, 0.15 mmol) was azeotroped from anhydrous acetonitrile (3 x 2 mL). The residue was dissolved in anhydrous acetonitrile (2.4 mL) and **201** (200 mg, 0.72 mmol) was added. The resulting suspension was heated to 80 ^{o}C in a sealed tube for 9 hours and then cooled to room temperature and diluted with dichloromethane and water. The organic layer was separated and the aqueous layer was extracted twice with dichloromethane. The combined organic extracts were dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. Purification of the residue *via* column chromatography eluting with 1:1 dichloromethane/petrol 40-60 afforded the title compound **257** as a white solid (133 mg, 76 %).

Melting point: 74-75 ^{o}C (dichloromethane/petrol 40-60);

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 8.62 (t, J = 1.7 Hz, 1H, H_1), 7.89 (d, J = 8.3 Hz, 1H, H_7), 7.84 (dd, J = 7.6, 1.6 Hz, 1H, H_9), 7.49-7.32 (m, 5H, H_5, H_6, H_{10}, H_{11} and H_{12});

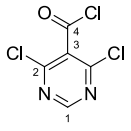
^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 169.5 (dd, J = 257.9, 13.9 Hz, Quat, C_2), 157.5 (t, J = 18.3 Hz, CH, C_1), 133.7 (Quat, C_{Ar}), 131.1 (Quat, C_{Ar}), 130.5 (CH, C_7), 128.8 (CH, C_8 and C_{Ar}), 127.3 (CH, C_{Ar}), 126.6 (CH, C_{Ar}), 125.2 (CH, C_{Ar}), 124.2 (CH, C_{Ar}), 122.6 (t, J = 3.2 Hz, Quat, C_4), 107.1 (t, J = 31.4 Hz, Quat, C_3);

^{19}F NMR (376 MHz, $CDCl_3$) δ_F = -58.0;

FTIR (neat) ν/cm^{-1} = 3059, 1612, 1510, 1428, 1393, 1340, 1035;

HRMS (FI^+) calculated for $C_{14}H_8F_2N_2$ = 242.0656; mass found = 242.0656.

4,6-Dichloropyrimidine-5-carbonyl chloride, 260*



This compound was prepared according to a literature procedure.[89]

N,*N*-Dimethylformamide (3.45 mL, 44.6 mmol) was added to phosphorus (V) oxychloride (10.4 mL, 112 mmol) at 0 °C and the resulting mixture was stirred at 0 °C for 1 hour. After this time, 4,6-dihydroxypyrimidine **258** (2.50 g, 22.3 mmol) was added and the resulting solution was warmed to room temperature and stirred for 30 minutes and then heated to 100 °C for 5 hours and then cooled to room temperature and carefully poured onto crushed ice. After warming to room temperature, the mixture was extracted six times with diethyl ether. The combined organic extracts were washed with 1 M $NaHCO_3$ and water, dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to afford crude **259** (1.80 g) which was used without further purification.

* This compound was prepared by Benjamin Rahemtulla

The crude aldehyde thus obtained (1.80 g) was dissolved in carbon tetrachloride (18 mL) and sulfuryl chloride (1.40 mL, 17.3 mmol) and AIBN (83 mg, 0.50 mmol) were added. The resulting solution was heated to reflux for 90 minutes and then cooled to room temperature and concentrated under reduced pressure. Purification of the residue *via* column chromatography eluting with dichloromethane afforded the title compound **260** as a colourless oil (1.66 g, 35 % over 2 steps). The spectral data matched that previously reported in the literature.[131]

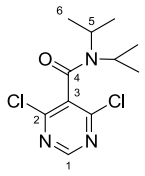
^{1}H NMR (400 MHz, DMSO-d_6) δ_H = 9.04 (s, 1H, H_1);

^{13}C NMR (101 MHz, DMSO-d_6) δ_C = 164.1 (Quat, C_4), 160.0 (CH, C_1), 158.2 (Quat, C_2), 129.8 (Quat, C_3);

FTIR (neat) ν/cm^{-1} = 1789, 1537, 1511, 1409, 1346, 1327, 1131;

HRMS (FI^{+}) calculated for $C_5HCl_2N_2O$ = 209.9155, mass found = 209.9155.

4,6-Dichloro-*N,N*-diisopropylpyrimidine-5-carboxamide, 261[*]



A solution of **260** (500 mg, 2.4 mmol) in THF (24 mL) was cooled to 0 °C and Et_3N (1.66 mL, 12 mmol) and diisopropylamine (168 µL, 1.2 mmol) were added dropwise. The reaction mixture was stirred at 0 ^{o}C for 2 hours and then warmed to room temperature and diethyl ether and brine were added. The organic layer was separated and washed successively with 1 M HCl, 1 M Na_2CO_3 and brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. Purification of the residue *via* column chromatography eluting with a gradient from dichloromethane to 1:20 methanol/dichloromethane afforded the title compound **261** as an orange solid (134 mg, 41 %).

[*] This compound was prepared by Benjamin Rahemtulla

Melting point: 102-104 °C (methanol/dichloromethane);

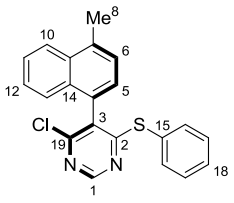
^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 8.76 (s, 1H, H_1), 3.58 (sept, J = 6.7 Hz, 1H, H_5), 3.50 (sept, J = 6.7 Hz, 1H, $H_{5'}$), 1.57 (d, J = 6.7 Hz, 6H, H_6), 1.25 (d, J = 6.7 Hz, 6H, $H_{6'}$);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 161.1 (Quat, C_4), 158.4 (Quat, C_2), 157.4 (CH, C_1), 131.3 (Quat, C_3), 52.5 (CH, $C_{5'}$), 47.1 (CH, C_5), 21.4 (CH_3, $C_{6'}$), 20.1 (CH_3, C_6);

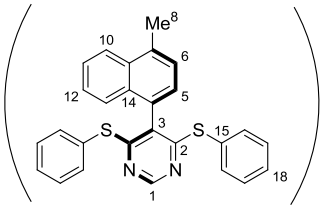
FTIR (neat) ν/cm^{-1} = 2976, 2936, 2197, 1643, 1566, 1543, 1514, 1473, 1445, 1406, 1371, 1304, 1230, 1210, 1160, 1137, 1032;

HRMS (ESI$^+$) calculated for $C_{11}H_{16}Cl_2N_3O$ = 270.0665, mass found = 276.0660.

(*R*)-4-chloro-5-(4-methylnaphthalen-1-yl)-6-(phenylthio)pyrimidine, 263



263



351

Asymmetric: According to **General Procedure E** with **241** (50 mg, 0.17 mmol), carbon tetrachloride (1.7 mL), *N*-benzylquininium chloride (8 mg, 0.017 mmol), thiophenol (19.5 μL, 0.19 mmol), 50 % w/w aqueous potassium carbonate (0.12 mL, 0.87 mmol) at room temperature for 48 hours. Purification *via* column chromatography eluting with 1:19 ethyl acetate/petrol 40-60 afforded the title compound **263** as a white solid (60 mg, 96 %, 96:4 e.r.).

Racemic: According to **General Procedure F** with **241** (100 mg, 0.35 mmol), toluene (3.5 mL), tetraammonium bromide (11 mg, 0.035 mmol), thiophenol (42.0 μL, 0.45 mmol), 50 % w/w aqueous potassium hydroxide (0.10 mL, 1.8 mmol) at room temperature for 2 hours. Purification *via* column chromatography eluting with 1:19 ethyl acetate/petrol 40-60 afforded

the title compound *rac*-**263** as a white solid (94 mg, 75 %) along with by-product **351** as a white solid (30 mg, 20 %).

Data for **263**

Melting point: 152-153 ^{o}C (ethyl acetate/petrol 40-60);

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 8.70 (s, 1H, H_1), 8.15 (d, J = 8.6 Hz, 1H, H_{10}), 7.63 (ddd, J = 8.3, 6.8, 1.4 Hz, 1H, H_{11}), 7.55 (ddd, J = 8.2, 6.9, 1.4 Hz, 1H, H_{12}), 7.53-7.38 (m, 8H, H_{Ar}), 2.83 (s, 3H, H_8);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 173.0 (Quat, C_2), 159.4 (Quat, C_{19}), 157.0 (CH, C_1), 136.9 (Quat, C_{Ar}), 135.5 (CH, C_{16}), 133.0 (Quat, C_{Ar}), 130.5 (Quat, C_{Ar}), 129.7 (CH, C_{Ar}), 129.4 (Quat, C_{Ar}), 129.3 (CH, C_{17}), 128.7 (Quat, C_{Ar}), 128.1 (Quat, C_{Ar}), 127.8 (CH, C_{Ar}), 126.8 (CH, C_{12}), 126.5 (CH, C_{Ar}), 126.5 (CH, C_{Ar}), 125.1 (CH, C_{10}), 124.8 (CH, C_{Ar}), 19.8 (CH_3, C_8);

FTIR (neat) ν/cm^{-1} = 3061, 1535, 1499, 1398, 1374, 1348, 1228;

HRMS (ESI^{+}) calculated for $C_{21}H_{15}ClN_2NaS$ = 385.0537, mass found = 385.0551;

Chiral HPLC (Chiralpak ADH, 15 % IPA, 85 % hexane, 1.0 mL/min, λ = 254 nm, 100 μL injection) τ_R (minor) = 11.8 min, τ_R (major) = 17.6 min;

$[\alpha]_D^{20}$ = –3 (*c* = 1.00, $CHCl_3$).

Data for **351**

Melting point: 178-179 ^{o}C (ethyl acetate/petrol 40-60);

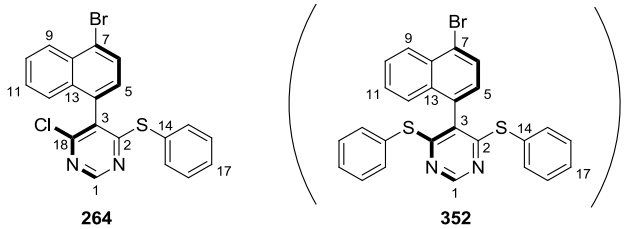
^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 8.59 (s, 1H, H_1), 8.17 (d, J = 8.17 Hz, 1H, H_{10}), 7.67-7.62 (m, 2H, H_{Ar}), 7.60-7.53 (m, 2H, H_{Ar}), 7.51 (d, J = 7.3 Hz, 1H, H_5), 7.49-7.44 (m, 4H, H_{16}), 7.41-7.36 (m, 6H, H_{17} and H_{18});

^{13}C NMR (121 MHz, $CDCl_3$) δ_C = 168.3 (Quat, C_2), 156.9 (Quat, C_1), 136.9 (Quat, C_{Ar}), 135.4 (CH, C_{16}), 133.2 (Quat, C_{Ar}), 130.7 (Quat, C_{Ar}), 129.3 (CH, C_{18}), 129.1 (CH, C_{17}), 129.0 (Quat, C_{Ar}), 128.8 (Quat, C_{15}), 128.5 (CH, C_{Ar}), 127.0 (Quat, C_{Ar}), 126.8 (CH, C_{Ar}), 126.7 (CH, C_{Ar}), 126.4 (CH, C_{Ar}), 125.1 (CH, C_{Ar}), 125.0 (CH, C_{Ar}), 19.9 (CH_3, C_8);

FTIR (neat) ν/cm^{-1} = 3060, 1506, 1397, 1343, 1234;

HRMS (ESI$^+$) calculated for $C_{27}H_{20}N_2NaS_2$ = 459.0960, mass found = 459.0967.

(*R*)-5-(4-bromonaphthalen-1-yl)-4-chloro-6-(phenylthio)pyrimidine, 264



Asymmetric: According to **General Procedure E** with **243** (70 mg, 0.20 mmol), carbon tetrachloride (2.0 mL), *N*-benzylquininium chloride (9 mg, 0.020 mmol), thiophenol (22.4 μL, 0.22 mmol), 50 % w/w aqueous potassium carbonate (0.14 mL, 0.99 mmol) at room temperature for 48 hours. Purification *via* column chromatography eluting with 1:19 ethyl acetate/petrol 40-60 afforded the title compound **264** as a white solid (82 mg, 97 %, 87:13 e.r.).

Racemic: According to **General Procedure F** with **243** (100 mg, 0.28 mmol), toluene (2.8 mL), tetrabutylammonium bromide (9 mg, 0.028 mmol), thiophenol (34.3 μL, 0.37 mmol), 50 % w/w aqueous potassium hydroxide (0.08 mL, 1.4 mmol) at room temperature for 2 hours. Purification *via* column chromatography eluting with 1:19 ethyl acetate/petrol 40-60 afforded the title compound *rac*-**264** as a white solid (108 mg, 89 %) along with by-product **352** as a white solid (25 mg, 18 %).

Data for **264**

Melting point: 157-159 ^{o}C (ethyl acetate/petrol 40-60);

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 8.71 (s, 1H, H_1), 8.40 (d, J = 8.3 Hz, 1H, H_9), 7.96 (d, J = 7.6 Hz, 1H, H_{Ar}), 7.70 (t, J = 7.6 Hz, 1H, H_{10}), 7.59 (t, J = 7.7 Hz, 1H, H_{11}), 7.48-7.39 (m, 6H, H_{Ar}), 7.37 (d, J = 7.6 Hz, 1H, H_{Ar});

^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 172.7 (Quat, C_2), 159.3 (Quat, C_{18}), 157.3 (CH, C_1), 135.5 (CH, C_{15}), 132.5 (Quat, C_{Ar}), 131.7 (Quat, C_{Ar}), 130.5 (Quat, C_{Ar}), 129.9 (CH, C_{Ar}), 129.9 (CH, C_{Ar}), 129.4 (CH, C_{16}), 128.4 (CH and Quat, C_{Ar}), 128.2 (CH, C_{Ar}), 128.1 (CH, C_{Ar}), 128.0 (CH, C_{Ar}), 127.7 (Quat, C_{Ar}), 125.2 (Quat, C_{Ar}), 124.7 (CH, C_{Ar});

FTIR (neat) ν/cm^{-1} = 3061, 1535, 1498, 1399, 1345, 1229, 963;

HRMS (ESI^{+}) calculated for $C_{20}H_{13}N_2BrClS$ = 426.9666, mass found = 426.9665;

Chiral HPLC (Chiralpak ADH, 15 % IPA, 85 % hexane, 1.0 mL/min, λ = 256 nm, 20 μL injection) τ_R (minor) = 10.0 min, τ_R (major) = 14.6 min;

$[\alpha]_D^{20}$ = –10 (*c* = 1.00, $CHCl_3$).

Data for **352**

Melting point: 214-216 ^{o}C (ethyl acetate/petrol 40-60);

^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 8.58 (s, 1H, H_1), 8.41 (d, J = 8.5 Hz, 1H, H_9), 7.99 (d, J = 7.4 Hz, 1H, $H_{5/6}$) 7.17 (ddd, J = 8.4, 5.4, 3.0 Hz, 1H, H_{10}), 7.63-7.60 (m, 2H, H_{11} and H_{12}), 7.47 (m, 5H, $H_{5/6}$ and H_{15}), 7.40-7.35 (m, 6H, H_{16} and H_{17});

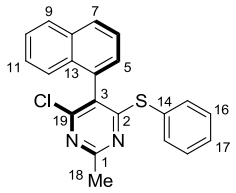
^{13}C NMR (121 MHz, $CDCl_3$) δ_C = 168.2 (Quat, C_2), 157.1 (CH, C_1), 135.4 (CH, C_{15}), 132.7 (Quat, C_{Ar}), 131.9 (Quat, C_{Ar}), 130.8 (Quat, C_{Ar}), 130.2 (CH, C_{Ar}), 129.4 (CH, C_{17}), 129.2 (CH, C_{16}), 129.1

(CH, C_{Ar}), 128.4 (Quat, C_{14}), 128.2 (CH, C_9), 128.0 (CH, C_{10}), 127.9 (CH, C_{11}), 125.9 (Quat, C_{Ar}), 125.2 (Quat, C_{Ar}), 124.9 (CH, C_{12});

FTIR (neat) ν/cm^{-1} = 3060, 1502, 1476, 1397, 1341, 1235, 1024;

HRMS (ESI^+) calculated for $C_{26}H_{18}N_2BrS_2$ = 501.0089, mass found = 501.0085.

(*R*)-4-Chloro-2-methyl-5-(naphthalen-1-yl)-6-(phenylthio)pyrimidine, 265



Asymmetric: According to **General Procedure E** with **252** (50 mg, 0.17 mmol), carbon tetrachloride (1.7 mL), *N*-benzylquininium chloride (8 mg, 0.017 mmol), thiophenol (19.5 μL, 0.19 mmol), 50 % w/w aqueous potassium carbonate (0.12 mL, 0.87 mmol) at room temperature for 48 hours. Purification *via* column chromatography eluting with 1:19 ethyl acetate/petrol 40-60 afforded the title compound **265** as a white solid (60 mg, 96 %, 96:4 e.r.).

Racemic: According to **General Procedure F** with **252** (50 mg, 0.17 mmol), toluene (1.7 mL), tetrabutylammonium bromide (6 mg, 0.017 mmol), thiophenol (19.5 μL, 0.19 mmol), 50 % w/w aqueous potassium hydroxide (0.05 mL, 0.86 mmol) at room temperature for 1 hour. Purification *via* column chromatography eluting with 1:19 ethyl acetate/petrol 40-60 afforded the title compound *rac*-**265** as a white solid (60 mg, 96 %).

Melting point: 152-155 ^oC (ethyl acetate/petrol 40-60);

^1H NMR (500 MHz, $CDCl_3$) δ_H = 8.02 (d, J = 8.2 Hz, 1H, H_7), 7.98 (d, J = 8.2 Hz, 1H, H_9), 7.64 (dd, J = 8.6, 6.8 Hz, 1H, H_6), 7.58 (ddd, J = 7.3, 6.4, 0.9 Hz, 1H, H_{10}), 7.55-7.48 (m, 3H, H_5, H_{11} and H_{12}), 7.47-7.31 (m, 5H, H_{15}, H_{16} and H_{17}), 2.59 (s, 3H, H_{18});

^{13}C NMR (126 MHz, $CDCl_3$) δ_C = 171.9 (Quat, C_2), 167.1 (Quat, C_1), 158.9 (Quat, C_{19}), 135.2 (CH, C_{15}), 133.8 (Quat, C_8), 130.8 (Quat, C_{Ar}), 130.7 (Quat, C_{Ar}), 129.9 (CH, C_7), 129.2 (CH, C_{17}), 128.9 (CH, C_{16}), 128.8 (CH, C_9), 128.4 (Quat, C_{Ar}), 128.3 (CH, C_5), 127.0 (CH, C_{11}), 126.4 (CH, C_{10}), 125.7 (Quat, C_{Ar}), 125.6 (CH, C_6), 124.4 (CH, C_{12}), 25.7 (CH_3, C_{18});

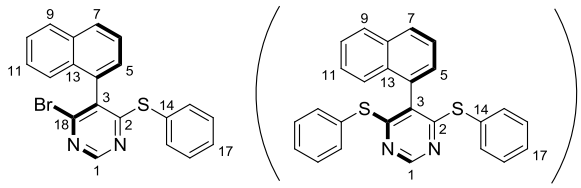
FTIR (neat) ν/cm^{-1} = 3058, 1545, 1490, 1417, 1390, 1358, 1291, 1024;

HRMS (ESI^+) calculated for $C_{21}H_{15}ClN_2NaS$ = 385.0537, mass found = 385.0553;

Chiral HPLC (Chiralpak ADH, 20 % IPA, 80 % hexane, 1.0 mL/min, λ = 291 nm, 20 μL injection) τ_R (minor) = 4.6 min, τ_R (major) = 5.8 min;

$[\alpha]_D^{20}$ = –1 (*c* = 1.00, $CHCl_3$).

(*R*)-4-Bromo-5-(naphthalen-1-yl)-6-(phenylthio)pyrimidine, 268



Asymmetric: According to **General Procedure E** with **256** (66 mg, 0.18 mmol), carbon tetrachloride (1.8 mL), *N*-benzylquininium chloride (8 mg, 0.018 mmol), thiophenol (20.5 μL, 0.20 mmol), 50 % w/w aqueous potassium carbonate (0.12 mL, 0.90 mmol) at room temperature for 48 hours. Purification *via* column chromatography eluting with 1:19 ethyl acetate/petrol 40-60 afforded the title compound **268** as a white solid (63 mg, 88 %, 92:8 e.r.) along with by-product **204** as a white solid (5.4 mg, 7 %). The spectral data for **204** matched that obtained previously.

Racemic: According to **General Procedure F** with **256** (100 mg, 0.28 mmol), toluene (2.8 mL), tetrabutylammonium bromide (9 mg, 0.028 mmol), thiophenol (33.4 μL, 0.36 mmol), 50 %

w/w aqueous potassium hydroxide (0.1 mL, 1.38 mmol) at room temperature for 2 hours. Purification *via* column chromatography eluting with 1:19 ethyl acetate/petrol 40-60 afforded the title compound *rac*-**268** as a white solid (81 mg, 75 %) along with by-product **204** as a white solid (18 mg, 16 %). The spectral data for **204** matched that obtained previously.

Melting point: 148-149 ^{o}C (ethyl acetate/petrol 40-60);

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 8.63 (s, 1H, H_1), 7.99 (d, J = 8.2 Hz, 1H, H_7), 7.99 (d, J = 8.2 Hz, 1H, H_9), 7.65 (dd, J = 8.2, 7.2 Hz, 1H, H_6), 7.59 (ddd, J = 7.9, 6.7, 1.3 Hz, 1H, H_{10}), 7.56-7.37 (m, 8H, H_5, H_{11}, H_{12}, H_{15}, H_{16} and H_{17});

^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 172.2 (Quat, C_2), 156.9 (CH, C_1), 152.9 (Quat, C_{18}), 135.5 (CH, C_{15}), 133.9 (Quat, C_{Ar}), 132.1 (Quat, C_{Ar}), 132.0 (Quat, C_{Ar}), 130.5 (Quat, C_{Ar}), 130.1 (CH, C_7), 129.8 (CH, C_{17}), 129.3 (CH, C_{16}), 128.9 (CH, C_9), 128.1 (CH and Quat, C_5 and C_{Ar}), 127.2 (CH, C_{11}), 126.6 (CH, C_{10}), 125.7 (CH, C_6), 124.2 (CH, C_{12});

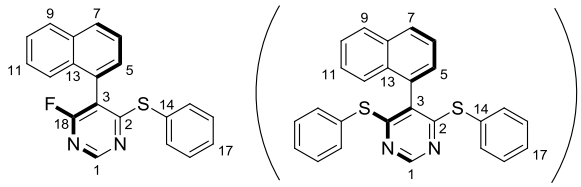
FTIR (neat) ν/cm^{-1} = 3056, 1528, 1492, 1389, 1341, 1260, 1224, 1022;

HRMS (ESI^{+}) calculated for $C_{20}H_{13}BrN_2NaS$ = 414.9875, mass found = 414.9890;

Chiral HPLC (Chiralpak ADH, 15 % IPA, 85 % hexane, 1.0 mL/min, λ = 220 nm, 20 μL injection) τ_R (minor) = 10.7 min, τ_R (major) = 13.6 min;

$[\alpha]_D^{20}$ = –17 (*c* = 1.00, $CHCl_3$).

(*S*)-4-Fluoro-5-(naphthalen-1-yl)-6-(phenylthio)pyrimidine, 269



269 **204**

Asymmetric: According to **General Procedure E** with **257** (30 mg, 0.12 mmol), carbon tetrachloride (1.2 mL), *N*-benzylquininium chloride (6 mg, 0.012 mmol), thiophenol (14.0 μL, 0.14 mmol), 50 % w/w aqueous potassium carbonate (86 μL, 0.62 mmol) at room temperature for 48 hours. Purification *via* column chromatography eluting with 1:19 ethyl acetate/petrol 40-60 afforded the title compound **269** as a white solid (37 mg, 93 %, 68:32 e.r.). An analytical quantity of highly enantioenriched **269** (98:2 e.r.) was obtained by semi-preparative HPLC (Chiralpak ADH, 20 % IPA, 80 % hexane, 1.0 mL/min).

Racemic: According to **General Procedure F** with **257** (40 mg, 0.17 mmol), toluene (1.7 mL), tetrabutylammonium bromide (5 mg, 0.017 mmol), thiophenol (18.7 μL, 0.18 mmol), 50 % w/w aqueous potassium hydroxide (46 μL, 0.82 mmol) at room temperature for 2 hours. Purification *via* column chromatography eluting with 7.5:92.5 ethyl acetate/petrol 40-60 afforded the title compound *rac*-**269** as a white solid (40 mg, 75 %) along with by-product **204** as a white solid (10 mg, 14 %). The spectral data for **204** matched that obtained previously.

Melting point: 164-165 ^{o}C (ethyl acetate/petrol 40-60);

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 8.55 (d, J = 1.8 Hz, 1H, H_1), 7.92 (d, J = 8.1 Hz, 1H, H_7), 7.87 (d, J = 8.2 Hz, 1H, H_9), 7.53 (t, J = 7.7 Hz, 1H, H_6), 7.50-7.41 (m, 4H, H_5, H_{10}, H_{11} and H_{12}), 7.40-7.35 (m, 2H, H_{15}), 7.34-7.27 (m, 3H, H_{16} and H_{17});

^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 174.5 (d, J = 4.8 Hz, Quat, C_2), 166.3 (d, J = 251.9 Hz, Quat, C_{18}), 157.4 (d, J = 15.1 Hz, CH, C_1), 135.5 (CH, C_{15}), 133.8 (Quat, C_{Ar}), 131.0 (Quat, C_{Ar}), 130.3 (CH, C_7),

129.7 (CH, C_{17}), 129.3 (CH, C_{16}), 128.9 (CH, C_9), 128.6 (CH, C_5), 128.0 (Quat, C_{Ar}), 127.1 (CH, C_{11}), 126.8 (d, J = 2.4 Hz, Quat, C_4), 126.6 (CH, C_{10}), 125.5 (CH, C_6), 124.4 (CH, C_{12}), 116.0 (d, J = 27.8 Hz, Quat, C_3);

^{19}F NMR (376 MHz, $CDCl_3$) δ_F = -64.9;

FTIR (neat) ν/cm^{-1} = 3058, 1596, 1573, 1514, 1417, 1401, 1355, 1295, 1259;

HRMS (ESI^+) calculated for $C_{20}H_{14}N_2FS$ = 333.0856, mass found = 333.0854;

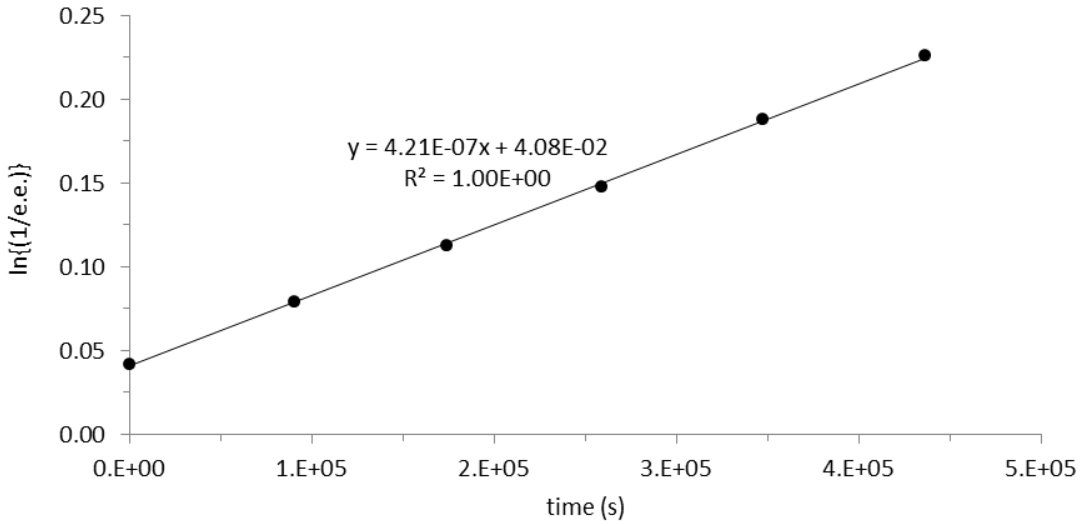
Chiral HPLC (Chiralpak IA, 5 % IPA, 95 % hexane, 1.0 mL/min, λ = 254 nm, 20 μL injection) τ_R (major) = 7.1 min, τ_R (minor) = 8.4 min;

Scheme 3.45 – Experiment to determine the rate of racemization of 269

A solution of **269** (98:2 e.r.) in 1:4 IPA/hexane was allowed to stand at room temperature. 20 μL aliquots were removed over the course of 5 days (7273 minutes) and the enantioenrichment was analysed by chiral HPLC (Chiralpak IA, 5 % IPA, 95 % hexane, 1.0 mL/min, λ= 254 nm).

time / min	t / s	% major ent.	% minor ent.	ln{1/e.e.}
0	0	97.94	2.06	0.042
1508	90480	96.19	3.81	0.079
2905	174300	94.67	5.33	0.113
4317	259020	93.14	6.86	0.148
5796	347760	91.43	8.57	0.188
7273	436380	89.9	10.1	0.226

A plot of ln(1/e.e.) *vs* time resulted in a straight line with a gradient of 4.21 x 10^{-7} s^{-1}.



$$ln\left\{\frac{1}{e.e.}\right\} = 2k_{ent}t + C$$

therefore k_{ent} = ½ slope = ½ (4.2 x 10^{-7}) = 2.1 x 10^{-7} s^{-1}

$k_{rac} = 2k_{ent}$ = 4.2 x 10^{-7} s^{-1}

$t_{1/2}^{rac} = \ln 2 / k_{rac}$ = 1.7 x 10^{6} s = 19 days

Employing the Eyring equation:

$$\Delta G^{\ddagger} = -RT\, ln\left\{\frac{k_{ent} \times h}{k_B \times T}\right\}$$

= 1.11 x 10^{5} J mol^{-1} (at 298 K)

= 26.6 kcal mol^{-1} (at 298 K)

Scheme 3.46 – The effect of catalyst counter-ion

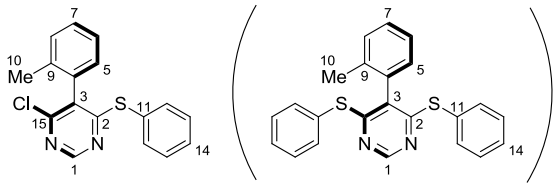
According to **General Procedure E** with **201** (50 mg, 0.18 mmol), carbon tetrachloride (1.8 mL), *N*-benzylquininium bromide (9 mg, 0.018 mmol), thiophenol (20.3 μL, 0.20 mmol), 50 % w/w aqueous potassium carbonate (0.12 mL, 0.90 mmol) at room temperature for 48 hours. Purification *via* column chromatography eluting with 1:19 ethyl acetate/petrol 40-60 afforded

203 as a white solid (57 mg, 90 %, 93:7 e.r.). The spectral data for **203** matched that obtained previously.

According to **General Procedure E** with **256** (66 mg, 0.18 mmol), carbon tetrachloride (1.8 mL), *N*-benzylquininium chloride (8 mg, 0.018 mmol), thiophenol (20.3 μL, 0.20 mmol), 50 % w/w aqueous potassium carbonate (0.12 mL, 0.90 mmol) at room temperature for 48 hours. Purification *via* column chromatography eluting with 1:19 ethyl acetate/petrol 40-60 afforded **268** as a white solid (63 mg, 88 %, 92:8 e.r.) along with by-product **204** as a white solid (5 mg, 7 %). The spectral data for **268** and **204** matched that obtained previously.

According to **General Procedure E** with **256** (66 mg, 0.18 mmol), carbon tetrachloride (1.8 mL), *N*-benzylquininium bromide (9 mg, 0.018 mmol), thiophenol (20.3 μL, 0.20 mmol), 50 % w/w aqueous potassium carbonate (0.12 mL, 0.90 mmol) at room temperature for 48 hours. Purification *via* column chromatography eluting with 1:19 ethyl acetate/petrol 40-60 afforded the **268** as a white solid (61 mg, 86 %, 90:10 e.r.) along with by-product **204** as a white solid (5 mg, 7 %). The spectral data for **268** and **204** matched that obtained previously.

(*R*)-4-Chloro-6-(phenylthio)-5-(*o*-tolyl)pyrimidine, 270



Asymmetric: According to **General Procedure E** with **245** (50 mg, 0.21 mmol), carbon tetrachloride (2.1 mL), *N*-benzylquininium chloride (9 mg, 0.021 mmol), thiophenol (23.6 μL, 0.23 mmol), 50 % w/w aqueous potassium carbonate (0.14 mL, 1.0 mmol) at room temperature for 48 hours. Purification *via* column chromatography eluting with 1:19 ethyl acetate/petrol 40-60 afforded the title compound **270** as a white solid (60 mg, 92 %, 93:7 e.r.) along with by-product **353** as a white solid (1.6 mg, 2 %).

Racemic: According to **General Procedure F** with **245** (100 mg, 0.42 mmol), toluene (4.2 mL), tetrabutylammonium bromide (13 mg, 0.042 mmol), thiophenol (55.8 μL, 0.54 mmol), 50 % w/w aqueous potassium hydroxide (0.12 mL, 2.1 mmol) at room temperature for 1 hour. Purification *via* column chromatography eluting with 1:19 ethyl acetate/petrol 40-60 afforded the title compound *rac*-**270** as a white solid (111 mg, 85 %) along with by-product **353** as a white solid (19 mg, 12 %).

Data for **270**

Melting point: 102-104 ^{o}C (ethyl acetate/petrol 40-60);

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 8.62 (s, 1H, H_1), 7.54-7.36 (m, 8H, H_6, H_7, H_8, H_{12}, H_{13}, H_{14}), 7.23 (d, J = 7.3 Hz, 1H, H_5), 2.23 (s, 3H, H_{10});

^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 171.9 (Quat, C_2), 158.5 (Quat, C_{15}), 156.8 (CH, C_1), 136.6 (Quat, C_{Ar}), 135.5 (CH, C_{12}), 132.5 (Quat, C_{Ar}), 130.8 (CH, C_{Ar}), 130.2 (Quat, C_{Ar}), 129.8 (CH, C_{Ar}), 129.8 (CH, C_{Ar}), 129.4 (CH, C_{13} and C_5), 128.0 (Quat, C_{Ar}), 126.7 (CH, C_6), 19.3 (CH_3, C_{10});

FTIR (neat) ν/cm^{-1} = 3061, 1539, 1502, 1398, 1375, 1351, 1228;

HRMS (ESI^{+}) calculated for $C_{17}H_{14}N_2ClS$ = 313.0561, mass found = 313.0555;

Chiral HPLC (Chiralpak ADH, 5 % IPA, 95 % hexane, 1.0 mL/min, λ = 210 nm, 20 μL injection) τ_R (minor) = 9.1 min, τ_R (major) = 10.1 min;

$[\alpha]_D^{20}$ = 0 (*c* = 1.00, $CHCl_3$).

Data for **353**

Melting point: 154-156 ^{o}C (ethyl acetate/petrol 40-60);

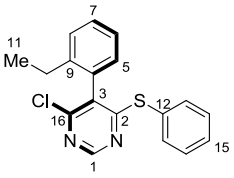
^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 8.51 (s, 1H, H_1), 7.53-7.38 (m, 13H, H_{Ar}), 7.30 (d, J = 7.4 Hz, 1H, H_5), 2.33 (s, 3H, H_{10});

^{13}C NMR (126 MHz, $CDCl_3$) δ_C = 167.1 (Quat, C_2), 156.7 (CH, C_1), 137.0 (Quat, C_{Ar}), 135.4 (CH, C_{12}), 132.5 (Quat, C_{Ar}), 130.9 (CH, C_{Ar}), 130.0 (CH, C_{Ar}), 129.9 (CH, C_{Ar}), 129.4 (CH, C_{Ar}), 129.2 (CH, C_{13}), 128.5 (Quat, C_{Ar}), 127.8 (Quat, C_{Ar}), 126.9 (CH, C_{Ar}), 19.3 (CH_3, C_{10});

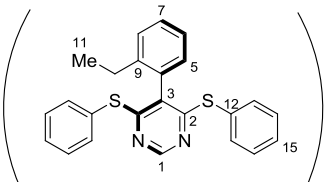
FTIR (neat) ν/cm^{-1} = 3059, 1508, 1398, 1345, 1232;

HRMS (ESI^+) calculated for $C_{23}H_{19}N_2S_2$ = 387.0984, mass found = 387.0976.

(*R*)-4-Chloro-5-(2-ethylphenyl)-6-(phenylthio)pyrimidine, 271



271



354

Asymmetric: According to **General Procedure E** with **246** (50 mg, 0.20 mmol), carbon tetrachloride (2.0 mL), *N*-benzylquininium chloride (9 mg, 0.020 mmol), thiophenol (22.4 μL, 0.22 mmol), 50 % w/w aqueous potassium carbonate (0.14 mL, 1.0 mmol) at room temperature for 48 hours. Purification *via* column chromatography eluting with 1:19 ethyl acetate/petrol 40-60 afforded the title compound **271** as a white solid (57 mg, 88 %, 96:4 e.r.).

Racemic: According to **General Procedure F** with **246** (100 mg, 0.40 mmol), toluene (4.0 mL), tetrabutylammonium bromide (13 mg, 0.040 mmol), thiophenol (52.8 μL, 0.51 mmol), 50 % w/w aqueous potassium hydroxide (0.11 mL, 2.0 mmol) at room temperature for 1 hour. Purification *via* column chromatography eluting with 1:19 ethyl acetate/petrol 40-60 afforded the title compound *rac*-**271** as a white solid (112 mg, 87 %) along with by-product **354** as a white solid (13 mg, 8 %).

Data for **271**

Melting point: 105-107 ^oC (ethyl acetate/petrol 40-60);

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 8.62 (s, 1H, H_1), 7.53-7.42 (m, 7H, H_{Ar}), 7.39 (td, J = 7.3, 1.5 Hz, 1H, H_6), 7.20 (dd, J = 7.4, 1.1 Hz, 1H, H_5), 2.59-2.44 (m, 2H, H_{10}), 1.24 (t, J = 7.6 Hz, 3H, H_{11});

^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 172.2 (Quat, C_2), 158.6 (Quat, C_{16}), 156.7 (CH, C_1), 142.4 (Quat, C_{Ar}), 135.5 (CH, C_{13}), 131.9 (Quat, C_{Ar}), 130.2 (Quat, C_{Ar}), 130.0 (CH, C_{Ar}), 129.8 (CH, C_{Ar}), 129.6 (CH, C_{Ar}), 129.4 (CH, C_{14}), 129.0 (CH, C_{Ar}), 128.1 (Quat, C_{Ar}), 126.7 (CH, C_{Ar}), 26.2 (CH_2, C_{10}), 14.7 (CH_3, C_{11});

FTIR (neat) ν/cm^{-1} = 2968, 1537, 1501, 1398, 1374, 1351, 1227, 1024;

HRMS (ESI$^+$) calculated for $C_{18}H_{15}ClN_2NaS$ = 349.0537, mass found = 349.0535;

Chiral HPLC (Chiralpak ADH, 5 % IPA, 95 % hexane, 1.0 mL/min, λ = 210 nm, 5 μL injection) τ_R (minor) = 8.6 min, τ_R (major) = 10.5 min;

$[\alpha]_D^{20}$ = +13 (*c* = 1.00, $CHCl_3$).

Data for **354**

Melting point: 136-137 ^{o}C (ethyl acetate/petrol 40-60);

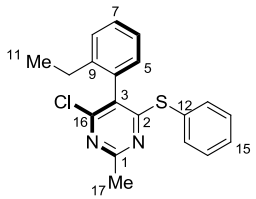
^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 8.50 (s, 1H, H_1), 7.55-7.46 (m, 6H, H_7, H_8 and H_{13}), 7.45-7.38 (m, 7H, H_6, H_{15} and H_{14}), 7.28 (dd, J = 7.5, 1.0 Hz, 1H, H_5), 2.62 (q, J = 7.6 Hz, 2H, H_{10}), 1.32 (t, J = 7.6 Hz, 3H, H_{11});

^{13}C NMR (126 MHz, $CDCl_3$) δ_C = 167.4 (Quat, C_2), 156.6 (CH, C_1), 142.8 (Quat, C_{Ar}), 135.4 (CH, C_{13}), 131.9 (Quat, C_{Ar}), 130.2 (CH, C_5), 130.1 (CH, C_{Ar}), 129.4 (CH, C_{15}), 129.2 (CH, C_{14}), 129.1 (CH, C_{Ar}), 128.6 (Quat, C_{12}), 127.8 (Quat, C_{Ar}), 126.9 (CH, C_6), 26.1 (CH_2, C_{10}), 14.8 (CH_3, C_{11});

FTIR (neat) ν/cm^{-1} = 2967, 1507, 1477, 1397, 1346, 1232, 1024, 993;

HRMS (ESI$^+$) calculated for $C_{24}H_{21}N_2S_2$ = 401.1141, mass found = 401.1139.

(*R*)-4-Chloro-5-(2-ethylphenyl)-2-methyl-6-(phenylthio)pyrimidine, 272



Asymmetric: According to **General Procedure E** with **350** (50 mg, 0.19 mmol), carbon tetrachloride (1.9 mL), *N*-benzylquininium chloride (8 mg, 0.019 mmol), thiophenol (21.1 μL, 0.21 mmol), 50 % w/w aqueous potassium carbonate (0.13 mL, 0.94 mmol) at room temperature for 48 hours. Purification *via* column chromatography eluting with 1:49 ethyl acetate/petrol 40-60 afforded the title compound **272** as a white solid (54 mg, 85 %, 97:3 e.r.).

Racemic: According to **General Procedure F** with **350** (50 mg, 0.19 mmol), toluene (1.9 mL), tetrabutylammonium bromide (6 mg, 0.019 mmol), thiophenol (21.1 μL, 0.21 mmol), 50 % w/w aqueous potassium hydroxide (0.05 mL, 0.9 mmol) at room temperature for 1 hour. Purification *via* column chromatography eluting with 1:49 ethyl acetate/petrol 40-60 afforded the title compound *rac*-**272** as a white solid (54 mg, 85 %).

Melting point: 81-83 ^{o}C (ethyl acetate/petrol 40-60);

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.52-7.34 (m, 8H, H_6, H_7, H_8, H_{13}, H_{14} and H_{15}), 7.18 (dd, J = 7.7, 1.1 Hz, 1H, H_5), 2.57-2.46 (m, 2H, H_{10}), 2.52 (s, 3H, H_{17}), 1.23 (t, J = 7.6 Hz, 3H, H_{11});

^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 171.3 (Quat, C_{Ar}), 166.8 (Quat, C_{Ar}), 158.3 (Quat, C_{Ar}), 142.7 (Quat, C_{Ar}), 135.3 (CH, C_{13}), 132.1 (Quat, C_{Ar}), 129.9 (CH, C_5), 129.8 (CH, C_{Ar}), 129.3 (CH, C_{Ar}), 129.0 (CH, C_{14}), 128.8 (CH, C_{Ar}), 128.5 (Quat, C_{Ar}), 126.8 (Quat, C_{Ar}), 126.6 (CH, C_6), 26.2 (CH_2, C_{10}), 25.7 (CH_3, C_{17}), 14.8 (CH_3, C_{11});

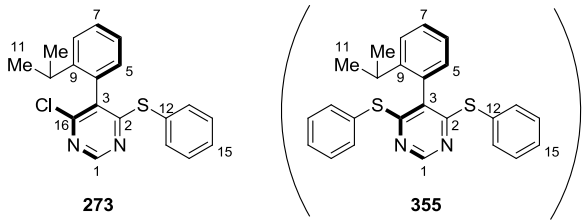
FTIR (neat) ν/cm^{-1} = 2967, 1545, 1487, 1476, 1439, 1404, 1290;

HRMS (ESI$^+$) calculated for $C_{19}H_{18}N_2ClS$ = 341.0879, mass found = 341.0870;

Chiral HPLC (Chiralpak ADH, 20 % IPA, 80 % hexane, 1.0 mL/min, λ = 292 nm, 20 μL injection) τ_R (minor) = 3.8 min, τ_R (major) = 4.5 min;

$[\alpha]_D^{20}$ = +14 (*c* = 1.00, $CHCl_3$).

(*R*)-4-Chloro-5-(2-isopropylphenyl)-6-(phenylthio)pyrimidine, 273



Asymmetric: According to **General Procedure E** with **247** (50 mg, 0.19 mmol), carbon tetrachloride (1.9 mL), *N*-benzylquininium chloride (8 mg, 0.019 mmol), thiophenol (21.1 μL, 0.21 mmol), 50 % w/w aqueous potassium carbonate (0.13 mL, 0.94 mmol) at room temperature for 48 hours. Purification *via* column chromatography eluting with 1:24 ethyl acetate/petrol 40-60 afforded the title compound **273** as a white solid (15 mg, 24 %, 85:15 e.r.) along with recovered starting material **247** (34 mg, 68 %).

Racemic: According to **General Procedure F** with **247** (100 mg, 0.37 mmol), toluene (3.7 mL), tetrabutylammonium bromide (12 mg, 0.037 mmol), thiophenol (50.0 μL, 0.49 mmol), 50 % w/w aqueous potassium hydroxide (0.10 mL, 1.9 mmol) at room temperature for 1 hour. Purification *via* column chromatography eluting with 1:19 ethyl acetate/petrol 40-60 afforded the title compound *rac*-**273** as a white solid (98 mg, 77 %) along with by-product **355** as a white solid (21 mg, 14 %).

Data for **273**

Melting point: 103-105 ^oC (ethyl acetate/petrol 40-60);

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 8.61 (s, 1H, H_1), 7.56-7.41 (m, 7H, H_7, H_8, H_{13}, H_{14} and H_{15}), 7.38 (ddd, J = 7.8, 6.2, 2.4 Hz, 1H, H_6), 7.19-7.15 (m, 1H, H_5), 2.63 (sept, J = 6.8 Hz, 1H, H_{10}), 1.34 (d, J = 6.8 Hz, 3H, H_{11A}), 1.24 (d, J = 6.6 Hz, 3H, H_{11B});

^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 172.4 (Quat, C_2), 158.7 (Quat, C_{16}), 156.7 (CH, C_1), 147.3 (Quat, C_{Ar}), 135.5 (CH, C_{13}), 131.1 (Quat, C_{Ar}), 130.3 (Quat, C_{Ar}), 130.2 (CH, C_7), 129.8 (CH, C_{15}), 129.4 (CH, C_5), 129.4 (CH, C_{14}), 128.1 (Quat, C_{Ar}), 126.6 (CH, C_6), 126.4 (CH, C_8), 31.1 (CH, C_{10}), 24.1 (CH_3, C_{11A}), 24.1 (CH_3, C_{11B});

FTIR (neat) ν/cm^{-1} = 2962, 1538, 1502, 1398, 1355, 1228;

HRMS (ESI^+) calculated for $C_{19}H_{17}ClN_2NaS$ = 363.0693, mass found = 363.0701;

Chiral HPLC (Chiralpak ADH, 5 % IPA, 95 % hexane, 1.0 mL/min, λ = 245 nm, 10 μL injection) τ_R (minor) = 7.7 min, τ_R (major) = 10.5 min;

$[\alpha]_D^{20}$ = +10 (*c* = 1.00, $CHCl_3$).

Data for **355**

Melting point: 148-149 ^{o}C (ethyl acetate/petrol 40-60);

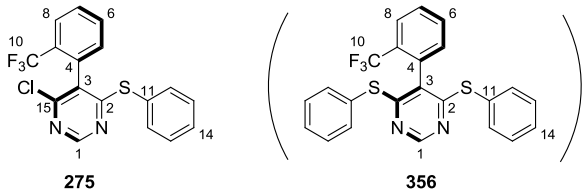
^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 8.42 (s, 1H, H_1), 7.50-7.45 (m, 2H, H_7 and H_8), 7.42-7.38 (m, 4H, H_{13}), 7.35-7.29 (m, 7H, H_6, H_{14} and H_{15}), 7.17 (d, J = 7.6 Hz, 1H, H_5), 2.69 (sept, J = 6.8 Hz, 1H, H_{10}), 1.28 (d, J = 6.8 Hz, 6H, H_{11});

^{13}C NMR (126 MHz, $CDCl_3$) δ_C = 167.6 (Quat, C_2), 156.4 (CH, C_1), 147.8 (Quat, C_{Ar}), 135.4 (CH, C_{13}), 131.1 (Quat, C_{Ar}), 130.3 (CH, C_{Ar}), 130.1 (CH, C_5), 129.4 (CH, C_{15}), 129.2 (CH, C_{14}), 128.7 (Quat, C_{12}), 128.0 (Quat, C_{Ar}), 126.8 (CH, C_6), 126.6 (CH, C_{Ar}), 31.0 (CH, C_{10}), 24.3 (CH, C_{11});

FTIR (neat) ν/cm^{-1} = 2962, 1508, 1476, 1397, 1341, 1233;

HRMS (ESI^+) calculated for $C_{25}H_{22}N_2NaS_2$ = 437.1117, mass found = 437.1120.

(*R*)-4-Chloro-6-(phenylthio)-5-(2-(trifluoromethyl)phenyl)pyrimidine, 275



275 **356**

Asymmetric: According to **General Procedure E** with **248** (50 mg, 0.17 mmol), carbon tetrachloride (1.7 mL), *N*-benzylquininium chloride (8 mg, 0.02 mmol), thiophenol (19.3 μL, 0.19 mmol), 50 % w/w aqueous potassium carbonate (0.12 mL, 0.56 mmol) at room temperature for 48 hours. Purification *via* column chromatography eluting with 7.5:92.5 ethyl acetate/petrol 40-60 afforded the title compound **275** as a white solid (55 mg, 88 %, 90:10 e.r.).

Racemic: According to **General Procedure F** with **248** (100 mg, 0.34 mmol), toluene (3.4 mL), tetrabutylammonium bromide (11 mg, 0.034 mmol), thiophenol (45.6 μL, 0.44 mmol), 50 % w/w aqueous potassium hydroxide (0.10 mL, 1.7 mmol) at room temperature for 1 hour. Purification *via* column chromatography eluting with 7.5:92.5 ethyl acetate/petrol 40-60 afforded the title compound *rac*-**275** as a white solid (92 mg, 74 %) along with by-product **356** as a white solid (39 mg, 26 %).

Data for **275**

Melting point: 121-123 ^{o}C (ethyl acetate/petrol 40-60);

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 8.62 (s, 1H, H_1), 7.89 (d, J = 7.8 Hz, 1H, H_8), 7.75 (t, J = 7.3 Hz, 1H, H_6), 7.67 (t, J = 7.7 Hz, 1H, H_7), 7.51-7.40 (m, 5H, H_{12}, H_{13} and H_{14}), 7.38 (d, J = 7.6 Hz, 1H, H_5);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 172.0 (Quat, C_2), 158.5 (Quat, C_{15}), 157.2 (CH, C_1), 135.5 (CH, C_{12}), 132.7 (CH, C_6), 131.6 (CH, C_5), 131.4 (q, J = 1.9 Hz, Quat, C_4) 130.0 (CH, $C_{7/14}$), 129.9 (CH,

$C_{7/14}$), 129.4 (CH, C_{13}), 129.1 (q, J = 30.7 Hz, Quat, C_9), 128.3 (Quat, C_{Ar}), 127.8 (Quat, C_{Ar}), 127.2 (q, J = 5.0 Hz, CH, C_8), 123.6 (q, J = 278.7 Hz, Quat, C_{10});

^{19}F NMR (376 MHz, $CDCl_3$) δ_F = -70.0;

FTIR (neat) ν/cm^{-1} = 3064, 1542, 1504, 1402, 1356, 1313, 1173, 1128;

HRMS (ESI$^+$) calculated for $C_{17}H_{11}N_2ClF_3S$ = 367.0278, mass found = 367.0272.

Chiral HPLC (Chiralpak IC, 2 % IPA, 98 % hexane, 1.0 mL/min, λ = 230 nm, 20 μL injection) τ_R (minor) = 6.5 min, τ_R (major) = 7.3 min.

$[\alpha]_D^{20}$ = –13 (*c* = 1.00, $CHCl_3$).

Data for **356**

Melting point: 150-151 ^{o}C (ethyl acetate/petrol 40-60);

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 8.52 (s, 1H, H_1), 7.93 (d, J = 7.8 Hz, 1H, H_8), 7.78 (t, J = 7.3 Hz, 1H, H_6), 7.69 (t, J = 7.7 Hz, 1H, H_7), 7.51-7.44 (m, 5H, H_5 and H_{12}), 7.43-7.37 (m, 6H, H_{13} and H_{14});

^{13}C NMR (101 MHz, $CDCl_3$)* δ_C = 167.5 (Quat, C_2), 157.0 (CH, C_1), 135.4 (CH, C_{12}), 132.8 (CH, C_6), 132.5 (CH, C_5), 131.8 (q, J = 2.1 Hz, Quat, C_4), 129.9 (CH, C_7), 129.4 (CH, C_{14}), 129.2 (CH, C_{13}), 128.6 (Quat, C_{Ar}), 127.5 (q, J = 4.8 Hz, CH, C_8), 126.1 (Quat, C_{Ar}), 123.7 (q, J = 274.4 Hz, Quat, C10).

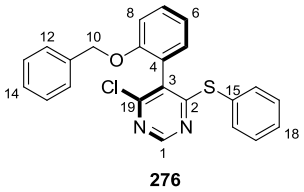
^{19}F NMR (376 MHz, $CDCl_3$) δ_F = -60.8;

FTIR (neat) ν/cm^{-1} = 3061, 1507, 1399, 1311, 1169, 1127, 1112, 1065, 1035;

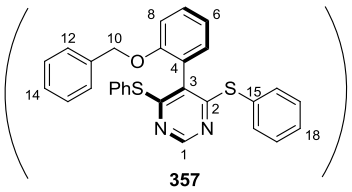
HRMS (ESI$^+$) calculated for $C_{23}H_{16}N_2F_3S_2$ = 441.0702, mass found = 441.0700.

* The quartet arising from C_9 was obscured by the peaks from C_{14} and C_{13} and is therefore not listed.

(*R*)-5-(2-(Benzyloxy)phenyl)-4-chloro-6-(phenylthio)pyrimidine, 276



276



357

Asymmetric: According to **General Procedure E** with **249** (50 mg, 0.15 mmol), carbon tetrachloride (1.5 mL), *N*-benzylquininium chloride (7 mg, 0.02 mmol), thiophenol (17.1 μL, 0.17 mmol), 50 % w/w aqueous potassium carbonate (0.10 mL, 0.80 mmol) at room temperature for 48 hours. Purification *via* column chromatography eluting with 1:9 ethyl acetate/petrol 40-60 afforded the title compound **276** as a white solid (57 mg, 93 %, 95:5 e.r.).

Racemic: According to **General Procedure F** with **249** (100 mg, 0.30 mmol), toluene (3.0 mL), tetrabutylammonium bromide (10 mg, 0.030 mmol), thiophenol (40.3 μL, 0.39 mmol), 50 % w/w aqueous potassium hydroxide (0.08 mL, 1.5 mmol) at room temperature for 1 hour. Purification *via* column chromatography eluting with 7.5:92.5 ethyl acetate/petrol 40-60 afforded the title compound *rac*-**276** as a white solid (110 mg, 90 %) along with by-product **357** as a colourless oil (9 mg, 6 %).

Data for **276**

Melting point: 105-108 ^{o}C (ethyl acetate/petrol 40-60);

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 8.60 (s, 1H, H_1), 7.52-7.39 (m, 6H, H_{Ar}), 7.38-7.27 (m, 6H, H_{Ar}), 7.16 (td, J = 7.5, 1.0 Hz, 1H, H_6), 7.12 (d, J = 8.6 Hz, 1H, H_8), 5.17 (s, 2H, H_{10});

^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 172.1 (Quat, C_2), 159.0 (Quat, C_{Ar}), 156.6 (CH, C_1), 155.9 (Quat, C_{Ar}), 136.8 (Quat, C_{Ar}), 135.5 (CH, C_{Ar}), 131.3 (CH, C_{Ar}), 130.9 (CH, C_{Ar}), 129.7 (CH, C_{Ar}), 129.3 (CH, C_{Ar}), 128.6 (CH, C_{Ar}), 128.3 (Quat, C_{Ar}), 128.0 (Quat, C_{Ar}), 127.9 (CH, C_{Ar}), 126.9 (CH, C_{Ar}), 122.2 (Quat, C_4), 121.4 (CH, C_6), 113.0 (CH, C_8), 70.4 (CH_2, C_{10});

FTIR (neat) ν/cm^{-1} = 3062, 1540, 1504, 1447, 1399, 1354, 1228, 1049, 1023;

HRMS (ESI$^+$) calculated for $C_{23}H_{18}ON_2ClS$ = 405.0823, mass found = 405.0815;

Chiral HPLC (Chiralpak ADH, 20 % IPA, 80 % hexane, 1.0 mL/min, λ = 212 nm, 20 μL injection) τ_R (minor) = 7.7 min, τ_R (major) = 11.2 min.

$[\alpha]_D^{20}$ = +41 (*c* = 1.00, $CHCl_3$).

Data for **357**

^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 8.52 (s, 1H, H_1), 7.50 (ddd, J = 8.3, 7.5, 1.7 Hz, 1H, H_7), 7.47-7.44 (m, 4H, H_{16}), 7.42-7.28 (m, 12H, H_5, H_{12}, H_{13}, H_{14}, H_{17} and H_{18}), 7.19 (td, J = 7.5, 0.9 Hz, 1H, H_6), 7.13 (d, J = 8.2 Hz, 1H, H_8), 5.21 (s, 2H, H_{10});

^{13}C NMR (121 MHz, $CDCl_3$) δ_C = 167.6 (Quat, C_2), 156.2 (CH, C_1), 156.1 (Quat, C_9), 137.0 (Quat, C_{Ar}), 135.3 (CH, C_{16}), 131.4 (CH, C_{Ar}), 131.4 (CH, C_{Ar}), 129.3 (CH, C_{Ar}), 129.2 (CH, C_{17}), 128.8 (Quat, C_{15}), 128.5 (CH, C_{Ar}), 127.8 (CH, C_{Ar}), 126.9 (CH, C_{Ar}), 125.9 (Quat, C_{Ar}), 122.2 (Quat, C_4), 121.7 (CH, C_6), 113.2 (CH, C_8), 70.4 (CH_2, C_{10});

FTIR (neat) ν/cm^{-1} = 3060, 1509, 1398, 1242, 1024;

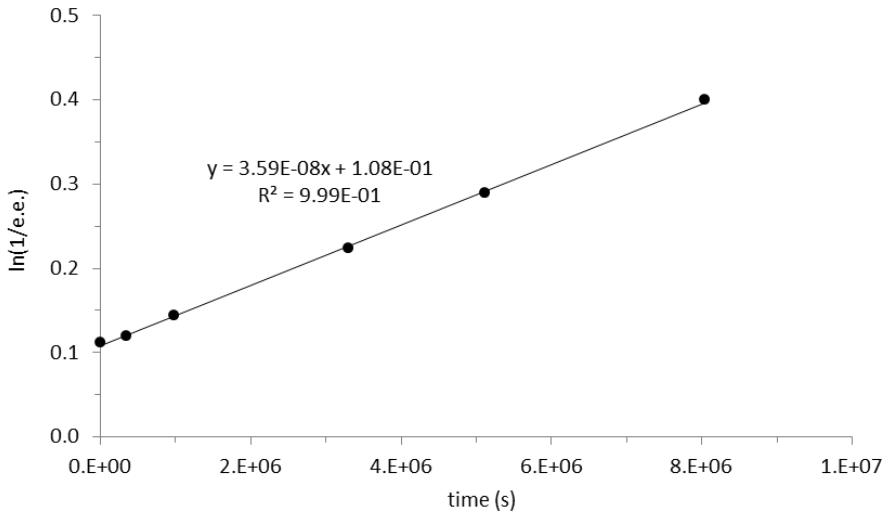
HRMS (ESI$^+$) calculated for $C_{29}H_{23}ON_2S_2$ = 479.1246, mass found = 479.1237.

Scheme 3.48 – Experiment to determine the rate of racemization of 276

A solution of **276** (95:5 e.r.) in IPA (1 mg/mL) was allowed to stand at room temperature. 20 μL aliquots were removed over the course of 93 days (2232 hours) and the enantioenrichment was analysed by chiral HPLC (Chiralpak ADH, 20 % IPA, 80 % hexane, 1.0 mL/min, λ= 212 nm).

time / h	t / s	% major ent.	% minor ent.	ln{1/e.e.}
0	0	94.71	5.29	0.112
95	342000	94.35	5.65	0.120
271	975600	93.31	6.69	0.144
918	3304800	89.96	10.04	0.224
1422	5119200	87.45	12.55	0.289
2232	8035200	83.52	16.48	0.400

A plot of ln(1/e.e.) *vs* time resulted in a straight line with a gradient of 3.59 x 10^{-8} s^{-1}.



$$ln\left\{\frac{1}{e.e.}\right\} = 2k_{ent}t + C$$

$k_{rac} = 2k_{ent} = 3.6 \times 10^{-8}\ s^{-1}$

$t_{1/2}^{rac} = \ln 2 / k_{rac} = 0.6$ years

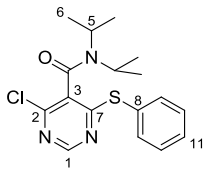
Employing the Eyring equation:

$$\Delta G^{\ddagger} = -RT\ ln\left\{\frac{k_{ent} \times h}{k_B \times T}\right\}$$

$= 1.17 \times 10^{5}$ J mol^{-1} (at 298 K)

= 28.0 kcal mol^{-1} (at 298 K)

4-Chloro-*N*,*N*-diisopropyl-6-(phenylthio)pyrimidine-5-carboxamide, 277[*]



Asymmetric: According to **General Procedure E** with **261** (30 mg, 0.11 mmol), carbon tetrachloride (1.1 mL), *N*-benzylquininium chloride (5 mg, 0.01 mmol), thiophenol (11.2 μL, 0.11 mmol), 50 % w/w aqueous potassium carbonate (0.12 mL, 0.9 mmol) at room temperature for 30 minutes. An analytical HPLC sample of **277** (50:50 e.r.) was obtained by preparative TLC (1:9 ethyl acetate/dichloromethane).

Racemic: According to **General Procedure F** with **261** (30 mg, 0.11 mmol), toluene (1.1 mL), tetrabutylammonium bromide (4 mg, 0.01 mmol), thiophenol (11.2 μL, 0.11 mmol), 50 % w/w aqueous potassium hydroxide (0.06 mL, 1.1 mmol) at room temperature for 30 minutes. Purification *via* column chromatography eluting with 1:19 ethyl acetate/dichloromethane afforded the title compound *rac*-**277** as a white solid (40 mg, quant.).

Melting point: 104-106 ^{o}C (ethyl acetate/dichloromethane);

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 8.53 (s, 1H, H_1), 7.57-7.51 (m, 2H, H_{10}), 7.50-7.40 (m, 3H, H_9 and H_{11}), 3.65 (sept, J = 6.6 Hz, 1H, H_5), 3.62 (sept, J = 6.8 Hz, 1H, $H_{5'}$), 1.65 (d, J = 6.8 Hz, 3H, $H_{6'A}$), 1.61 (d, J = 6.8 Hz, 3H, $H_{6'B}$), 1.38 (d, J = 6.6 Hz, 3H, H_{6A}), 1.29 (d, J = 6.6 Hz, 3H, H_{6B});

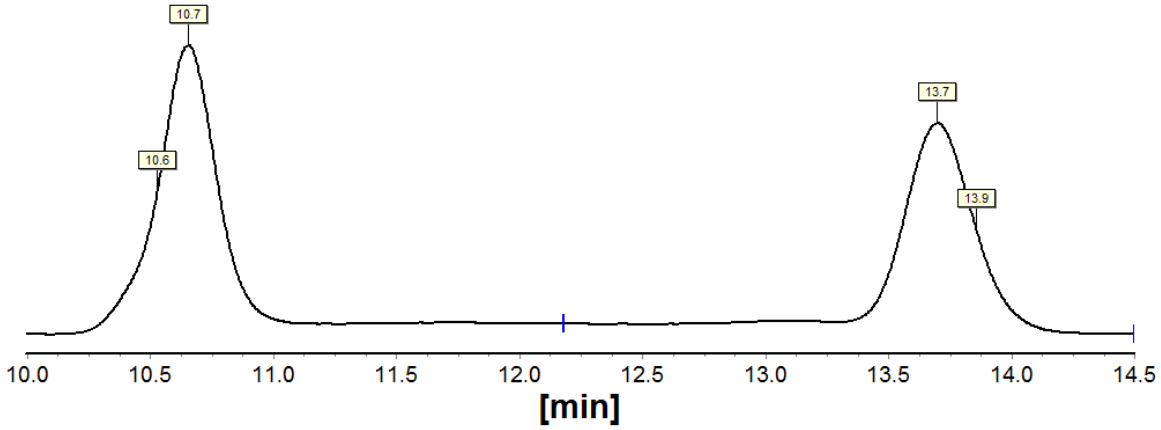
^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 169.0 (Quat, C_4), 162.4 (Quat, C_7), 157.0 (CH, C_1), 155.6 (Quat, C_2), 136.0 (CH, C_{10}), 135.8 (Quat, C_8), 130.5 (CH, C_{11}), 129.8 (CH, C_9), 127.0 (Quat, C_3), 52.5 (CH, C_5), 47.0 (CH, $C_{5'}$), 21.8 (CH_3, C_{6A}), 21.4 (CH_3, C_{6B}), 20.4 (CH_3, $C_{6'A}$), 20.4 (CH_3, $C_{6'B}$);

FTIR (neat) ν/cm^{-1} = 2972, 1637, 1537, 1501, 1475, 1443, 1403, 1370, 1299, 1232, 1210, 1158;

[*] This compound was synthesised by Benjamin Rahemtulla.

HRMS (ESI$^+$) calculated for $C_{17}H_{21}ClSN_3O$ = 350.10884, mass found = 350.10845;

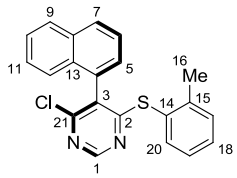
Chiral HPLC (Chiralpak ADH, 10 % IPA, 90 % hexane, 1.0 mL/min, λ = 206 nm, 20 μL injection) τ_R = 10.7 min, τ_R (major) = 13.7 min. The raw data was analysed using DCXplotter to obtain thermodynamic parameters shown below.[93]



tR1 [min]	tR2 [min]	wh1 [s]	wh2 [s]	h1 [%]	hp [%]	h2 [%]	A1	A2
10.687	13.730	15.2	19.2	100.00	3.55	72.99	53.61	46.39

k1 [1/s]
3.090E-0004

(*R*)-4-Chloro-5-(naphthalen-1-yl)-6-(*o*-tolylthio)pyrimidine, 278



Asymmetric: According to **General Procedure E** with **201** (50 mg, 0.18 mmol), carbon tetrachloride (1.8 mL), *N*-benzylquininium chloride (8 mg, 0.018 mmol), *o*-thiocresol (25 mg, 0.20 mmol), 50 % w/w aqueous potassium carbonate (0.12 mL, 0.90 mmol) at room temperature for 48 hours. Purification *via* column chromatography eluting with 1:19 ethyl acetate/petrol 40-60 afforded the title compound **278** as a white solid (23 mg, 35 %, 76:24 e.r.).

Racemic: According to **General Procedure F** with **201** (85 mg, 0.31 mmol), toluene (3.1 mL), tetrabutylammonium bromide (10 mg, 0.031 mmol), *o*-thiocresol (38 mg, 0.31 mmol), 50 % w/w aqueous potassium hydroxide (0.09 mL, 1.55 mmol) at room temperature for 2 hours. Purification *via* column chromatography eluting with 1:19 ethyl acetate/petrol 40-60 afforded the title compound *rac*-**278** as a white solid (89 mg, 80 %).

Melting point: 171-173 ^{o}C (ethyl acetate/petrol 40-60);

^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 8.70 (s, 1H, H_1), 8.07 (d, J = 8.4 Hz, 1H, H_7), 8.01 (d, J = 8.0 Hz, 1H, H_9), 7.67 (dd, J = 8.9, 6.4 Hz, 1H, H_6), 7.61 (ddd, J = 8.0, 6.9, 1.3 Hz, 1H, H_{10}), 7.58-7.54 (m, 2H, H_5 and H_{11}), 7.50 (d, J = 8.5 Hz, 1H, H_{12}), 7.44 (dd, J = 7.6, 0.9 Hz, 1H, H_{20}), 7.39 (td, J = 7.4, 1.3 Hz, 1H, H_{18}), 7.35 (dd, J = 7.6, 1.1 Hz, 1H, H_{17}), 7.24 (td, J = 7.4, 1.3 Hz, 1H, H_{19}), 2.33 (s, 3H, H_{16});

^{13}C NMR (126 MHz, $CDCl_3$) δ_C = 172.6 (Quat, C_2), 159.3 (Quat, C_{21}), 157.2 (CH, C_1), 143.2 (Quat, C_{Ar}), 136.5 (CH, C_{20}), 133.9 (Quat, C_{Ar}), 130.8 (CH, C_{17}), 130.6 (Quat, C_{Ar}), 130.6 (Quat, C_{Ar}), 130.5 (CH, C_{18}), 130.1 (CH, C_7), 129.3 (Quat, C_{Ar}), 128.9 (CH, C_9), 128.0 (CH, C_5), 127.4 (Quat, C_{Ar}), 127.1 (CH, C_{11}), 126.8 (CH, C_{19}), 126.6 (CH, C_{10}) 125.7 (CH, C_6), 124.1 (CH, C_{12}), 20.7 (CH_3, C_{16});

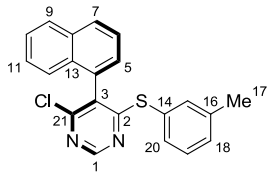
FTIR (neat) ν/cm^{-1} = 3059, 1739, 1536, 1501, 1396, 1374, 1346, 1230;

HRMS (ESI$^+$) calculated for $C_{21}H_{15}ClN_2NaS$ = 385.0537, mass found = 385.0537;

Chiral HPLC (Chiralpak IC, 10 % IPA, 90 % hexane, 1.0 mL/min, λ = 272 nm, 20 μL injection) τ_R (minor) = 5.4 min, τ_R (major) = 5.8 min;

$[\alpha]_D^{20}$ = + 7 (*c* = 1.00, $CHCl_3$).

(*R*)-4-Chloro-5-(naphthalen-1-yl)-6-(*m*-tolylthio)pyrimidine, 279



Asymmetric: According to **General Procedure E** with **201** (50 mg, 0.18 mmol), carbon tetrachloride (1.8 mL), *N*-benzylquininium chloride (8 mg, 0.018 mmol), *m*-thiocresol (25 mg, 0.20 mmol), 50 % w/w aqueous potassium carbonate (0.12 mL, 0.90 mmol) at room temperature for 48 hours. Purification *via* column chromatography eluting with 7.5:92.5 ethyl acetate/petrol 40-60 afforded the title compound **279** as a white solid (57 mg, 87 %, 91:9 e.r.).

Racemic: According to **General Procedure F** with **201** (50 mg, 0.18 mmol), toluene (1.8 mL), tetrabutylammonium bromide (6 mg, 0.018 mmol), *m*-thiocresol (23 mg, 0.18 mmol), 50 % w/w aqueous potassium hydroxide (0.05 mL, 0.90 mmol) at room temperature for 30 min. Purification *via* column chromatography eluting with 1:19 ethyl acetate/petrol 40-60 afforded the title compound *rac*-**279** as a white solid (59 mg, 90 %).

Melting point: 141-143 ^{o}C (ethyl acetate/petrol 40-60);

^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 8.62 (s, 1H, H_1), 7.94 (d, J = 8.0 Hz, 1H, H_7), 7.89 (d, J = 8.2 Hz, 1H, H_9), 7.55 (dd, J = 8.2, 7.1 Hz, 1H, H_6), 7.49 (ddd, J = 8.0, 6.9, 1.2 Hz, 1H, H_{10}), 7.46-7.40 (m, 2H, H_5 and H_{11}), 7.37 (d, J = 8.2 Hz, 1H, H_{12}), 7.23-7.12 (m, 4H, H_{15}, H_{18}, H_{19} and H_{20}), 2.27 (s, 3H, H_{17});

^{13}C NMR (126 MHz, $CDCl_3$) δ_C = 173.0 (Quat, C_2), 159.3 (Quat, C_{21}), 157.1 (CH, C_1), 139.2 (Quat, C_{Ar}), 135.9 (CH, $C_{m\text{-Tol}}$), 133.9 (Quat, C_{Ar}), 132.5 (CH, $C_{m\text{-Tol}}$), 130.7 (CH, $C_{m\text{-Tol}}$), 130.5 (Quat, C_{Ar}), 130.5 (Quat, C_{Ar}), 130.1 (CH, C_7), 129.1 (CH, $C_{m\text{-Tol}}$), 129.0 (Quat, C_{Ar}), 128.9 (CH, C_9), 128.1 (CH, C_5), 127.6 (Quat, C_{Ar}), 127.2 (CH, C_{11}), 126.6 (CH, C_{10}), 125.7 (CH, C_6), 124.2 (CH, C_{12}), 21.3 (CH_3, C_{17});

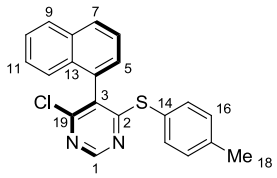
FTIR (neat) ν/cm^{-1} = 3057, 1536, 1500, 1396, 1345, 1231;

HRMS (ESI^+) calculated for $C_{21}H_{15}ClN_2NaS$ = 385.0537, mass found = 385.0539;

Chiral HPLC (Chiralpak IC, 20 % IPA, 80 % hexane, 1.0 mL/min, λ = 272 nm, 20 μL injection) τ_R (minor) = 5.0 min, τ_R (major) = 5.4 min;

$[\alpha]_D^{20}$ = + 4 (*c* = 1.00, $CHCl_3$).

(*R*)-4-Chloro-5-(naphthalen-1-yl)-6-(*p*-tolylthio)pyrimidine, 280



Asymmetric: According to **General Procedure E** with **201** (50 mg, 0.18 mmol), carbon tetrachloride (1.8 mL), *N*-benzylquininium chloride (8 mg, 0.018 mmol), *p*-thiocresol (25 mg, 0.20 mmol), 50 % w/w aqueous potassium carbonate (0.12 mL, 0.90 mmol) at room temperature for 48 hours. Purification *via* column chromatography eluting with 7.5:92.5 ethyl acetate/petrol 40-60 afforded the title compound **280** as a white solid (42 mg, 64 %, 57:43 e.r.).

Racemic: According to **General Procedure F** with **201** (50 mg, 0.18 mmol), toluene (1.8 mL), tetrabutylammonium bromide (6 mg, 0.018 mmol), *p*-thiocresol (25 mg, 0.20 mmol), 50 % w/w aqueous potassium hydroxide (0.05 mL, 0.90 mmol) at room temperature for 1 hour. Purification *via* column chromatography eluting with 1:19 ethyl acetate/petrol 40-60 afforded the title compound *rac*-**280** as a white solid (45 mg, 68 %).

Melting point: 133-135 ^oC (ethyl acetate/petrol 40-60);

^1H NMR (500 MHz, $CDCl_3$) δ_H = 8.62 (s, 1H, H_1), 7.94 (d, J = 8.4 Hz, 1H, H_7), 7.89 (d, J = 7.9 Hz, 1H, H_9), 7.56 (dd, J = 8.4, 7.1 Hz, 1H, H_6), 7.49 (ddd, J = 8.0, 6.2, 1.2 Hz, 1H, H_{10}), 7.46-7.41 (m,

2H, H_5 and H_{11}), 7.37 (d, J = 8.4 Hz, 1H, H_{12}), 7.24 (d, J = 8.0 Hz, 2H, H_{15}), 7.13 (d, J = 7.9 Hz, 2H, H_{16}), 2.29 (s, 3H, H_{18});

^{13}C NMR (126 MHz, $CDCl_3$) δ_C = 172.2 (Quat, C_2), 158.1 (Quat, C_{19}), 156.1 (CH, C_1), 139.0 (Quat, C_{Ar}), 134.3 (CH, C_{15}), 132.8 (Quat, C_{Ar}), 129.5 (Quat, C_{Ar}), 129.4 (Quat, C_{Ar}), 129.1 (CH, C_{16}), 129.0 (CH, C_7), 127.9 (Quat, C_{Ar}), 127.8 (CH, C_9), 127.0 (CH, C_5), 126.1 (CH, C_{11}), 125.5 (CH, C_{10}), 124.6 (CH, C_6), 123.3 (Quat, C_{Ar}), 123.1 (CH, C_{12}), 20.4 (CH_3, C_{18});

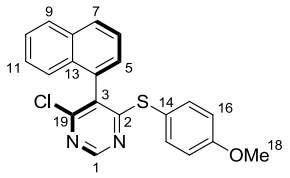
FTIR (neat) ν/cm^{-1} = 3058, 1537, 1500, 1397, 1345;

HRMS (ESI^+) calculated for $C_{21}H_{15}ClN_2NaS$ = 385.0537, mass found = 385.0542;

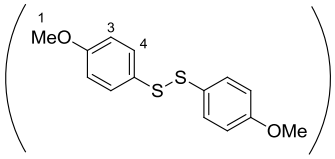
Chiral HPLC (Chiralpak ADH, 15 % IPA, 85 % hexane, 1.0 mL/min, λ = 272 nm, 20 μL injection) τ_R (major) = 10.4 min, τ_R (minor) = 14.0 min;

$[\alpha]_D^{20}$ = 0 (*c* = 1.00, $CHCl_3$).

(*R*)-4-Chloro-6-((4-methoxyphenyl)thio)-5-(naphthalen-1-yl)pyrimidine, 283



283



284

Asymmetric: According to **General Procedure E** with **201** (50 mg, 0.18 mmol), carbon tetrachloride (1.8 mL), *N*-benzylquininium chloride (8 mg, 0.018 mmol), 4-methoxythiophenol (28 mg, 0.20 mmol), 33 % w/w aqueous potassium carbonate (0.25 mL, 0.90 mmol) at room temperature for 24 hours. Purification *via* column chromatography eluting with 1:9 ethyl acetate/petrol 40-60 afforded the title compound **283** as a white solid (26 mg, 38 %, 51:49 e.r.) along with an inseparable mixture of starting material **201** and by-product **284** (1.13:1.00 **201**:**284**, 21 mg).

Racemic: According to **General Procedure F** with **201** (50 mg, 0.18 mmol), toluene (1.8 mL), tetrabutylammonium bromide (6 mg, 0.018 mmol), 4-methoxythiophenol (28 mg, 0.20 mmol), 50 % w/w aqueous potassium hydroxide (0.05 mL, 0.90 mmol) at room temperature for 1 hour. Purification *via* column chromatography eluting with 1:9 ethyl acetate/petrol 40-60 afforded the title compound *rac*-**283** as a white solid (63 mg, 91 %).

Data for **283**

Melting point: 167-169 ^{o}C (ethyl acetate/petrol 40-60);

^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 8.71 (s, 1H, H_1), 8.04 (d, J = 8.2 Hz, 1H, H_7), 7.99 (d, J = 8.2 Hz, 1H, H_9), 7.65 (dd, J = 7.7, 7.4 Hz, 1H, H_6), 7.60 -7.57 (m, 1H, H_{10}), 7.56-7.50 (m, 2H, H_5 and H_{11}), 7.46 (d, J = 8.5 Hz, 1H, H_{12}), 7.36 (d, J = 8.8 Hz, 2H, H_{15}), 6.93 (d, J = 8.8 Hz, 2H, H_{16}), 3.83 (s, 3H, H_{18});

^{13}C NMR (126 MHz, $CDCl_3$) δ_C = 173.5 (Quat, C_2), 160.8 (Quat, C_{17}), 159.1 (Quat, C_{19}), 157.1 (CH, C_1), 137.0 (CH, C_{15}), 133.8 (Quat, C_8), 130.5 (Quat, C_{Ar}), 130.4 (Quat, C_{Ar}), 130.0 (CH, C_7), 128.8 (CH, C_9), 128.0 (CH, C_5), 127.1 (CH, C_{11}), 126.5 (CH, C_{10}), 125.6 (CH, C_6), 124.2 (CH, C_{12}), 118.3 (Quat, C_{14}), 115.0 (CH, C_{16}), 55.3 (CH_3, C_{18});

FTIR (neat) ν/cm^{-1} = 3060, 1592, 1537, 1494, 1397, 1345, 1250, 1230;

HRMS (ESI^{+}) calculated for $C_{21}H_{15}ClN_2NaOS$ = 401.0486, mass found = 401.0484;

Chiral HPLC (Chiralpak ADH, 20 % IPA, 80 % hexane, 1.0 mL/min, λ = 223 nm, 20 μL injection) τ_R (major) = 14.6 min, τ_R (minor) = 18.7 min.

Data for **284**

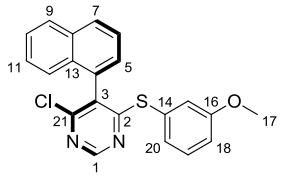
Data quoted is for disulfide **284** (peaks from **201** are omitted for clarity). The spectral data matched that previously reported in the literature.[132]

^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 7.41 (d, J = 8.8 Hz, 4H, H_4), 6.84 (d, J = 8.8 Hz, 4H, H_3), 3.81 (s, 6H, H_1);

^{13}C NMR (126 MHz, $CDCl_3$) δ_C = 159.9 (Quat, C_2), 132.7 (CH, C_4), 128.4 (Quat, C_5), 114.6 (CH, C_3), 55.35 (CH_3, C_1);

LRMS (ESI^+) 279 ($[M + H]^+$).

(*R*)-4-Chloro-6-((3-methoxyphenyl)thio)-5-(naphthalen-1-yl)pyrimidine, 285



Asymmetric: According to **General Procedure E** with **201** (50 mg, 0.18 mmol), carbon tetrachloride (1.8 mL), *N*-benzylquininium chloride (8 mg, 0.018 mmol), 3-methoxythiophenol (28 mg, 0.20 mmol), 33 % w/w aqueous potassium carbonate (0.25 mL, 0.90 mmol). Reaction conditions: room temperature for 48 hours. Purification *via* column chromatography eluting with 1:9 ethyl acetate/petrol 40-60 afforded the title compound **285** as a white solid (17 mg, 25 %, 70:30 e.r.).

Racemic: According to **General Procedure F** with **201** (50 mg, 0.18 mmol), toluene (1.8 mL), tetrabutylammonium bromide (6 mg, 0.018 mmol), 3-methoxythiophenol (28 mg, 0.20 mmol), 50 % w/w aqueous potassium hydroxide (0.05 mL, 0.90 mmol). Reaction conditions: room temperature for 1 hour. Purification *via* column chromatography eluting with 1:9 ethyl acetate/petrol 40-60 afforded the title compound *rac*-**285** as a white solid (62 mg, 90 %).

Melting point: 168-170 ^{o}C (ethyl acetate/petrol 40-60);

^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 8.73 (s, 1H, H_1), 8.04 (d, J = 8.5 Hz, 1H, H_7), 7.99 (d, J = 7.8 Hz, 1H, H_9), 7.66 (dd, J = 8.2, 6.9 Hz, 1H, H_6), 7.59 (ddd, J = 8.0, 6.8, 1.3 Hz, 1H, H_{10}), 7.56-7.50 (m,

2H, H_5 and H_{11}), 7.47 (d, J = 8.5 Hz, 1H, H_{12}), 7.32 (t, J = 8.0 Hz, 1H, H_{19}), 7.06-7.03 (m, 1H, H_{20}), 7.01-6.99 (m, 1H, H_{15}), 6.97 (ddd, J = 8.3, 2.5, 0.6 Hz, 1H, H_{18}), 3.80 (s, 3H, H_{17});

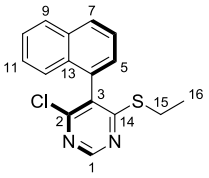
^{13}C NMR (126 MHz, $CDCl_3$) δ_C = 172.7 (Quat, C_2), 159.9 (Quat, C_{16}), 159.3 (Quat, C_{21}), 157.1 (CH, C_1), 133.8 (Quat, C_8), 130.5 (Quat, C_{Ar}), 130.4 (Quat, C_{Ar}), 130.1 (CH, C_7), 130.0 (CH, C_{19}), 129.1 (Quat, C_{14}), 128.9 (CH, C_9), 128.8 (Quat, C_{Ar}), 128.0 (CH, C_5), 127.5 (CH, C_{20}), 127.1 (CH, C_{11}), 126.6 (CH, C_{10}), 125.6 (CH, C_6), 124.1 (CH, C_{12}), 120.5 (CH, C_{15}), 115.7 (CH, C_{18}), 55.4 (CH_3, C_{17});

FTIR (neat) ν/cm^{-1} = 3061, 1591, 1536, 1501, 1396, 1345, 1248, 1231, 1040;

HRMS (ESI$^+$) calculated for $C_{21}H_{15}ClN_2NaOS$ = 401.0486, mass found = 401.0486;

Chiral HPLC (Chiralpak ADH, 20 % IPA, 80 % hexane, 1.0 mL/min, λ = 272 nm, 20 μL injection) τ_R (minor) = 9.3 min, τ_R (major) = 12.4 min.

4-Chloro-6-(ethylthio)-5-(naphthalen-1-yl)pyrimidine, 286[*]



According to **General Procedure F** with **201** (30 mg, 0.11 mmol), toluene (1.1 mL), tetrabutylammonium bromide (4 mg, 0.01 mmol), ethanethiol (10 μL, 0.13 mmol), 50 % w/w aqueous potassium hydroxide (61 μL, 1.1 mmol) at room temperature for 1 hour. Purification *via* column chromatography eluting with 1:9 ethyl acetate/petrol 40-60 afforded the title compound *rac*-**286** as white solid (26 mg, 80 %).

Melting point: 78-80 °C (ethyl acetate/petrol 40-60);

[*] This compound was prepared by Benjamin Rahemtulla

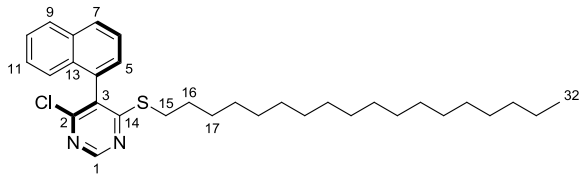
^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 8.77 (s, 1H, H_1), 8.00-7.85 (m, 2H, H_{Ar}), 7.55-7.20 (m, 5H, H_{Ar}), 3.05 (dq, J = 13.1, 7.4 Hz, 1H, H_{15A}), 2.99 (dq, J = 13.1, 7.4 Hz, 1H, H_{15B}), 1.19 (s, t = 7.4 Hz, 3H, H_{16});

^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 173.1 (Quat, C_{Ar}), 158.7 (Quat, C_{Ar}), 156.8 (CH, C_1), 133.8 (Quat, C_{Ar}), 130.7 (Quat, C_{Ar}), 130.5 (Quat, C_{Ar}), 129.9 (CH, C_{Ar}), 129.7 (Quat, C_{Ar}), 128.8 (CH, C_{Ar}), 127.8 (CH, C_{Ar}), 127.0 (CH, C_{Ar}), 126.5 (CH, C_{Ar}), 125.4 (CH, C_{Ar}), 124.1 (CH, C_{Ar}), 25.1 (CH_2, C_{15}), 13.9 (CH_3, C_{16});

FTIR (neat) ν/cm^{-1} = 3059, 2971, 2929, 1593, 1538, 1507, 1464, 1398, 1376, 1346, 1261, 1230, 1160, 1055, 1018;

HRMS (ESI$^+$) calculated for $C_{16}H_{13}ClN_2NaS$ = 323.0380, mass found = 323.0375.

4-Chloro-5-(naphthalen-1-yl)-6-(octadecylthio)pyrimidine, 287[*]



According to **General Procedure F** with **201** (30 mg, 0.11 mmol), toluene (1.1 mL), tetrabutylammonium bromide (4 mg, 0.01 mmol), octadecanethiol (10 µL, 0.13 mmol), 50 % w/w aqueous potassium hydroxide (61 µL, 1.1 mmol) at room temperature for 1 hour. Purification *via* column chromatography eluting with petrol 40-60 afforded *rac*-**287** as a white solid (27 mg, 58 %).

Melting point: 76-78 °C (petrol 40-60);

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 8.74 (s, 1H, H_1), 7.91 (d, J = 8.2 Hz, 1H, H_7), 7.86 (d, J = 8.1 Hz, 1H, H_9), 7.51 (dd, J = 8.2, 7.1 Hz, 1H, H_6), 7.46 (ddd, J = 8.1, 6.9, 1.0 Hz, 1H, H_{10}), 7.38 (ddd,

[*] This compound was prepared by Benjamin Rahemtulla

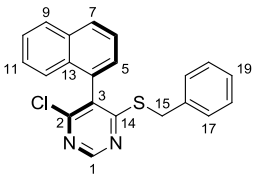
J = 8.3, 6.9, 1.1 Hz, 1H, H_{11}), 7.31 (dd, J = 7.1, 1.0 Hz, 1H, H_5), 7.28 (d, J = 8.4 Hz, 1H, H_{12}), 3.01 (m, 2H, C_{15}), 1.50 (dt, J = 14.7, 7.3 Hz, 2H, H_{16}), 1.18 (m, 28H, $H_{17\text{-}31}$), 0.80 (t, J = 6.8 Hz, 3H, H_{32});

^{13}C NMR (101 MHz, $CDCl_3$)* δ_C = 173.2 (Quat, C_{14}), 158.7 (Quat, C_2), 156.7 (CH, C_1), 133.8 (Quat, C_8), 130.7 (Quat, C_4), 130.5 (Quat, C_3), 129.8 (CH, C_7), 129.7 (Quat, C_{13}), 128.8 (CH, C_9), 127.8 (CH, C_5), 127.0 (CH, C_{11}), 126.5 (CH, C_{10}), 125.6 (CH, C_6), 124.2 (CH, C_{12}), 32.0 (CH_2, C_{Alk}), 30.7 (CH_2, C_{15}), 29.7 (CH_2, C_{Alk}), 29.7 (CH_2, C_{Alk}), 29.7 (CH_2, C_{Alk}), 29.6 (CH_2, C_{Alk}), 29.4 (CH_2, C_{Alk}), 29.4 (CH_2, C_{Alk}), 29.1 (CH_2, C_{Alk}), 28.8 (CH_2, C_{Alk}), 28.7 (CH_2, C_{Alk}), 22.7 (CH_2, C_{Alk}), 14.2 (CH_3, C_{32});

FTIR (neat) ν/cm^{-1} = 2923, 2853, 1537, 1502, 1465, 1397, 1376, 1346, 1230;

HRMS (ESI$^+$) calculated for $C_{32}H_{45}ClN_2NaS$ = 547.2884, mass found 547.2882.

4-Chloro-6-(benzylthio)-5-(naphthalen-1-yl)pyrimidine, 288†



According to **General Procedure F** with **201** (30 mg, 0.11 mmol), toluene (1.1 mL), tetrabutylammonium bromide (4 mg, 0.01 mmol), ethanethiol (10 µL, 0.13 mmol), 50 % w/w aqueous potassium hydroxide (61 µL, 1.1 mmol) at room temperature for 1 hour. Purification *via* column chromatography eluting with 1:19 ethyl acetate/petrol 40-60 afforded *rac*-**288** as a white solid (23 mg, 58 %).

Melting point: 134-136 °C (ethyl acetate/petrol 40-60);

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 8.78 (s, 1H, H_1), 7.88 (d, J = 8.3 Hz, 1H, H_{Ar}), 7.83 (d, J = 8.1 Hz, 1H, H_{Ar}), 7.50-7.41 (m, 2H, H_{Ar}), 7.37 (ddd, J = 8.3, 6.9, 1.3 Hz, 1H, H_{Ar}), 7.30 (dd, J = 7.0, 1.1 Hz,

* there were fewer peaks in the ^{13}C NMR spectrum than expected due to many coincident peaks in the region 29.7-29.2 ppm.
† This compound was prepared by Benjamin Rahemtulla.

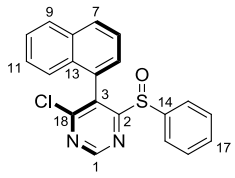
1H, H_{Ar}), 7.25 (d, J = 8.2 Hz, 1H, H_{Ar}), 7.21-7.09 (m, 5H, H_{Ar}), 4.35 (d, J = 13.4 Hz, 1H, H_{15A}), 4.21 (d, J = 13.4 Hz, 1H, H_{15B});

^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 172.4 (Quat, C_{14}), 158.9 (Quat, C_2), 156.7 (CH, C_1), 136.4 (Quat, C_{Ar}), 133.8 (Quat, C_{Ar}), 130.4 (Quat, C_{Ar}), 130.4 (Quat, C_{Ar}), 130.0 (CH, C_{Ar}), 129.5 (Quat, C_{Ar}), 129.2 (CH, C_{Ar}), 128.8 (CH, C_{Ar}), 128.5 (CH, C_{Ar}), 127.9 (CH, C_{Ar}), 127.4 (CH, C_{Ar}), 127.0 (CH, C_{Ar}), 126.5 (CH, C_{Ar}), 125.6 (CH, C_{Ar}), 124.2 (CH, C_{Ar}), 35.2 (CH_2, C_{15});

FTIR (neat) ν/cm^{-1} = 3060, 1593, 1537, 1501, 1454, 1397, 1375, 1346, 1259, 1228, 1195, 1158, 1100, 1071, 1030, 1017;

HRMS (ESI^+) calculated for $C_{21}H_{15}ClN_2NaS$ = 385.0537, mass found = 385.0540.

4-Chloro-5-(naphthalen-1-yl)-6-(phenylsulfinyl)pyrimidine, 290



To a solution of *rac*-**203** (50 mg, 0.14 mmol) in dichloromethane (1.4 mL) was added *meta*-chloroperoxybenzoic acid (≥77 %, 39 mg, 0.17 mmol) in one portion. The resulting mixture was stirred at -30 ^oC for 2 days and then warmed to 0 ^oC and stirred for 22 hours. A further portion of *meta*-chloroperoxybenzoic acid (≥77 %, 26 mg, 0.11 mmol) in one portion and the reaction mixture was warmed to room temperature and stirred for 2 hours and then dichloromethane and saturated aqueous sodium thiosulfate were added. The organic layer was separated and the aqueous layer was extracted twice with dichloromethane. The combined organic extracts were washed with saturated aqueous sodium carbonate, dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. Purification of the residue *via* column chromatography eluting with 45:65 ethyl acetate/petrol 40-60

afforded the title compound *rac*-**290** as a 1:1 mixture of diastereoisomers[*] as a colourless oil (59 mg, quant). An analytical sample of each diastereoisomer was obtained by column chromatography eluting with 2:3 ethyl acetate/petrol 40-60.

Data for **290a** (colourless oil)

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 9.22 (s, 1H, H_1), 7.99 (d, J = 8.3 Hz, 1H, H_7), 7.93 (d, J = 8.2 Hz, 1H, H_9), 7.54 (ddd, J = 8.0, 6.9, 1.1 Hz, 1H, H_{10}), 7.48 (ddd, J = 8.4, 7.1, 1.4 Hz, 1H, H_{11}), 7.42-7.36 (m, 2H, H_6 and H_{17}), 7.32-7.23 (m, 5H, H_{12}, H_{15} and H_{16}), 6.76 (dd, J = 8.9, 0.9 Hz, 1H, H_5);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 173.3 (Quat, C_{Ar}), 162.7 (Quat, C_{Ar}), 158.8 (CH, C_1), 142.1 (Quat, C_{Ar}), 133.6 (Quat, C_{Ar}), 132.4 (CH, C_{17}), 131.3 (Quat, C_{Ar}), 130.8 (CH, C_7), 130.6 (Quat, C_{Ar}), 129.5 (CH, C_5), 129.3 (CH, $C_{15/16}$), 128.9 (CH, C_9), 128.0 (CH, C_{11}), 127.2 (Quat, C_{Ar}), 127.1 (CH, C_{10}), 126.4 (CH, $C_{15/16}$), 124.9 (CH, C_6), 124.1 (CH, C_{12});

FTIR (neat) ν/cm^{-1} = 3059, 1593, 1539, 1403, 1386, 1348, 1147, 1084, 1058;

HRMS (ESI^+) calculated for $C_{20}H_{13}ON_2ClNaS$ = 387.0329, mass found = 387.0321.

Data for **290b** (colourless oil)

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 9.24 (s, 1H, H_1), 7.98 (d, J = 8.3 Hz, 1H, H_7), 7.81 (d, J = 8.3 Hz, 1H, H_9), 7.59 (dd, J = 8.3, 7.1 Hz, 1H, H_6), 7.46 (dd, J = 7.1, 1.2 Hz, 1H, H_5), 7.35 (ddd, J = 8.2, 7.0, 1.2 Hz, 1H, H_{10}), 7.04-6.97 (m, 2H, H_{11} and H_{17}), 6.82 (t, J = 8.0 Hz, 2H, H_{16}), 6.75 (dd, J = 8.3, 1.2 Hz, 2H, H_{15}), 6.42 (d, J = 8.6 Hz, 1H, H_{12});

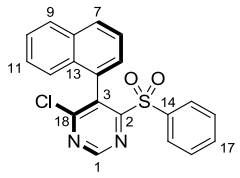
^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 173.6 (Quat, C_{Ar}), 162.3 (Quat, C_{Ar}), 158.7 (CH, C_1), 140.7 (Quat, C_{Ar}), 133.4 (Quat, C_{Ar}), 132.0 (CH, C_{17}), 131.6 (Quat, C_{Ar}), 131.0 (CH, C_7), 130.6 (Quat, C_{Ar}), 128.9 (CH, C_{16}), 128.6 (CH, C_9), 128.1 (CH, C_5), 127.5 (Quat, C_{Ar}), 127.1 (CH, C_{11}), 126.5 (CH, C_{10}), 126.2 (CH, C_{15}), 125.4 (CH, C_6), 123.7 (CH, C_{12});

[*] We were careful to isolate all of the mixed diastereoisomers before measuring the d.r.

FTIR (neat) ν/cm^{-1} = 3059, 2236, 1505, 1404, 1387, 1348, 1151, 1085, 1060;

HRMS (ESI^+) calculated for $C_{20}H_{13}ON_2ClNaS$ = 387.0329, mass found = 387.0320.

(*R*)-4-Chloro-5-(naphthalen-1-yl)-6-(phenylsulfonyl)pyrimidine, 291



Asymmetric: To a solution of **203** (50 mg, 0.14 mmol, 97:3 e.r.) in dichloromethane (1.4 mL) was added *meta*-chloroperoxybenzoic acid (≥77 %, 161 mg, 0.72 mmol) in one portion. The resulting mixture was stirred at room temperature for 16 hours and then dichloromethane and saturated aqueous sodium thiosulfate were added. The organic layer was separated and the aqueous layer was extracted twice with dichloromethane. The combined organic extracts were washed with saturated aqueous sodium carbonate, dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. Purification of the residue *via* column chromatography eluting with 1:4 ethyl acetate/petrol 40-60 afforded the title compound **291** as a white solid (54 mg, 99 %, 97:3 e.r.).

Racemic: To a solution of *rac*-**203** (20 mg, 0.057 mmol) in dichloromethane (0.6 mL) was added *meta*-chloroperoxybenzoic acid (≥77 %, 65 mg, 0.29 mmol) in one portion. The resulting mixture was stirred at room temperature for 16 hours and then dichloromethane and saturated aqueous sodium thiosulfate were added. The organic layer was separated and the aqueous layer was extracted twice with dichloromethane. The combined organic extracts were washed with saturated aqueous sodium carbonate, dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. An analytical HPLC sample of *rac*-**291** was obtained by small scale preparative TLC (1:3 ethyl acetate/petrol 40-60).

Melting point: 173-175 ^oC (ethyl acetate/petrol 40-60);

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 9.11 (s, 1H, H_1), 7.93 (d, J = 8.3 Hz, 1H, H_7), 7.81 (d, J = 8.3 Hz, 1H, H_9), 7.52 (dd, J = 8.3, 7.1 Hz, 1H, H_6), 7.41-7.36 (m, 3H, H_{10} and H_{15}), 7.34 (dd, J = 7.1, 1.0 Hz, 1H, H_5), 7.31-7.26 (m, 1H, H_{17}), 7.21 (ddd, J = 8.4, 7.0, 1.2 Hz, 1H, H_{11}), 7.21-7.08 (m, 2H, H_{16}), 6.80 (d, J = 8.5 Hz, 1H, H_{12});

^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 165.9 (Quat, C_{Ar}), 165.6 (Quat, C_{Ar}), 157.4 (CH, C_1), 137.0 (Quat, C_{Ar}), 134.0 (CH, C_{17}), 133.2 (Quat, C_{Ar}), 131.8 (Quat, C_{Ar}), 130.8 (Quat, C_{Ar}), 130.4 (CH, C_7), 129.1 (CH, C_{15}), 129.0 (CH, C_5), 128.7 (CH, C_{16} and C_9), 127.8 (Quat, C_{Ar}), 126.9 (CH, C_{11}), 126.3 (CH, C_{10}), 125.1 (CH, C_6), 124.1 (CH, C_{12});

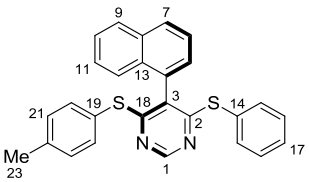
FTIR (neat) ν/cm^{-1} = 3061, 1507, 1392, 1349, 1329, 1158, 1143, 1081;

HRMS (ESI$^+$) calculated for $C_{20}H_{13}O_2N_2ClNaS$ = 403.0279, mass found = 403.0276;

Chiral HPLC (Chiralpak ADH, 20 % IPA, 80 % hexane, 1.0 mL/min, λ = 219 nm, 20 μL injection) τ_R (major) = 12.1 min, τ_R (minor) = 14.3 min;

$[\alpha]_D^{20}$ = –48 (*c* = 1.00, $CHCl_3$).

(*R*)-5-(Naphthalen-1-yl)-4-(phenylthio)-6-(p-tolylthio)pyrimidine, 292



Asymmetric: To a rapidly stirred suspension of **203** (50 mg, 0.14 mmol, 97:3 e.r.), *p*-thiocresol (23 mg, 0.19 mmol) and tetrabutylammonium bromide (5 mg, 0.014 mg) in toluene (1.4 mL) was added 50 % aqueous potassium hydroxide (0.08 mL, 1.4 mmol). The resulting biphasic mixture was stirred rapidly at room temperature for 16 hours and then saturated aqueous ammonium chloride and dichloromethane were added. The organic layer was separated and the aqueous layer was extracted twice with dichloromethane. The combined organic extracts

were dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. Purification of the residue *via* column chromatography eluting with 3:47 ethyl acetate/petrol 40-60 afforded the title compound **292** as a white solid (52 mg, 83 %, 97:3 e.r.).

Racemic: To a rapidly stirred suspension of *rac*-**203** (20 mg, 0.057 mmol), *p*-thiocresol (9 mg, 0.074 mmol) and tetrabutylammonium bromide (2 mg, 0.006 mmol) in toluene (0.6 mL) was added 50 % aqueous potassium hydroxide (0.03 mL, 0.57 mmol). The resulting biphasic mixture was stirred rapidly at room temperature for 16 hours and then saturated aqueous ammonium chloride and ethyl acetate were added. The organic layer was separated and an analytical HPLC sample of *rac*-**292** was obtained by small scale preparative TLC (1:3 ethyl acetate/petrol 40-60).

Melting point: 151-153 ^{o}C (ethyl acetate/petrol 40-60);

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 8.51 (s, 1H, H_1), 8.06 (d, J = 8.0 Hz, 1H, H_7), 8.00 (dd, J = 7.7, 1.5 Hz, 1H, H_9), 7.69 (dd, J = 7.9, 7.4 Hz, 1H, H_6), 7.65-7.56 (m, 4H, H_5, H_{10}, H_{11} and H_{12}), 7.69-7.44 (m, 2H, H_{15}), 7.41-7.37 (m, 3H, H_{16} and H_{17}), 7.35 (d, J = 8.1 Hz, 2H, H_{20}), 7.20 (d, J = 8.0 Hz, 2H, H_{21}), 2.37 (s, 3H, H_{23});

^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 168.7 (Quat, C_{Ar}), 168.1 (Quat, C_{Ar}), 156.9 (CH, C_1), 139.7 (Quat, C_{Ar}), 135.4 (CH, C_{15} and C_{20}), 134.0 (Quat, C_{Ar}), 130.7 (Quat, C_{Ar}), 130.7 (Quat, C_{Ar}), 130.1 (CH, C_7), 130.1 (CH, C_{21}), 129.4 (CH, C_{17}), 129.2 (CH, C_{16}), 128.9 (CH, C_9), 128.8 (CH, C_{Ar}), 128.6 (Quat, C_{Ar}), 127.1 (CH, C_{Ar}), 126.7 (Quat, C_{Ar}), 126.6 (CH, C_{Ar}), 126.0 (CH, C_6), 124.9 (Quat, C_{Ar}), 124.4 (CH, C_{Ar}), 21.5 (CH_3, C_{23});

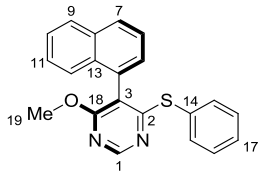
FTIR (neat) ν/cm^{-1} = 3057, 1506, 1396, 1341, 1235;

HRMS (ESI^{+}) calculated for $C_{27}H_{21}N_2S_2$ = 437.1141, mass found = 437.1133;

Chiral HPLC (Chiralpak ODH, 20 % IPA, 80 % hexane, 1.0 mL/min, λ = 292 nm, 10 μL injection) τ_R (minor) = 7.8 min, τ_R (major) = 10.3 min;

$[\alpha]_D^{20}$ = +2 (*c* = 1.00, $CHCl_3$).

(*S*)-4-Methoxy-5-(naphthalen-1-yl)-6-(phenylthio)pyrimidine, 293



Asymmetric: To a rapidly stirred suspension of **203** (50 mg, 0.14 mmol, 97:3 e.r.), methanol (29 μL, 0.72 mmol) and tetrabutylammonium hydrogen sulfate (5 mg, 0.014 mg) in toluene (1.4 mL) was added cesium hydroxide monohydrate (48 mg, 0.29 mmol). The resulting biphasic mixture was stirred rapidly at room temperature for 24 hours and then saturated aqueous ammonium chloride and dichloromethane were added. The organic layer was separated and the aqueous layer was extracted twice with dichloromethane. The combined organic extracts were dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. Purification of the residue *via* column chromatography eluting with 7.5:92.5 ethyl acetate/petrol 40-60 afforded the title compound **293** as a white solid (40 mg, 81 %, 97:3 e.r.).

Racemic: To a rapidly stirred suspension of *rac*-**203** (20 mg, 0.057 mmol), methanol (12 μL, 0.29 mmol) and tetrabutylammonium hydrogen sulfate (2 mg, 0.0057 mg) in toluene (0.6 mL) was added cesium hydroxide monohydrate (19 mg, 0.11 mmol). The resulting biphasic mixture was stirred rapidly at room temperature for 16 hours and then saturated aqueous ammonium chloride and ethyl acetate were added. The organic layer was separated and an analytical HPLC sample of *rac*-**293** was obtained by small scale preparative TLC (dichloromethane).

Melting point: 180-184 ^oC (ethyl acetate/petrol 40-60);

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 8.50 (s, 1H, H_1), 7.89-7.82 (m, 2H, H_7 and H_9), 7.54-7.33 (m, 7H, H_{Ar}), 7.30-7.24 (m, 3H, H_{16} and H_{17}), 3.75 (s, 3H, H_{19});

^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 169.2 (Quat, C_{Ar}), 166.5 (Quat, C_{Ar}), 156.9 (CH, C_1), 135.3 (CH, C_{15}), 133.8 (Quat, C_{Ar}), 131.3 (Quat, C_{Ar}), 130.0 (Quat, C_{Ar}), 129.4 (Quat, C_{Ar}), 129.3 (CH, C_{Ar}), 129.1 (CH, C_{Ar}), 129.0 (CH, C_{16}), 128.7 (CH, C_{Ar}), 128.4 (CH, C_{Ar}), 126.6 (CH, C_{Ar}), 126.2 (CH, C_{Ar}), 125.6 (CH, C_{Ar}), 124.8 (CH, C_{Ar}), 116.4 (Quat, C_{Ar}), 54.3 (CH_3, C_{19});

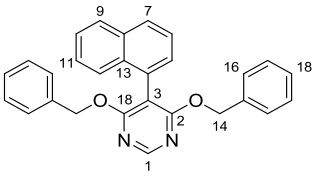
FTIR (neat) ν/cm^{-1} = 3057, 1551, 1530, 1468, 1398, 1358, 1314, 1036;

HRMS (ESI$^+$) calculated for $C_{21}H_{17}ON_2S$ = 345.1056, mass found = 345.1050;

Chiral HPLC (Chiralpak ADH, 4 % IPA, 96 % hexane, 1.0 mL/min, λ = 221 nm, 20 μL injection) τ_R (major) = 11.8 min, τ_R (minor) = 12.6 min;

$[\alpha]_D^{20}$ = –5 (*c* = 1.00, $CHCl_3$).

4,6-Bis(benzyloxy)-5-(naphthalen-1-yl)pyrimidine, 294



To a stirred solution of benzyl alcohol (31 mg, 0.29 mmol) in *N*,*N*-dimethylformamide (1.4 mL) was added sodium hydride (60 % w/w dispersion in mineral oil, 12 mg, 0.30 mmol) and the resulting suspension was stirred at room temperature for 5 minutes. After this time, *rac*-**203** (50 mg, 0.14 mmol) was added and the resulting mixture was stirred at room temperature for 4.5 hours. After this time, benzyl alcohol (45 μl, 0.43 mmol) and sodium hydride (60 % w/w dispersion in mineral oil, 17 mg, 0.43 mmol) were added. The resulting mixture was stirred for 30 minutes at room temperature and then ammonium chloride and dichloromethane were added. The organic layer was separated and the aqueous layer was extracted twice with

dichloromethane. The combined organic extracts were dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. Purification of the residue *via* column chromatography eluting with 6:94 ethyl acetate/petrol 40-60 afforded the title compound **294** as a white solid (55 mg, 92 %).

Melting point: 126-127 ^{o}C (ethyl acetate/petrol 40-60);

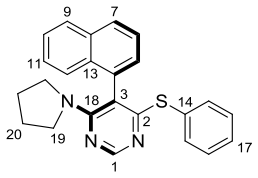
^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 8.45 (s, 1H, H_1), 7.83-7.78 (m, 2H, H_7 and H_9), 7.45 (dd, J = 7.8, 7.6 Hz, 1H, H_6), 7.42-7.32 (m, 3H, H_5, H_{10}, and H_{12}), 7.27 (ddd, J = 8.4, 6.8, 1.4 Hz, 1H, H_{11}), 7.13-7.09 (m, 6H, H_{17} and H_{18}), 7.06-7.01 (m, 4H, H_{16}), 5.31 (s, 4H, H_{14});

^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 167.9 (Quat, C_2), 156.2 (CH, C_1), 136.8 (Quat, C_{Ar}), 133.7 (Quat, C_{Ar}), 131.9 (Quat, C_{Ar}), 128.8 (Quat, C_{Ar}), 128.4 (CH, $C_{7/9}$), 128.4 (CH, $C_{7/9}$), 128.3 (CH, C_5), 128.2 (CH, C_{17}), 127.6 (CH, C_{18}), 127.3 (CH, C_{16}), 125.9 (CH, C_{11}), 125.7 (CH, $C_{10/12}$), 125.6 (CH, $C_{10/12}$), 125.4 (CH, C_6), 104.7 (Quat, C_3), 68.0 (CH_2, C_{14});

FTIR (neat) ν/cm^{-1} = 3034, 1560, 1454, 1424, 1354, 1300, 1098;

HRMS (ESI^{+}) calculated for $C_{28}H_{23}O_2N_2$ = 419.1754, mass found = 419.1746.

(*S*)-5-(Naphthalen-1-yl)-4-(phenylthio)-6-(pyrrolidin-1-yl)pyrimidine, 295



Asymmetric: A solution of **203** (50 mg, 0.14 mmol, 97:3 e.r.), pyrrolidine (59 μL, 0.72 mmol) and *N*,*N*-diisopropylethylamine (125 μL, 0.72 mmol) in *N*,*N*-dimethylformamide (1.0 mL) was stirred at room temperature for 3 hours and then saturated aqueous ammonium chloride and ethyl acetate were added. The organic layer was separated and the aqueous layer was extracted twice with ethyl acetate. The combined organic extracts were dried over anhydrous

magnesium sulfate, filtered and concentrated under reduced pressure. Purification of the residue *via* column chromatography eluting with 1:3 ethyl acetate/petrol 40-60 afforded the title compound **295** as a white solid (54 mg, 98 %, 97:3 e.r.).

Racemic: A solution of *rac*-**203** (20 mg, 0.058 mmol), pyrrolidine (24 μL, 0.29 mmol) and *N*,*N*-diisopropylethylamine (50 μL, 0.29 mmol) in *N*,*N*-dimethylformamide (0.4 mL) was stirred at room temperature for 3 hours and then saturated aqueous ammonium chloride and ethyl acetate were added. The organic layer was separated and an analytical HPLC sample of *rac*-**295** was obtained by small scale preparative TLC (1:3 ethyl acetate/petrol 40-60).

Melting point: 153-155 ^{o}C (ethyl acetate/petrol 40-60);

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 8.34 (s, 1H, H_1), 7.88-7.79 (m, 2H, H_{Ar}), 7.63-7.55 (m, 1H, H_{Ar}), 7.47-7.39 (m, 4H, H_{Ar}), 7.33-7.27 (m, 2H, H_{15}), 7.24-7.19 (m, 3H, H_{16} and H_{17}), 3.02 (br s, 2H, H_{19A}), 2.80 (br s, 2H, H_{19B}), 1.53-1.43 (m, 4H, H_{20});

^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 167.7 (Quat, C_2), 157.8 (Quat, C_{18}), 156.4 (CH, C_1), 135.1 (CH, C_{15}), 133.7 (Quat, C_{Ar}), 133.3 (Quat, C_{Ar}), 133.2 (Quat, C_{Ar}), 130.7 (Quat, C_{Ar}), 130.0 (CH, C_{Ar}), 129.1 (CH, C_{Ar}), 128.8 (CH, C_{Ar}), 128.7 (CH, C_{Ar}), 128.6 (CH, C_{Ar}), 126.9 (CH, C_{Ar}), 126.3 (CH, C_{Ar}), 125.7 (CH, C_{Ar}), 125.1 (CH, C_{Ar}), 112.1 (Quat, C_{Ar}), 48.6 (CH_2, C_{19}), 25.3 (CH_2, C_{20});

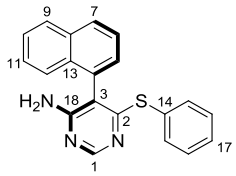
FTIR (neat) ν/cm^{-1} = 2971, 2873, 1540, 1515, 1474, 1455, 1380, 1340, 1060, 1015;

HRMS (ESI^{+}) calculated for $C_{24}H_{22}N_3S$ = 384.1529, mass found = 384.1518;

Chiral HPLC (Chiralpak ADH, 20 % IPA, 80 % hexane, 1.0 mL/min, λ = 226 nm, 20 μL injection) τ_R (major) = 17.0 min, τ_R (minor) = 25.4 min;

$[\alpha]_D^{20}$ = –67 (*c* = 1.00, $CHCl_3$).

(*S*)-5-(Naphthalen-1-yl)-6-(phenylthio)pyrimidin-4-amine, 297



Racemic Azide S_NAr/reduction: A solution of *rac*-**203** (300 mg, 0.86 mmol), and sodium azide (168 mg, 2.59 mmol) in DMSO (2 mL) was heated in a sealed vial to 70 ^oC for 3 hours and then cooled to room temperature and then ethyl acetate and water were added. The organic layer was separated and the aqueous layer was extracted twice with ethyl acetate. The combined organic extracts were washed successively with water (x 2) and brine, dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure until approximately 10 mL of solvent remained. At this point methanol (10 mL) and Pd/C (35 mg, 10 wt. %) were added and the resulting stirred suspension was sparged with hydrogen for 30 minutes and then stirred under an atmosphere of hydrogen (balloon pressure) for 16 hours. The reaction mixture was filtered through a plug of Celite®, washing with dichloromethane and the filtrate was concentrated under reduced pressure. Purification of the residue *via* column chromatography eluting with 1:1 ethyl acetate/petrol 40-60 afforded the title compound *rac*-**297** as a white solid (226 mg, 80 %).

Asymmetric azide S_NAr/reduction (70 ^oC): A solution of **203** (30 mg, 0.086 mmol, 97:3 e.r.), and sodium azide (16.8 mg, 0.26 mmol) in DMSO (0.2 mL) was heated in a sealed vial to 70 ^oC for 3 hours and then cooled to room temperature and then ethyl acetate and water were added. The organic layer was separated and the aqueous layer was extracted twice with ethyl acetate. The combined organic extracts were washed successively with water (x 2) and brine, dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure until approximately 1 mL of solvent remained. At this point methanol (1 mL) and Pd/C (4 mg, 10 wt. %) were added and the resulting stirred suspension was sparged with hydrogen for

30 minutes and then stirred under an atmosphere of hydrogen (balloon pressure) for 16 hours. The reaction mixture was filtered through a plug of Celite®, washing with dichloromethane and the filtrate was concentrated under reduced pressure. An analytical HPLC sample of **297** was obtained by preparative TLC (1:1 ethyl acetate/petrol 40-60, 57:43 e.r.).

Asymmetric azide S_NAr/reduction (room temperature): A solution of **203** (20 mg, 0.057 mmol, 97:3 e.r.), and sodium azide (19 mg, 0.29 mmol) in DMSO (0.1 mL) was stirred at room temperature for 20 hours and then ethyl acetate and water were added. The organic layer was separated and the aqueous layer was extracted twice with ethyl acetate. The combined organic extracts were washed successively with water (x 2) and brine, dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure until approximately 0.5 mL of solvent remained. At this point methanol (0.5 mL) and Pd/C (2 mg, 10 wt. %) were added and the resulting stirred suspension was sparged with hydrogen for 30 minutes and then stirred under an atmosphere of hydrogen (balloon pressure) for 16 hours. The reaction mixture was filtered through a plug of Celite®, washing with dichloromethane and the filtrate was concentrated under reduced pressure. Purification of the residue *via* column chromatography eluting with 1:1 ethyl acetate/petrol 40-60 afforded the title compound **297** as a white solid (3 mg, 6 %, 75:25 e.r.). A solution of this material (c.a. 0.5 mg mL^{-1} in IPA) was heated in a sealed vial to 100 ^oC for 14 hours. After this time an aliquot was analysed by chiral HPLC and determined to be 75:25 e.r.

Racemic ammonia S_NAr: A 15 mL ACE pressure tube containing a stirred solution of *rac*-**203** (20 mg, 0.057 mmol) in DMSO (0.5 mL) was cooled to -78 ^oC which caused the DMSO to solidify. 28 % Aqueous ammonia (0.1 mL) was added and the pressure tube was rapidly sealed and then allowed to warm to room temperature. The reaction mixture (now homogeneous) was heated to 100 ^oC and stirred for 20 hours and then cooled to room temperature and ethyl

acetate and water were added. The organic layer was separated and the aqueous layer was extracted twice with ethyl acetate. The combined organic extracts were dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. Purification of the residue *via* column chromatography eluting with 1:1 ethyl acetate/petrol 40-60 afforded the title compound *rac*-**297** as a white solid (16 mg, 82 %) along with recovered starting material *rac*-**203** (3.3 mg, 17 %).

Asymmetric ammonia S_NAr: A 30 mL ACE pressure tube containing a stirred solution of **203** (261 mg, 0.75 mmol, 97:3 e.r.) in DMSO (6.5 mL) was cooled to -78 ^oC which caused the DMSO to solidify. 28 % Aqueous ammonia (1.3 mL) was added and the pressure tube was rapidly sealed and then allowed to warm to room temperature. The reaction mixture (now homogeneous) was heated to 100 ^oC and stirred for 20 hours and then cooled to room temperature and ethyl acetate and water were added. The organic layer was separated and the aqueous layer was extracted twice with ethyl acetate. The combined organic extracts were dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. Purification of the residue *via* column chromatography eluting with 1:1 ethyl acetate/petrol 40-60 afforded the title compound **297** as a white solid (165 mg, 67 %, 94:6 e.r.) along with recovered starting material **203** (104 mg, 38 %, 97:3 e.r.). **297** was further purified by recrystallization from boiling toluene/ethyl acetate to afford **297** (118 mg, 95:5 e.r.).

Melting point: 188-190 ^oC (ethyl acetate/petrol 40-60);

^1H NMR (400 MHz, $CDCl_3$) δ_H = 8.28 (s, 1H, H_1), 7.90 (d, J = 8.3 Hz, 1H, H_{Ar}), 7.87 (d, J = 8.2 Hz, 1H, H_{Ar}), 7.57-7.40 (m, 5H, H_{Ar}), 7.37-7.31 (m, 2H, H_{15}), 7.26-7.19 (m, 3H, H_{16} and H_{17}), 4.70 (br s, 2H, NH_2);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 167.2 (Quat, C_{Ar}), 160.3 (Quat, C_{Ar}), 157.4 (CH, C_1), 135.2 (CH, C_{15}), 134.2 (Quat, C_{Ar}), 130.9 (Quat, C_{Ar}), 130.1 (Quat, C_{Ar}), 129.8 (CH, C_{Ar}), 129.6 (Quat, C_{Ar}),

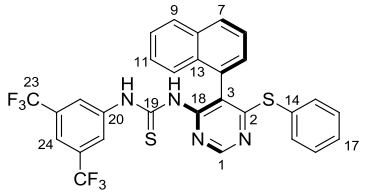
128.9 (CH, C_{16}), 128.9 (CH, C_{Ar}), 128.9 (CH, C_{Ar}), 128.9 (CH, C_{Ar}), 127.1 (CH, C_{Ar}), 126.7 (CH, C_{Ar}), 126.2 (CH, C_{Ar}), 124.6 (CH, C_{Ar}), 112.4 (Quat, C_3);

FTIR (neat) ν/cm^{-1} = 3466, 3293, 3154, 1626, 1545, 1465, 1379, 1339;

HRMS (ESI^+) calculated for $C_{20}H_{16}N_3S$ = 330.1059, mass found = 330.1050;

$[\alpha]_D^{20}$ = -9 (*c* = 0.50, $CHCl_3$).

(*S*)-1-(3,5-Bis(trifluoromethyl)phenyl)-3-(5-(naphthalen-1-yl)-6-(phenylthio)pyrimidin-4-yl)thiourea, 298



Asymmetric: This compound was prepared by analogy to a literature procedure.[133]

A solution of **297** (111 mg, 0.34 mmol, 95:5 e.r.) in *N*,*N*-dimethylformamide (2.05mL) was added dropwise to a stirred suspension of sodium hydride (60 % w/w dispersion in mineral oil, 15 mg, 0.34 mmol) in *N*,*N*-dimethylformamide (0.72 mL) at 0 ^oC. A solution of 3,5-bis(trifluoromethyl)phenyl isothiocyanate (68 μL, 0.37 mmol) in *N*,*N*-dimethylformamide (0.5 mL) was added dropwise and the resulting solution was warmed to room temperature and stirred for 40 minutes and then 1 M HCl and dichloromethane were added. The organic layer was separated and the aqueous layer was extracted twice with dichloromethane. The combined organic extracts were dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. Purification of the residue *via* column chromatography eluting with 7.5:92.5 ethyl acetate/petrol 40-60 followed by column chromatography eluting with 1:1 dichloromethane/petrol 40-60 afforded the title compound **298** as a white solid (94 mg, 46 %, 95:5 e.r.).

Racemic: A solution of *rac*-**297** (92 mg, 0.30 mmol) in *N*,*N*-dimethylformamide (1.7 mL) was added to a stirred suspension of sodium hydride (60 % w/w dispersion in mineral oil, 12 mg, 0.30 mmol) in *N*,*N*-dimethylformamide (0.6 mL) at 0 ^{o}C. A solution of 3,5-bis(trifluoromethyl)phenyl isothiocyanate (56 μL, 0.33 mmol) in *N*,*N*-dimethylformamide (0.4 mL) was added and the resulting solution was warmed to room temperature and stirred for 3 hours and then 1 M HCl and ethyl acetate were added. The organic layer was separated and the aqueous layer was extracted twice with ethyl acetate. The combined organic extracts were dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. Purification of the residue *via* column chromatography eluting with 7.5:92.5 ethyl acetate/petrol 40-60 followed by column chromatography eluting with 1:1 dichloromethane/petrol 40-60 afforded the title compound *rac*-**298** as a white solid (104 mg, 62 %).

Melting point: 97-100 ^{o}C (ethyl acetate/petrol 40-60);

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 13.7 (s, 1H, N*H*), 8.56 (s, 1H, H_1), 8.10 (s, 2H, H_{21}), 8.03 (d, J = 8.2 Hz, 1H, H_7), 7.95 (d, J = 8.2 Hz, 1H, H_9), 7.66-7.60 (m, 3H, H_6, H_{24} and N*H*), 7.58-7.48 (m, 3H, H_5, H_{10}, H_{11}), 7.43 (d, J = 8.3 Hz, 1H, H_{12}), 7.40-7.29 (m, 5H, H_{15}, H_{16} and H_{17});

^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 179.2 (Quat, C_{Ar}), 172.0 (Quat, C_{Ar}), 154.9 (CH, C_1), 154.1 (Quat, C_{Ar}), 139.8 (Quat, C_{Ar}), 135.5 (CH, C_{15}), 134.4 (Quat, C_{Ar}), 132.1 (q, J = 33.8 Hz, Quat, C_{22}), 131.5 (CH, C_7), 130.6 (Quat, C_{Ar}), 129.8 (CH, C_{17}), 129.3 (CH, C_{Ar}), 129.3 (CH, C_{16}), 129.2 (CH, C_{Ar}), 128.0 (CH, C_{Ar}), 127.8 (Quat, C_{Ar}), 127.3 (CH, C_{Ar}), 126.4 (Quat, C_{Ar}), 126.3 (CH, C_6), 124.6 (br, CH, C_{21}), 123.7 (CH, C_{12}), 123.0 (q, J = 272.1 Hz, Quat, C_{23}), 119.8 (br, CH, C_{24}), 115.2 (Quat, C_{Ar});

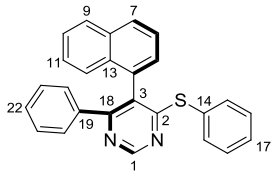
^{19}F NMR (376 MHz, $CDCl_3$) δ_F = -62.9;

FTIR (neat) ν/cm^{-1} = 3384, 2946, 1567, 1525, 1495, 1406, 1383, 1278, 1179, 1135;

HRMS (ESI^+) calculated for $C_{29}H_{19}N_4F_6S_2$ = 601.0950 , mass found = 601.0943;

$[\alpha]_D^{20}$ = -41 (*c* = 0.50, $CHCl_3$).

(*S*)-5-(Naphthalen-1-yl)-4-phenyl-6-(phenylthio)pyrimidine, 299



Asymmetric: An oven dried Schlenk tube was charged sequentially with **203** (50 mg, 0.14 mmol, 97:3 e.r.), phenylboronic acid (26 mg, 0.22 mmol), potassium carbonate (40 mg, 0.29 mmol) and tetrakis(triphenylphosphine)palladium(0) (17 mg, 0.014 mg). The atmosphere was purged with argon three times and anhydrous toluene (1.0 mL) was added. The resulting mixture was stirred under an atmosphere of nitrogen at 75 ^oC for 16 hours and then cooled to room temperature and diluted with dichloromethane and ammonium chloride. The organic layer was separated and the aqueous layer was extracted twice with dichloromethane. The combined organic extracts were dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. Purification of the residue *via* column chromatography eluting with 1:9 ethyl acetate/petrol 40-60 afforded the title compound **299** as a white solid (50 mg, 89 %, 97:3 e.r.).*

Racemic: An oven dried schlenk tube was charged sequentially with *rac*-**203** (50 mg, 0.14 mmol), phenylboronic acid (26 mg, 0.22 mmol), potassium carbonate (40 mg, 0.29 mmol) and tetrakis(triphenylphosphine)palladium(0) (17 mg, 0.014 mg). The atmosphere was purged with argon three times and anhydrous toluene (1.0 mL) was added. The resulting mixture was stirred under an atmosphere of nitrogen at 100 ^oC for 16 hours and then cooled to room temperature and diluted with dichloromethane and ammonium chloride. The organic layer was separated and the aqueous layer was extracted twice with dichloromethane. The combined organic extracts were dried over anhydrous magnesium sulfate, filtered and

* The other results described in Table 3.5 were obtained under analogous reaction conditions.

concentrated under reduced pressure. Purification of the residue *via* column chromatography eluting with 1:9 ethyl acetate/petrol 40-60 afforded the title compound *rac*-**299** as a white solid (55 mg, 98 %).

Melting point: 52-55 ^{o}C (ethyl acetate/petrol 40-60);

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 8.91 (s, 1H, H_1), 7.84-7.78 (m, 2H, H_7 and H_9), 7.49 (d, J = 8.1 Hz, 1H, H_{Ar}), 7.44-7.34 (m, 5H, H_6, H_{10}, H_{15} and H_{Ar}), 7.33-7.26 (m, 4H, H_{16}, H_{17} and H_{Ar}), 7.23-7.19 (m, 2H, H_{20}), 7.07-7.01 (m, 1H, H_{22}), 6.99-6.93 (m, 2H, H_{21});

^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 172.1 (Quat, C_2), 162.3 (Quat, C_{18}), 157.2 (CH, C_1), 137.4 (Quat, C_{Ar}), 135.5 (CH, C_{15}), 133.7 (Quat, C_{Ar}), 132.3 (Quat, C_{Ar}), 131.6 (Quat, C_{Ar}), 129.5 (CH, C_{Ar}), 129.4 (CH, C_{Ar}), 129.2 (CH, C_{16} and C_{22}), 129.0 (CH, C_{20}), 128.9 (Quat and CH, C_{Ar}), 128.8 (CH, C_{Ar}), 128.4 (Quat, C_{Ar}), 127.9 (CH, C_{21}), 127.0 (CH, C_{Ar}), 126.4 (CH, C_{Ar}), 125.7 (CH, C_{Ar}), 124.9 (CH, C_{Ar});

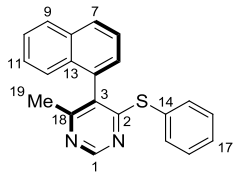
FTIR (neat) ν/cm^{-1} = 3058, 1526, 1417, 1345, 1213, 1079, 957;

HRMS (ESI^{+}) calculated for $C_{26}H_{19}N_2S$ = 391.1264, mass found = 391.1255;

Chiral HPLC (Chiralpak ADH, 10 % IPA, 90 % hexane, 1.0 mL/min, λ = 225 nm, 20 μL injection) τ_R (major) = 12.3 maj, τ_R (minor) = 13.1 min;

$[\alpha]_D^{20}$ = –76 (*c* = 1.00, $CHCl_3$).

(*S*)-4-Methyl-5-(naphthalen-1-yl)-6-(phenylthio)pyrimidine, 300



Asymmetric:[*] This compound was prepared by analogy to a literature procedure.[98]

A solution of **203** (14.4 mg, 0.041 mmol, 98:2 e.r.) in a mixture of THF (0.5 mL) and NMP (0.05 mL) was cooled to 0 °C and iron(III) acetylacetonate (1 mg, 0.002 mmol) and methylmagnesium chloride (3 M in THF, 30 μL, 0.09 mmol) were sequentially added. The resulting solution was warmed to room temperature and stirred for 30 minutes and then ammonium chloride and dichloromethane were added. The organic layer was separated and the aqueous layer was extracted twice with dichloromethane. The combined organic extracts were dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. Purification of the residue *via* column chromatography eluting with 1:9 ethyl acetate/petrol 40-60 afforded the title compound **300** as a white solid (10.3 mg, 76 %, 98:2 e.r.).

Melting point: 118-119 °C (ethyl acetate/petrol 40-60);

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 8.81 (s, 1H, H_1), 8.00 (d, J = 8.3 Hz, 1H, H_{Ar}), 7.97 (d, J = 8.3 Hz, 1H, H_{Ar}), 7.63 (dd, J = 8.3, 7.2 Hz, 1H, H_{Ar}), 7.57 (ddd, J = 8.1, 6.9, 1.3 Hz, 1H, H_{Ar}), 7.50 (ddd, J = 8.3, 6.9, 1.4 Hz, 1H, H_{Ar}), 7.48-7.41 (m, 4H, H_{Ar}), 7.41-7.36 (m, 3H, H_{Ar}), 2.14 (s, 3H, H_{19});

^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 169.9 (Quat, C_{Ar}), 163.8 (Quat, C_{Ar}), 157.1 (CH, C_1), 135.4 (CH, $C_{15/16}$), 133.9 (Quat, C_{Ar}), 132.1 (Quat, C_{Ar}), 130.9 (Quat, C_{Ar}), 129.5 (Quat, C_{Ar}), 129.4 (CH, C_{Ar}), 129.3 (CH, C_{Ar}), 129.1 (CH, $C_{15/16}$), 128.8 (CH, C_{Ar}), 128.8 (Quat, C_{Ar}), 127.8 (CH, C_{Ar}), 127.0 (CH, C_{Ar}), 126.5 (CH, C_{Ar}), 125.8 (CH, C_{Ar}), 124.3 (CH, C_{Ar}), 22.3 (CH_3, C_{19});

[*] The racemate for this compound was prepared in our work on kinetic resolution (see Chapter 5).

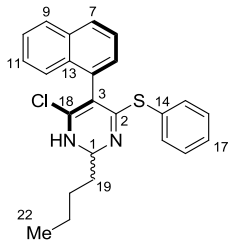
FTIR (neat) ν/cm^{-1} = 3057, 1535, 1476, 1425, 1345, 1206;

HRMS (ESI^+) calculated for $C_{21}H_{17}N_2S$ = 329.1107, mass found = 329.1099;

Chiral HPLC (Chiralpak IC, 2 % IPA, 98 % hexane, 1.0 mL/min, λ = 230 nm, 20 μL injection) τ_R (minor) = 13.1 min, τ_R (major) = 14.2 min;

$[\alpha]_D^{20}$ = +32 (*c* = 0.74, $CHCl_3$).

_n_-Butyl-6-chloro-5-(naphthalen-1-yl)-4-(phenylthio)-1,2-dihydropyrimidine, 301

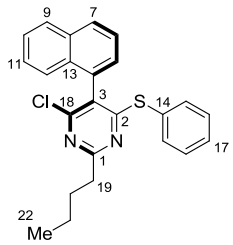


A stirred solution of *rac*-**203** (50 mg, 0.14 mmol) in THF (2.0 mL) was cooled to -78 ^oC and *n*-butyllithium (1.6 M in hexanes, 0.09 mL, 0.14 mmol) was added. The resulting solution was stirred at -78 ^oC for 10 minutes and then saturated aqueous ammonium chloride and dichloromethane were added. The organic layer was separated and the aqueous layer was extracted twice with dichloromethane. The combined organic extracts were dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. Purification of the residue *via* column chromatography eluting with 1:19 ethyl acetate/petrol 40-60 afforded two products which could be almost fully separated. However, we found that after standing at room temperature for around 10 minutes, each of the previously pure fractions contained a mixture of both components. The ^1H NMR spectra from the separated fractions were identical, each consisting of a 1:1 mixture of products which we tentatively assign as two diastereoisomers of **301**. This material was unstable, and the ^1H NMR was contaminated by **302** which is fully characterised further below. Key data for **301** and **301'** are given here.

^{1}H NMR (200 MHz, $CDCl_3$)* δ_H = **301**: 5.31 (t, J = 6.7 Hz, H_1), **301'**: 5.11 (t, J = 6.4 Hz, 1H, H_1);

LRMS (ESI^+) 199.1 ($[M+H]^+$).

(*R*)-2-Butyl-4-chloro-5-(naphthalen-1-yl)-6-(phenylthio)pyrimidine, 302



Asymmetric: A stirred solution of **203** (50 mg, 0.14 mmol, 97:3 e.r.) in THF (2.0 mL) was cooled to -78 °C and *n*-butyllithium (1.6 M in hexanes, 0.10 mL, 0.16 mmol) was added. The resulting solution was stirred at -78 °C for 10 minutes. After this time, water (0.5 mL) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (36 mg, 0.16 mmol) were sequentially added and the mixture was allowed to warm to room temperature and stirred for 5 minutes. 1 M Aqueous sodium hydroxide and dichloromethane were added. The organic layer was separated and the aqueous layer was extracted twice with dichloromethane. The combined organic extracts were dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. Purification of the residue *via* column chromatography eluting with 1:19 ethyl acetate/petrol 40-60 afforded the title compound **302** as a white solid (49 mg, 84 %, 97:3 e.r.).

Racemic: A stirred solution of *rac*-**203** (20 mg, 0.057 mmol) in THF (0.8 mL) was cooled to -78 °C and *n*-butyllithium (1.6 M in hexanes, 0.04 mL, 0.063 mmol) was added. The resulting solution was stirred at -78 °C for 10 minutes. After this time, water (0.2 mL) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (14 mg, 0.063 mmol) were sequentially added and the mixture was allowed to warm to room temperature and stirred for 5 minutes. 1 M Aqueous sodium hydroxide and dichloromethane were added. The organic layer was separated and an

* The remainder of the signals overlapped with those from **302** which was also present. The assignment of these signals to **301** *vs* **301'** is arbitrary.

analytical HPLC sample of *rac*-**302** was obtained by small scale preparative TLC (1:9 ethyl acetate/petrol 40-60).

Melting point: 116-117 ^{o}C (ethyl acetate/petrol 40-60);

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.93 (d, J = 8.1 Hz, 1H, H_7), 7.88 (d, J = 7.8 Hz, 1H, H_9), 7.54 (dd, J = 8.2, 6.7 Hz, 1H, H_6), 7.48 (ddd, J = 8.0, 6.4, 1.7 Hz, 1H, H_{10}), 7.45-7.24 (m, 8H, H_5, H_{11}, H_{12}, H_{15}, H_{16} and H_{17}), 2.73 (t, J = 7.6 Hz, 2H, H_{19}), 1.59-1.49 (m, 2H, H_{20}), 1.21 (sext, J = 7.4 Hz, 2H, H_{21}), 0.79 (t, J = 7.3 Hz, 3H, H_{22});

^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 171.9 (Quat, C_{Ar}), 170.2 (Quat, C_{Ar}), 158.9 (Quat, C_{18}), 135.5 (CH, C_{15}), 133.8 (Quat, C_{Ar}), 130.9 (Quat, C_{Ar}), 130.8 (Quat, C_{Ar}), 129.9 (CH, C_7), 129.2 (CH, C_{17}), 128.9 (CH, C_{16}), 128.8 (CH, C_9), 128.6 (Quat, C_{Ar}), 128.3 (CH, C_5), 127.0 (CH, C_{11}), 126.5 (CH, C_{10}), 125.7 (Quat, C_{Ar}), 125.6 (CH, C_6), 124.4 (CH, C_{12}), 38.3 (CH_2, C_{19}), 29.5 (CH_2, C_{20}), 22.2 (CH_2, C_{21}), 14.0 (CH_3, C_{22});

FTIR (neat) ν/cm^{-1} = 2957, 1545, 1489, 1414, 1386, 1303;

HRMS (ESI$^+$) calculated for $C_{24}H_{22}N_2ClS$ = 405.1187, mass found = 405.1179;

Chiral HPLC (Chiralpak ADH, 5 % IPA, 95 % hexane, 1.0 mL/min, λ = 223 nm, 20 μL injection) τ_R (minor) = 5.2 min, τ_R (major) = 6.4 min;

$[\alpha]_D^{20}$ = +8 (*c* = 1.00, $CHCl_3$).

Table 4.1 – Varied loadings of thiophenol

Entry 1: According to **General Procedure E** with **201** (50 mg, 0.18 mmol), carbon tetrachloride (1.8 mL), *N*-benzylquininium chloride (8 mg, 0.018 mmol), thiophenol (18.5 μL, 0.18 mmol), 50 % w/w aqueous potassium carbonate (0.12 mL, 0.90 mmol). Reaction conditions: room temperature for 48 h. Purification *via* column chromatography eluting with 1:19 ethyl

acetate/petrol 40-60 afforded recovered starting material **201** (3.4 mg, 7%) along with **203** as a white solid (58 mg, 98 % brsm., 95:5 e.r.). The spectral data for **201** and **203** matched that described previously.

Entry 2: See result from Chapter 3.

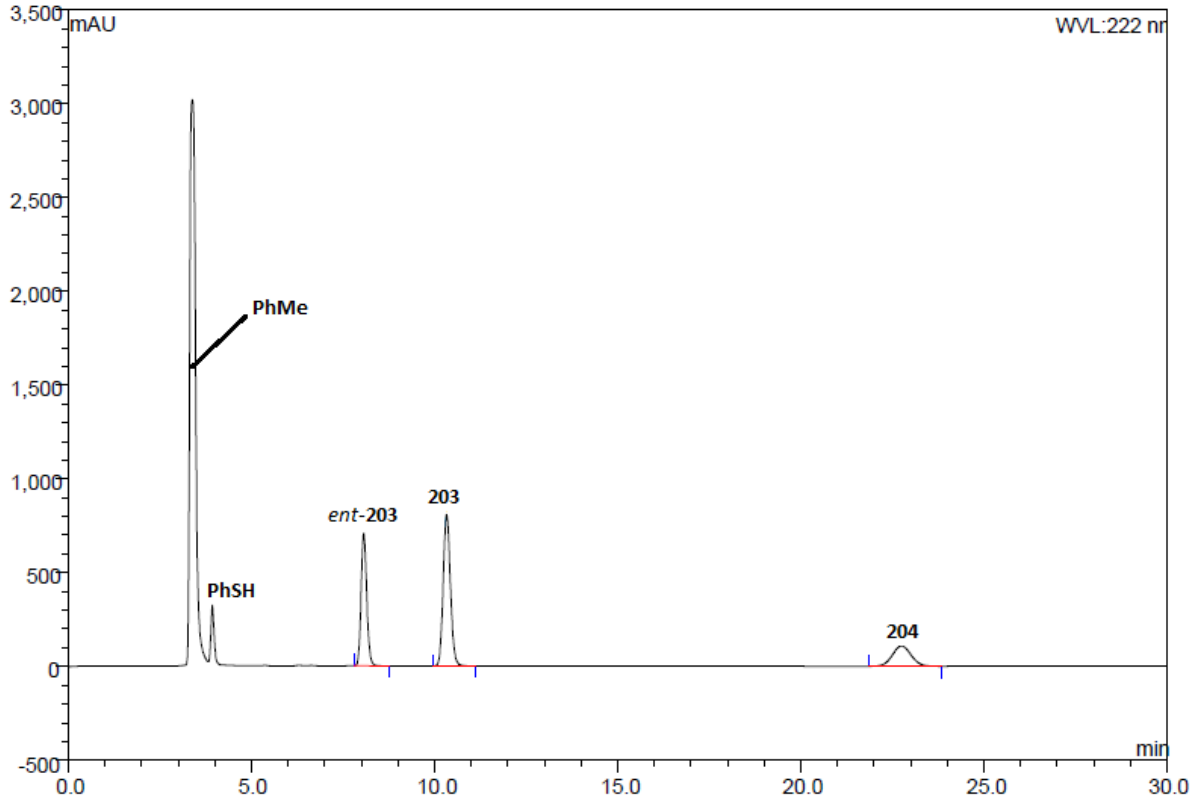
Entry 3**:** According to **General Procedure E** with **201** (50 mg, 0.18 mmol), carbon tetrachloride (1.8 mL), *N*-benzylquininium chloride (8 mg, 0.018 mmol), thiophenol (24.0 μL, 0.23 mmol), 50 % w/w aqueous potassium carbonate (0.12 mL, 0.90 mmol). Reaction conditions: room temperature for 48 h. Purification *via* column chromatography eluting with 1:19 ethyl acetate/petrol 40-60 afforded **203** as a white solid (57 mg, 90 %, 98:2 e.r.) along with by-product **204** as a white solid (5.8 mg, 8%).

Entry 4: According to **General Procedure E** with **201** (50 mg, 0.18 mmol), carbon tetrachloride (1.8 mL), *N*-benzylquininium chloride (8 mg, 0.018 mmol), thiophenol (27.7 μL, 0.27 mmol), 50 % w/w aqueous potassium carbonate (0.12 mL, 0.90 mmol). Reaction conditions: room temperature for 48 h. Purification *via* column chromatography eluting with 1:19 ethyl acetate/petrol 40-60 afforded **203** as a white solid (59 mg, 93 %, 98:2 e.r.) along with by-product **204** as a white solid (5.1 mg, 7 %).

Scheme 4.2 - Kinetic Resolution of *rac*-203

In a 7 mL screw capped vial, *rac*-**203** (50 mg, 0.14 mmol) was dissolved in carbon tetrachloride (1.4 mL) and *N*-benzylquninium chloride (6 mg, 0.014 mmol), thiophenol (16.3 μL, 0.16 mmol) and 50 % aqueous potassium carbonate (0.10 mL, 0.72 mmol) were added sequentially. The atmosphere was purged with nitrogen, and the biphasic reaction mixture was rapidly stirred at room temperature for 6 days. After this time, an aliquot of 21 μL was removed from the stirring reaction mixture and diluted into a mixture of toluene (0.5 mL) and isopropanol (1.0 mL). The resulting suspension was filtered through a small plug of magnesium sulfate and

the filtrate was analysed by chiral HPLC (Chiralpak ADH, 20 % IPA, 80 % hexane, 1.0 mL/min, λ = 222 nm, 20 μL injection). The peaks corresponding to the minor and major enantiomers of **203** (τ_R = 8.1 min and τ_R = 10.3 min respectively) were clearly resolved from each other and from the peak corresponding to **204** (τ_R = 22.8 min). The enantioenrichment of **203** was determined to be 60:40 e.r. (19 % e.e.) by simple integration. The conversion was determined to be 17 % (see calibration curve in the following section). Based on 19 % e.e. at 17 % conversion, a selectivity factor of 32 was calculated. The crude HPLC trace is shown below.



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	8.07	n.a.	708.361	126.315	33.59	n.a.	BMB*
2	10.33	n.a.	807.103	185.921	49.45	n.a.	BMB
3	22.75	n.a.	108.277	63.778	16.96	n.a.	BMB
Total:			1623.741	376.013	100.00	0.000	

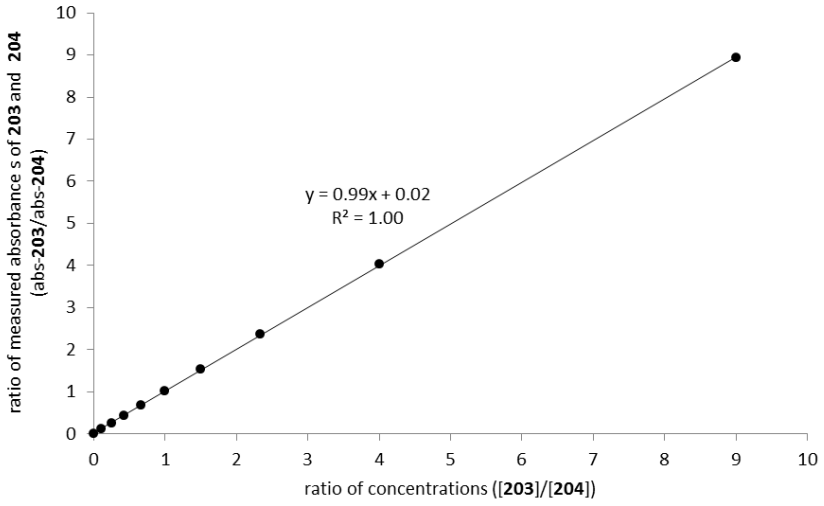
Kinetic Analysis

HPLC Calibration of 203 *vs* 204: A calibration curve was constructed by analysing 11 samples of mixtures of *rac*-**203** and **204** of known molar ratio dissolved in 1:2 toluene/isopropanol by chiral HPLC (Chiralpak ADH, 20 % IPA, 80 % hexane, 1.0 mL/min, λ = 222 nm, 20 μL injection). A plot of [**203**]/[**204**] *vs* abs-**203**/abs-**204** measured by HPLC afforded a straight line of gradient = 1.0 implying that the conversion could be measured directly by integration from the HPLC spectrum.

HPLC data used to construct calibration plot:

mol fraction			Mesaured HPLC absorbance			
203 (%)	**204** (%)	[**203**]/[**204**]	**203** (%)	*ent*-**203** (%)	**204** (%)	abs-**203**/abs-**204**
100	0	-	49.92	50.08	0.00	-
90	10	9.00	44.96	44.98	10.06	8.94
80	20	4.00	40.06	40.09	19.85	4.04
70	30	2.33	35.21	35.12	29.67	2.37
60	40	1.50	30.20	30.25	39.55	1.53
50	50	1.00	25.15	25.23	49.62	1.02
40	60	0.67	20.17	20.18	59.65	0.68
30	70	0.43	15.14	15.18	69.68	0.44
20	80	0.25	10.21	10.23	79.56	0.26
10	90	0.11	5.17	5.19	89.64	0.12
0	100	0.00	0.00	0.00	100.00	0.00

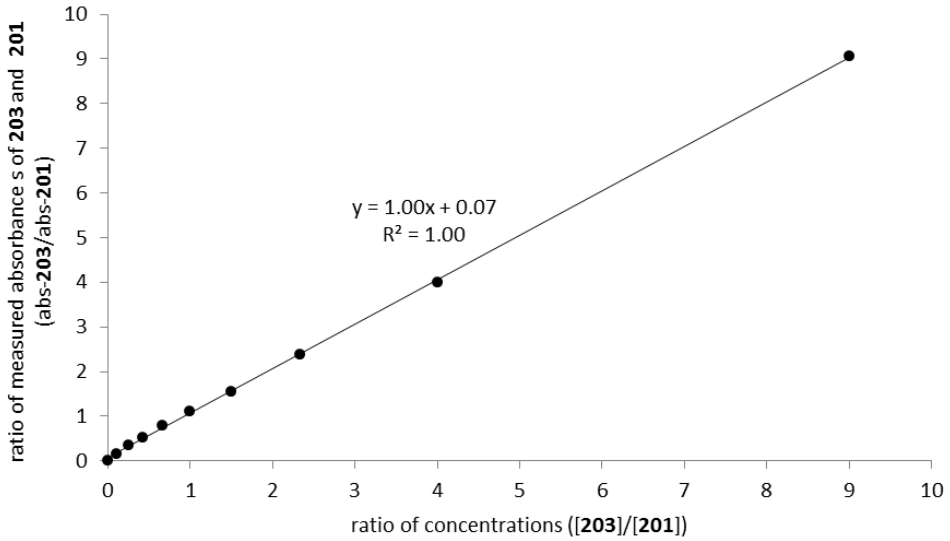
Calibration plot to analyse conversion by HPLC:



HPLC Calibration of 201 *vs* 203: A calibration curve was constructed by analysing 11 samples of mixtures of **201** and *rac*-**203** of known molar ratio dissolved in 1:2 toluene/isopropanol by chiral HPLC (Chiralpak ADH, 20 % IPA, 80 % hexane, 1.0 mL/min, λ = 222 nm, 20 μL injection). A plot of [**203**]/[**201**] *vs* abs-**203**/abs-**201** measured by HPLC afforded a straight line of gradient = 1.0 implying that the conversion could be measured directly by integration from the HPLC spectrum.

mol fraction			Mesaured HPLC absorbance			
201 (%)	**203** (%)	[**203**]/[**201**]	**201** (%)	**203** (%)	*ent*-**203** (%)	abs-**203**/abs-**201**
100	0	0.00	100.00	0.00	0.00	0.00
90	10	0.11	86.22	6.87	6.91	0.16
80	20	0.25	74.26	12.85	12.89	0.35
70	30	0.43	65.30	17.32	17.38	0.53
60	40	0.67	55.83	22.05	22.12	0.79
50	50	1.00	47.31	26.30	26.39	1.11
40	60	1.50	39.09	30.40	30.51	1.56
30	70	2.33	29.55	35.13	35.32	2.38
20	80	4.00	20.03	39.85	40.13	3.99
10	90	9.00	9.94	44.85	45.21	9.06
0	100	-	0.00	50.00	50.00	-

Calibration plot to analyse conversion by HPLC:



Scheme 4.3 – Monitoring the reaction mixture over 48 h

According to **General Procedure G** with **201** (50 mg, 0.18 mmol), carbon tetrachloride (1.8 mL), *N*-benzylquininium chloride (8 mg, 0.018 mmol), thiophenol (20.3 μL, 0.20 mmol), 50 % w/w aqueous potassium carbonate (0.12 mL, 0.90 mmol) afforded the following data:

t / min	**201** / %	*ent*-**203** / %	**203** / %	**204** / %	total **203** / %	e.r. **203** / % maj ent
1	98.89	0.52	0.59	0.00	1.11	53.15
5	97.57	0.89	1.52	0.05	2.41	63.02
10	96.68	0.97	2.31	0.06	3.28	70.36
15	94.90	1.30	3.75	0.07	5.05	74.31
20	93.33	1.54	5.06	0.06	6.61	76.64
25	91.55	1.67	6.70	0.08	8.37	80.01
30	90.13	1.77	8.01	0.10	9.78	81.94
35	88.89	1.83	9.17	0.10	11.00	83.34
40	86.58	2.16	11.16	0.10	13.32	83.78
45	85.87	2.01	12.02	0.11	14.02	85.69
50	84.12	2.11	13.64	0.12	15.75	86.58
55	82.56	2.22	15.10	0.12	17.32	87.20
60	82.12	2.32	15.45	0.11	17.77	86.94
65	80.39	2.44	17.05	0.13	19.49	87.48
70	78.49	2.58	18.78	0.14	21.36	87.94
75	78.52	2.44	18.91	0.14	21.35	88.57
80	76.79	2.58	20.49	0.14	23.07	88.82
85	75.43	2.48	21.95	0.15	24.43	89.85
90	75.78	2.25	21.83	0.14	24.08	90.66
100	72.58	2.41	24.87	0.15	27.28	91.16
110	69.32	2.94	27.59	0.17	30.53	90.38
120	68.23	2.64	28.98	0.17	31.61	91.66
150	62.24	2.79	34.82	0.16	37.61	92.58
187	57.32	2.93	39.59	0.17	42.52	93.11
248	47.89	3.31	48.61	0.19	51.92	93.62
330	38.00	3.83	57.95	0.22	61.78	93.80
465	23.99	4.38	71.38	0.28	75.76	94.22
690	12.16	5.13	82.29	0.42	87.42	94.13
1245	2.04	5.63	91.47	0.85	97.10	94.20
1643	0.00	4.89	93.70	1.41	98.59	95.04
1890	0.00	4.82	93.08	2.10	97.90	95.08
2730	0.00	3.34	92.71	3.95	96.05	96.52

Figure 4.2: 1st, 2nd and 3rd order plots

The data given above for Scheme 4.3 was used to carry out this analysis. Based on a starting concentration of **201** of 0.1 M, the concentration of **201** (in M) was calculated (see Appendix G for details).

Figure 4.3 – Initial rate plot for standard reaction

According to **General Procedure G** with **201** (50 mg, 0.18 mmol), carbon tetrachloride (1.8 mL), *N*-benzylquininium chloride (8 mg, 0.018 mmol), thiophenol (20.3 μL, 0.20 mmol), 50 % w/w aqueous potassium carbonate (0.12 mL, 0.90 mmol). The reaction was sampled every 5 minutes over the course of 1 hour and this data was fitted to a linear regression line in order to obtain an initial rate.

The reaction was carried out in triplicate (see Appendix H for data). The three initial rates measured using this method were 3.25×10^{-4}, 3.00×10^{-4} and 2.90×10^{-4} M s^{-1}. From this, we calculated the average initial rate to be 3.0×10^{-4} M s^{-1}, with a standard deviation of 0.2×10^{-4} M s^{-1}.

Figure 4.4 – Determination of kinetic order with respect to substrate

According to **General Procedure G** with **201** (5-100 mg, 0.018-0.36 mmol), carbon tetrachloride (1.8 mL), *N*-benzylquininium chloride (8 mg, 0.018 mmol), thiophenol (20.3 μL, 0.20 mmol), 50 % w/w aqueous potassium carbonate (0.12 mL, 0.90 mmol). The reaction was sampled every 5 minutes over the course of 1 hour and this data was fitted to a linear regression line in order to obtain an initial rate. For each concentration two or three independent runs were carried out. The data obtained were as follows:

		Run 1		Run 2		Run 3		Avg $\log_{10}\nu_0$	st dev
[SM]/ M	$\log_{10}$[SM]	ν_0 / M min^{-1}	$\log_{10}\nu_0$	ν_0 / M min^{-1}	$\log_{10}\nu_0$	ν_0 / M min^{-1}	$\log_{10}\nu_0$		
0.01	-2.00	3.52E-05	-4.45	4.54E-05	-4.34			-4.40	0.078
0.03	-1.52	8.91E-05	-4.05	1.04E-04	-3.98			-4.02	0.048
0.05	-1.30	1.42E-04	-3.85	1.75E-04	-3.76			-3.80	0.063
0.10	-1.00	3.25E-04	-3.49	2.91E-04	-3.54	2.90E-04	-3.54	-3.52	0.028
0.15	-0.82	5.10E-04	-3.29	5.59E-04	-3.25			-3.27	0.028
0.20	-0.70	6.90E-04	-3.16	8.19E-04	-3.09			-3.12	0.053

Figure 4.5 – Determination of kinetic behaviour with respect to thiol

According to **General Procedure G** with **201** (50 mg, 0.18 mmol), carbon tetrachloride (1.8 mL), *N*-benzylquininium chloride (8 mg, 0.018 mmol), thiophenol (1.1-82 μL, 0.01-0.80 mmol), 50 % w/w aqueous potassium carbonate (0.12 mL, 0.90 mmol). The reaction was sampled every 5 minutes over the course of 1 hour and this data was fitted to a linear regression line in order to obtain an initial rate. For each concentration two or three independent runs were carried out. The data obtained were as follows:

		Run 1		Run 2		Run 3		Avg ν_0	st dev
[PhSH]/ M	$\log_{10}$[PhSH]	ν_0 / M min^{-1}	$\log_{10}\nu_0$	ν_0 / M min^{-1}	$\log_{10}\nu_0$	ν_0 / M min^{-1}	$\log_{10}\nu_0$		
0.0055	-2.26	2.35E-05	-4.63	3.86E-05	-4.41			3.10E-05	1.1E-05
0.011	-1.96	9.39E-05	-4.03	7.95E-05	-4.10			8.67E-05	1.0E-05
0.022	-1.66	1.53E-04	-3.82	1.39E-04	-3.86			1.46E-04	9.8E-06
0.055	-1.26	2.70E-04	-3.57	2.97E-04	-3.53			2.84E-04	1.8E-05
0.11	-0.96	3.25E-04	-3.49	2.91E-04	-3.54	2.90E-04	-3.54	3.02E-04	2.0E-05
0.22	-0.66	2.68E-04	-3.57	3.53E-04	-3.45			3.11E-04	6.0E-05
0.33	-0.48	3.52E-04	-3.45	3.52E-04	-3.45			3.52E-04	3.6E-08
0.44	-0.36	3.59E-04	-3.45	3.40E-04	-3.47			3.50E-04	1.3E-05

Figure 4.6 – Determination of kinetic order with respect to catalyst

According to **General Procedure G** with **201** (50 mg, 0.18 mmol), carbon tetrachloride (1.8 mL), *N*-benzylquininium chloride (4-41 mg, 0.09-0.9 mmol), thiophenol (20.3 μL, 0.20 mmol), 50 % w/w aqueous potassium carbonate (0.12 mL, 0.90 mmol). The reaction was

sampled every 5 minutes over the course of 1 hour and this data was fitted to a linear regression line in order to obtain an initial rate. For each concentration two or three independent runs were carried out. The data obtained were as follows:

		Run 1		Run 2		Run 3		Avg $\log_{10}v_0$	st dev
[catalyst]/ M	$\log_{10}$[catalyst]	v_0 / M min^{-1}	$\log_{10}v_0$	v_0 / M min^{-1}	$\log_{10}v_0$	v_0 / M min^{-1}	$\log_{10}v_0$		
0.005	-2.30	2.19E-04	-3.66	2.18E-04	-3.66			-3.661	0.001
0.010	-2.00	3.25E-04	-3.49	2.91E-04	-3.54	2.90E-04	-3.54	-3.520	0.028
0.015	-1.82	3.76E-04	-3.42	3.36E-04	-3.47			-3.449	0.035
0.020	-1.70	4.23E-04	-3.37	4.07E-04	-3.39			-3.382	0.012
0.025	-1.60	3.95E-04	-3.40	3.67E-04	-3.44			-3.420	0.022
0.030	-1.52	3.67E-04	-3.44	3.96E-04	-3.40			-3.419	0.024
0.050	-1.30	2.94E-04	-3.53	3.40E-04	-3.47			-3.500	0.044

Figure 4.7 – Variation of the concentration of K_2CO_3

According to **General Procedure G** with **201** (50 mg, 0.18 mmol), carbon tetrachloride (1.8 mL), *N*-benzylquininium chloride (8 mg, 0.018 mmol), thiophenol (20.3 μL, 0.20 mmol), 10-50 % w/w aqueous potassium carbonate (0.12 mL). The reaction was sampled every 5 minutes over the course of 1 hour and this data was fitted to a linear regression line in order to obtain an initial rate. The data obtained were as follows:

$[K_2CO_3]$ / % w/w	v_0 / M min^{-1}
50	3.64E-04
40	7.74E-05
30	1.99E-05
20	2.36E-05
10	2.65E-05

Figure 4.8 – Variation of the rate of stirring

According to **General Procedure G** with **201** (50 mg, 0.18 mmol), carbon tetrachloride (1.8 mL), *N*-benzylquininium chloride (8 mg, 0.018 mmol), thiophenol (20.3 μL, 0.20 mmol),

50 % w/w aqueous potassium carbonate (0.12 mL, 0.90 mmol). Four runs were carried out with stirring speeds between 250-1400 r.p.m. The reaction was sampled every 5 minutes over the course of 1 hour and this data was fitted to a linear regression line in order to obtain an initial rate. The data obtained were as follows:

approx. stirring speed / r.p.m.	ν_0 / M min^{-1}
1400	3.64E-04
1000	2.82E-04
500	1.35E-04
250	3.80E-05

Scheme 4.6 – Product addition experiments

No additive: See method and data given above for Scheme 4.3

With **263**: According to a modification of **General Procedure G**. In a 7 mL screw capped vial, **201** (50 mg, 0.18 mmol) and **263** (>99.5:0.5 e.r., 5.3 mg, 0.018 mmol) were dissolved in carbon tetrachloride (1.8 mL) and *N*-benzylquininium chloride (8 mg, 0.018 mmol), thiophenol (20.3 μL, 0.20 mmol) and 50 % w/w aqueous potassium carbonate (0.12 mL, 0.90 mmol) were added sequentially. The biphasic reaction mixture was rapidly stirred at room temperature and sampled every 5 minutes over the course of 90 minutes as described in the general procedure.

With KCl: According to a modification of **General Procedure G**. In a 7 mL screw capped vial, **201** (50 mg, 0.18 mmol) and potassium chloride (14 mg, 0.18 mmol) were suspended in carbon tetrachloride (1.8 mL) and *N*-benzylquininium chloride (8 mg, 0.018 mmol), thiophenol (20.3 μL, 0.20 mmol) and 50 % w/w aqueous potassium carbonate (0.12 mL, 0.90 mmol) were added sequentially. The biphasic reaction mixture was rapidly stirred at room temperature

and sampled every 5 minutes over the course of 90 minutes as described in the general procedure.

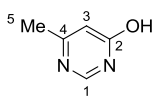
Scheme 4.6 and Figure 4.9 – Order of addition experiments

Control: See method and data given above for Scheme 4.3

Thiol Last: According to a modification of **General Procedure G**. In a 7 mL screw capped vial, **201** (50 mg, 0.18 mmol) was dissolved in carbon tetrachloride (1.8 mL) and *N*-benzylquininium chloride (8 mg, 0.018 mmol) and 50 % w/w aqueous potassium carbonate (0.12 mL, 0.90 mmol) were added sequentially. The biphasic mixture was rapidly stirred at room temperature for 5 hours and then thiophenol (20.3 μL, 0.20 mmol) was added. From this time, the reaction was sampled every 5 minutes over the course of 100 minutes as described in the general procedure.

Substrate Last: According to a modification of **General Procedure G**. To a 7 mL screw capped vial was sequentially added carbon tetrachloride (1.8 mL), *N*-benzylquininium chloride (8 mg, 0.018 mmol), 50 % w/w aqueous potassium carbonate (0.12 mL, 0.90 mmol) and thiophenol (20.3 μL, 0.20 mmol). The biphasic mixture was rapidly stirred at room temperature for 5 hours and then **201** (50 mg, 0.18 mmol) was added in a single portion. From this time, the reaction was sampled every 5 minutes over the course of 100 minutes as described in the general procedure.

6-Methylpyrimidin-4-ol, 308



This compound was prepared according to a modified literature procedure.[99a]

To a stirred room temperature suspension of sodium methoxide, prepared *in situ* by the portionwise addition of metallic sodium (2.13 g, 92.6 mmol) to anhydrous methanol (50 mL), was added formamidine acetate salt (7.72 g, 74.1 mmol) in a single portion. The resulting suspension was stirred at room temperature for 10 minutes and then methyl acetoacetate (5.00 mL, 46.3 mmol) was added dropwise. The reaction mixture was stirred at room temperature for 20 hours and then the solution was cooled to 0 ^{o}C and acidified to pH 7 by dropwise addition of glacial acetic acid. The resulting solution was warmed to room temperature and concentrated under reduced pressure. Purification of the residue *via* column chromatography eluting with 12:1 ethyl acetate/methanol afforded the title compound **308** as a yellow solid (2.02 g, 40 %). The spectral data matched that previously reported in the literature.[99a]

Melting point: 139-141 ^{o}C (ethyl acetate/methanol);

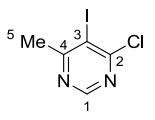
^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 13.25 (br s, 1H, O*H*), 8.06 (s, 1H, H_1), 6.26 (t, J = 0.8 Hz, 1H, H_3), 2.27 (d, J = 0.7 Hz, 3H, H_5);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 166.7 (Quat, $C_{2/4}$), 164.5 (Quat, $C_{2/4}$), 148.0 (CH, C_1), 113.3 (CH, C_3), 24.0 (CH_3, C_5);

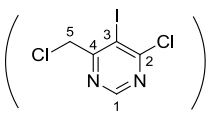
FTIR (neat) ν/cm^{-1} = 3200-2800 (br), 2970, 1646, 1605, 1546, 1414, 1332, 1166;

LRMS (ESI^{+}) 111 ([M + H]$^{+}$).

5-Iodo-6-methylpyrimidin-4-ol, 306



306



358

This compound was prepared according to a modified literature procedure.[99b]

Iodination: A solution of sodium hydroxide (832 mg, 20.8 mmol), **308** (1.94 g, 17.6 mmol) and iodine (4.83 g, 19.0 mmol) in water (28 mL) was heated to reflux for 3 hours and then cooled to room temperature. The precipitate was collected by vacuum filtration and the filter cake was washed twice with water and dried under high vacuum to afford crude iodoarene **309** as a beige solid (2.56 g). Chlorination: A suspension of crude **309** (2.44 g, *c.a.* 10.3 mmol), phosphorus(V) oxychloride (14.4 mL) and *N*,*N*-dimethylaniline (1.44 mL, 11.4 mmol) was stirred at 130 ^{o}C for 3 hours and then cooled to room temperature and carefully poured onto crushed ice and then allowed to warm to room temperature. Dichloromethane was added and the organic layer was separated and the aqueous layer was extracted twice with dichloromethane. The combined organic extracts were washed with 1 M HCl, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. Initial purification of the residue *via* column chromatography eluting with 1:19 ethyl acetate/petrol 40-60 afforded a mixture of **306** and **358**. These compounds were separated by column chromatography eluting with a gradient from toluene to 1:9 ethyl acetate/toluene to afford the title compound **306** as a white solid (1.07 g, 25 % over 2 steps) along with by-product **358** as a white solid (669 mg, 14 % over 2 steps).

Data for **306**

Melting point: 113-114 ^{o}C (ethyl acetate/toluene);

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 8.64 (s, 1H, H_1), 2.73 (s, 3H, H_5);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 172.6 (Quat, $C_{2/4}$), 164.8 (Quat, $C_{2/4}$), 156.8 (CH, C_1), 99.0 (Quat, C_3), 30.4 (CH_3, C_5);

FTIR (neat) ν/cm^{-1} = 1661, 1532, 1499, 1416, 1374, 1318, 1267, 1191, 1024;

HRMS (ESI^{+}) calculated for $C_5H_5N_2ClI$ = 254.9181, mass found = 254.9176.

Data for **358**

Melting point: 59-61 ^{o}C (ethyl acetate/toluene);

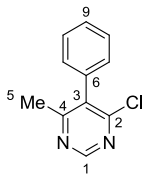
^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 8.77 (s, 1H, H_1), 4.73 (s, 2H, H_5);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 168.7 (Quat, C_{Ar}), 166.2 (Quat, C_{Ar}), 157.5 (CH, C_1), 98.0 (Quat, C_3), 49.6 (CH_2, C_5);

FTIR (neat) ν/cm^{-1} = 1528, 1504, 1414, 1319, 1286, 1183, 1016;

HRMS (ESI^{+}) calculated for $C_5H_4N_2Cl_2I$ = 288.8791, mass found = 288.8785.

4-Chloro-6-methyl-5-phenylpyrimidine, 359



This compound was prepared by analogy to a literature procedure.[100]

A Schlenk tube was charged with **306** (50 mg, 0.20 mmol), phenylboronic acid (31 mg, 0.26 mmol), $Pd(dppf)Cl_2{\cdot}CH_2Cl_2$ (16 mg, 0.020 mmol) and potassium phosphate tribasic (124 mg, 0.59 mmol) and the atmosphere was purged with argon three times. Degassed 1,4-dioxane was added and the stirred solution was heated to 70 ^{o}C for 20 hours and then cooled to room temperature and water and diethyl ether were added. The organic layer was separated and the aqueous layer was extracted twice with diethyl ether. The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. Purification of the residue *via* column chromatography eluting with 1:9 ethyl acetate/petrol 40-60 afforded the title compound **359** as a yellow oil

(17 mg, 42 %) which was contaminated by *c.a.* 10 % of an unknown impurity. The majority of the spectral data* matched that previously reported in the literature.[100]

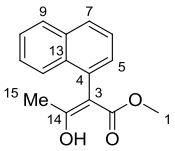
^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 8.86 (s, 1H, H_1), 7.54-7.44 (m, 3H, H_{Ar}), 7.27-7.21 (m, 2H, H_{Ar}), 2.36 (s, 3H, H_5);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C =167.4 (Quat, C_{Ar}), 160.2 (Quat, C_{Ar}), 156.7 (CH, C_1), 134.4 (Quat, C_{Ar}), 134.0 (Quat, C_{Ar}), 128.9 (CH, $C_{7/8}$), 128.9 (CH, $C_{7/8}$), 128.8 (CH, C_9), 23.5 (CH_3, C_5);

FTIR (neat) ν/cm^{-1} = 3059, 1550, 1528, 1421, 1371, 1194;

LRMS (ESI$^+$) 205 ([M + H]$^+$).

Methyl 3-hydroxy-2-(naphthalen-1-yl)but-2-enoate, 307



A stirred solution of 1-naphthaleneacetic acid (10.0 g, 53.7 mmol) in methanol (130 mL) was cooled to 0 ^{o}C. Thionyl chloride (4.70 mL, 64.7 mmol) was added and the resulting solution was warmed to room temperature and stirred for 3 hours. After this time, the reaction mixture was concentrated to dryness under reduced pressure. The residue was redissolved in ethyl acetate and washed successively with brine (x 2), 2 M aqueous sodium carbonate, brine and then dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to afford the crude methyl ester **310** (10.8 g) which was used without purification in the next step.

A stirred solution of diisopropylamine (12.1 mL, 86.2 mmol) in THF (100 mL) was cooled to -78 ^{o}C and *n*-butyllithium (1.6 M in hexanes, 51.5 mL, 82.3 mmol) was added dropwise. The

* The ^{1}H spectrum matched the literature (200 MHz, $CDCl_3$). In the ^{13}C spectrum all of our CH and CH_3 peaks exactly matched the literature values (50 MHz, $CDCl_3$). However, three of the four quaternary peaks were significantly different.

resulting solution was warmed to 0 ^{o}C and stirred for 5 minutes and then cooled to -78 ^{o}C. A -78 ^{o}C solution of crude methyl ester **310** (7.85 g, 39.2 mmol) in THF (80 mL) was added dropwise *via* an insulated cannula. The resulting mixture was stirred at -78 ^{o}C for 10 minutes. Acetic anhydride (4.45 mL, 47.1 mmol) was added and the reaction mixture was stirred at -78 ^{o}C for 5 minutes and then warmed to 0 ^{o}C and stirred for 20 minutes and then saturated aqueous ammonium chloride was added. The mixture was warmed to room temperature and diluted with diethyl ether and 1 M HCl and the organic layer was separated. The aqueous layer was extracted twice with diethyl ether and the combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. Purification of the residue *via* column chromatography eluting with 3:47 ethyl acetate/petrol 40-60 afforded the title compound **307** as an off white solid (4.61 g, 49 % over 2 steps).

Melting point: 103-105 ^{o}C (ethyl acetate/petrol 40-60);

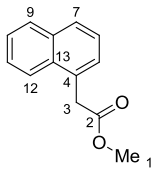
^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 13.44 (s, 1H, O*H*), 8.15-8.07 (m, 2H, H_{Ar}), 8.03-7.98 (m, 1H, H_{Ar}), 7.77-7.69 (m, 3H, H_{Ar}), 7.55 (dd, J = 7.0, 1.1 Hz, 1H, H_{Ar}), 3.84 (s, 3H, H_1), 1.97 (s, 3H, H_{15});

^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 174.9 (Quat, $C_{2/14}$), 173.3 (Quat, $C_{2/14}$), 133.8 (Quat, C_{Ar}), 133.1 (Quat, C_{Ar}), 132.5 (Quat, C_{Ar}), 129.1 (CH, C_{Ar}), 128.4 (CH, C_{Ar}), 128.1 (CH, C_{Ar}), 126.2 (CH, C_{Ar}), 125.8 (CH, C_{Ar}), 125.5 (CH, C_{Ar}), 125.2 (CH, C_{Ar}), 101.3 (Quat, C_3), 51.8 (CH_3, C_1), 19.8 (CH_3, C_{15});

FTIR (neat) ν/cm^{-1} = 2952, 1643, 1611, 1440, 1343, 1275, 1249, 1229, 1065;

HRMS (ESI^{+}) calculated for $C_{15}H_{14}NaO_3$ = 265.0835; mass found = 265.0829.

Methyl 2-(naphthalen-1-yl)acetate, 310



To a stirred room temperature suspension of sodium methoxide, prepared *in situ* by the portionwise addition of metallic sodium (190 mg, 8.26 mmol) to anhydrous methanol (5 mL), was added formamidine acetate salt (688 mg, 6.61 mmol) in a single portion. The resulting suspension was stirred at room temperature for 10 minutes and then **307** (1.00 g, 4.13 mmol) was added. The reaction mixture was stirred at room temperature for 24 hours and then the solution was cooled to 0 ^{o}C and acidified to pH 7 by dropwise addition of glacial acetic acid. The resulting solution was warmed to room temperature and concentrated under reduced pressure. Purification of the residue *via* column chromatography eluting with 1:19 ethyl acetate/methanol afforded the title compound **310** as a colourless oil (227 mg, 34 %). The spectral data matched that previously reported in the literature.[134]

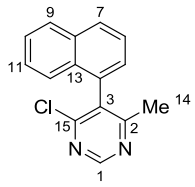
^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 8.03 (d, J = 8.3 Hz, 1H, H_{Ar}), 7.89 (d, J = 7.3 Hz, 1H, H_{Ar}), 7.83 (d, J = 7.3 Hz, 1H, H_{Ar}), 7.61-7.83 (m, 4H, H_{Ar}), 4.10 (s, 2H, H_3), 3.70 (s, 3H, H_1);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 172.1 (Quat, C_2), 133.9 (Quat, C_{Ar}), 132.2 (Quat, C_{Ar}), 130.6 (Quat, C_{Ar}), 128.8 (CH, C_{Ar}), 128.2 (CH, C_{Ar}), 128.1 (CH, C_{Ar}), 126.5 (CH, C_{Ar}), 125.9 (CH, C_{Ar}), 125.5 (CH, C_{Ar}), 123.8 (CH, C_{Ar}), 52.2 (CH_3, C_1), 39.1 (CH_2, C_3);

FTIR (neat) ν/cm^{-1} = 3047, 2951, 1732, 1598, 1511, 1434, 1399, 1335, 1265, 1195, 1008;

LRMS (ESI^{+}) $[M + Na]^{+}$ = 223.

4-Chloro-6-methyl-5-(naphthalen-1-yl)pyrimidine, 305



This compound was prepared by analogy to a literature procedure.[98]

A solution of **201** (836 mg, 3.04 mmol) in a mixture of THF (17 mL) and NMP (1.7 mL) was cooled to 0 °C and iron(III) acetylacetonate (54 mg, 0.15 mmol) and methylmagnesium chloride (3 M in THF, 1.22 mL, 3.64 mmol) were sequentially added. The resulting solution was warmed to room temperature and stirred for 30 minutes and then ammonium chloride and dichloromethane were added. The organic layer was separated and the aqueous layer was extracted twice with dichloromethane. The combined organic extracts were dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. Purification of the residue *via* column chromatography eluting with 1:9 ethyl acetate/petrol 40-60 afforded the title compound *rac*-**305** as a white solid (317 mg, 41 %).

Melting point: 114-116 °C (ethyl acetate/petrol 40-60);

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 8.97 (s, 1H, H_1), 7.98 (d, J = 8.3, 1H, H_7), 7.95 (d, J = 8.8 Hz, 1H, H_9), 7.59 (dd, J = 8.3, 7.1 Hz, 1H, H_6), 7.54 (ddd, J = 8.3, 6.9, 1.3 Hz, 1H, H_{10}), 7.46 (ddd, J = 8.4, 6.9, 1.4 Hz, 1H, H_{11}), 7.34 (dd, J = 7.0, 1.1 Hz, 1H, H_5), 7.27 (dd, J = 8.4, 0.9 Hz, 1H, H_{12}), 2.24 (s, 3H, H_{14});

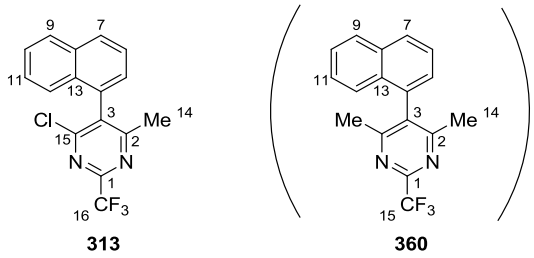
^{13}C NMR (101 MHz, $CDCl_3$) δ_C =168.6 (Quat, $C_{2/15}$), 161.1 (Quat, $C_{2/15}$), 157.3 (CH, C_1), 133.7 (Quat, C_{Ar}), 132.3 (Quat, C_{Ar}), 131.9 (Quat, C_{Ar}), 130.7 (Quat, C_{Ar}), 129.4 (CH, C_7), 128.8 (CH, C_9), 127.1 (CH, C_{11}), 127.0 (CH, C_5), 126.5 (CH, C_{10}), 125.6 (CH, C_6), 124.2 (CH, C_{12}), 23.2 (CH_3, C_{14});

FTIR (neat) ν/cm^{-1} =3058, 1549, 1522, 1424, 1356, 1234, 1201;

HRMS (ESI^+) calculated for $C_{15}H_{12}N_2Cl$ = 255.0684, mass found = 255.0678.

Chiral HPLC (Chiralpak IC, 2 % IPA, 98 % hexane, 1.0 mL/min, λ = 230 nm, 20 μL injection) τ_R = 9.5, 10.0 min.

4-Chloro-6-methyl-5-(naphthalen-1-yl)-2-(trifluoromethyl)pyrimidine, 313



This compound was prepared by analogy to a literature procedure.[98]

A solution of **254** (62 mg, 0.18 mmol) in a mixture of THF (1 mL) and NMP (0.1 mL) was cooled to 0 ^oC and iron(III) acetylacetonate (3 mg, 0.009 mmol) and methylmagnesium chloride (3 M in THF, 0.07 mL, 0.20 mmol) were sequentially added. The resulting solution was warmed to room temperature and stirred for 30 minutes and then ammonium chloride and dichloromethane were added. The organic layer was separated and the aqueous layer was extracted twice with dichloromethane. The combined organic extracts were dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. Purification of the residue *via* column chromatography eluting with 1:49 ethyl acetate/petrol 40-60 afforded the title compound *rac*-**313** as a white solid (23 mg, 39 %) along with recovered starting material **254** (5 mg, 8 %) and by-product **360** (5 mg, 9 %).

Data for **313**

Melting point: 131-132 ^oC (ethyl acetate/petrol 40-60);

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.94 (d, J = 8.2 Hz, 1H, H_7), 7.90 (d, J = 8.2 Hz, 1H, H_9), 7.54 (dd, J = 8.3, 7.1 Hz, 1H, H_6), 7.50 (ddd, J = 8.2, 6.9, 1.1 Hz, 1H, H_{10}), 7.41 (ddd, J = 8.3, 6.9, 1.3 Hz, 1H, H_{11}), 7.27 (dd, J = 7.1, 1.2 Hz, 1H, H_5), 7.15 (d, J = 8.3 Hz, 1H, H_{12}), 2.26 (s, 3H, H_{14});

^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 170.4 (Quat, $C_{2/15}$), 162.3 (Quat, $C_{2/15}$), 155.3 (q, J = 38.1 Hz, Quat, C_1), 134.6 (Quat, C_{Ar}), 133.7 (Quat, C_{Ar}), 130.8 (Quat, C_{Ar}), 130.3 (Quat, C_{Ar}), 129.9 (CH, C_7), 129.0 (CH, C_9), 127.4 (CH, C_{11}), 126.9 (CH, C_5), 126.8 (CH, C_{10}), 125.6 (CH, C_6), 123.8 (CH, C_{12}), 119.1 (q, J = 276.6 Hz, Quat, C_{16}), 23.4 (CH_3, C_{14});

^{19}F NMR (376 MHz, $CDCl_3$) δ_F = -70.2;

FTIR (neat) ν/cm^{-1} = 3057, 1557, 1314, 1187, 1142;

HRMS (ESI$^+$) calculated for $C_{16}H_{11}N_2ClF_3$ = 323.0557, mass found = 323.0551.

Data for **360**

Melting point: 158-159 ^{o}C (ethyl acetate/petrol 40-60);

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.98 (d, J = 8.3 Hz, 1H, H_7), 7.97 (d, J = 8.2 Hz, 1H, H_9), 7.60 (dd, J = 8.4, 7.1 Hz, 1H, H_6), 7.56 (ddd, J = 8.0, 7.1, 1.0 Hz, 1H, H_{10}), 7.46 (ddd, J = 8.4, 7.0, 1.3 Hz, 1H, H_{11}), 7.30 (dd, J = 7.1, 1.1 Hz, 1H, H_5), 7.21 (dd, J = 8.5, 0.7 Hz, 1H, H_{12}), 2.25 (s, 6H, H_{14});

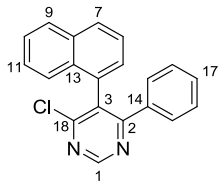
^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 166.3 (Quat, C_2), 154.0 (q, J = 35.9 Hz, Quat, C_1), 133.2 (Quat, C_{Ar}), 132.8 (Quat, C_{Ar}), 131.6 (Quat, C_{Ar}), 129.6 (Quat, C_{Ar}), 128.2 (CH, $C_{7/9}$), 127.9 (CH, $C_{7/9}$), 126.2 (CH, C_{11}), 125.6 (CH, C_{10}), 125.5 (CH, C_5), 124.7 (CH, C_6), 123.0 (CH, C_{12}), 118.8 (q, J = 275.9 Hz, Quat, C_{15}), 21.8 (CH_3, C_{14});

^{19}F NMR (376 MHz, $CDCl_3$) δ_F = -70.3;

FTIR (neat) ν/cm^{-1} = 3053, 1594, 1399, 1354, 1249, 1193, 1147;

HRMS (ESI$^+$) calculated for $C_{17}H_{14}N_2F_3$ = 303.1104, mass found = 303.1097.

4-Chloro-5-(naphthalen-1-yl)-6-phenylpyrimidine, 315



An oven dried schlenk tube was charged sequentially with **201** (300 mg, 1.09 mmol), phenylboronic acid (159 mg, 1.30 mmol), potassium carbonate (301 mg, 2.18 mmol) and tetrakis(triphenylphosphine)palladium(0) (63 mg, 0.054 mmol). The atmosphere was purged with argon three times and anhydrous toluene (7.6 mL) was added. The resulting mixture was stirred under an atmosphere of nitrogen at 100 ^{o}C for 2 hours and then cooled to room temperature and diluted with dichloromethane and ammonium chloride. The organic layer was separated and the aqueous layer was extracted twice with dichloromethane. The combined organic extracts were dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. Purification of the residue *via* column chromatography eluting with 1:9 ethyl acetate/petrol 40-60 afforded the title compound *rac*-**315** as a white solid (241 mg, 70 %).

Melting point: 153-154 ^{o}C (ethyl acetate/petrol 40-60);

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 9.07 (s, 1H, H_1), 7.82 (d, J = 7.7 Hz, 1H, H_9), 7.80 (d, J = 7.9 Hz, 1H, H_7), 7.44-7.36 (m, 3H, H_{10}, H_{11} and H_{12}), 7.32 (dd, J = 8.3, 7.1 Hz, 1H, H_6), 7.20-7.17 (m, 2H, H_{15}), 7.13-7.06 (m, 2H, H_5 and H_{17}), 6.98 (t, J = 7.7 Hz, 2H, H_{16});

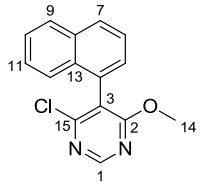
^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 166.9 (Quat, $C_{2/18}$), 162.7 (Quat, $C_{2/18}$), 157.6 (CH, C_1), 137.0 (Quat, C_{Ar}), 133.5 (Quat, C_{Ar}), 132.3 (Quat, C_{Ar}), 131.6 (Quat, C_{Ar}), 131.1 (Quat, C_{Ar}), 129.7 (CH, C_{17}), 129.3 (CH, C_7), 129.1 (CH, C_{15}), 128.8 (CH, C_9), 128.1 (CH, C_5), 128.0 (CH, C_{16}), 127.1 (CH, C_{11}), 126.4 (CH, C_{10}), 125.4 (CH, C_6), 124.7 (CH, C_{12});

FTIR (neat) ν/cm^{-1} = 3058, 1540, 1514, 1493, 1414, 1353, 1206, 1079;

HRMS (ESI^+) calculated for $C_{20}H_{14}N_2Cl$ = 317.0840, mass found = 317.0840;

Chiral HPLC (Chiralpak ADH, 10 % IPA, 90 % hexane, 1.0 mL/min, λ = 225 nm, 20 μL injection) τ_R = 12.3, 13.1 min.

4-Chloro-6-methoxy-5-(naphthalen-1-yl)pyrimidine, 316



To a rapidly stirred suspension of **201** (300 mg, 1.09 mmol), methanol (220 μL, 5.45 mmol) and tetrabutylammonium bromide (35 mg, 0.11 mmol) in toluene (11 mL) was added potassium hydroxide (122 mg, 2.18 mmol). The resulting biphasic mixture was stirred rapidly at room temperature for 16 hours and then saturated aqueous ammonium chloride and dichloromethane were added. The organic layer was separated and the aqueous layer was extracted twice with dichloromethane. The combined organic extracts were dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. Purification of the residue *via* column chromatography eluting with 1:9 ethyl acetate/petrol 40-60 afforded the title compound *rac*-**316** as a white solid (199 mg, 67 %).

Melting point: 118-119 ^oC (ethyl acetate/petrol 40-60);

^1H NMR (400 MHz, $CDCl_3$) δ_H = 8.74 (s, 1H, H_1), 7.99 (d, J = 8.4 Hz, 1H, H_7), 7.97 (d, J = 8.5 Hz, 1H, H_9), 7.61 (dd, J = 8.2, 7.2 Hz, 1H, H_6), 7.55 (ddd, J = 8.1, 6.8, 1.2 Hz, 1H, H_{10}), 7.48 (ddd, J = 8.4, 6.9, 1.4 Hz, 1H, H_{11}), 7.43-7.38 (m, 2H, H_5 and H_{12}), 3.93 (s, 3H, H_{14});

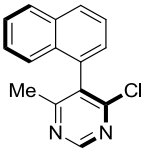
^{13}C NMR (101 MHz, $CDCl_3$) δ_C =168.8 (Quat, $C_{2/15}$), 160.4 (Quat, $C_{2/15}$), 157.1 (CH, C_1), 133.6 (Quat, C_{Ar}), 131.1 (Quat, C_{Ar}), 129.4 (Quat, C_{Ar}), 129.3 (CH, C_7), 128.7 (CH, C_9), 127.8 (CH, C_5), 126.7 (CH, C_{11}), 126.2 (CH, C_{10}), 125.4 (CH, C_6), 124.6 (CH, C_{12}), 119.5 (Quat, C_3), 55.0 (CH_3, C_{14});

FTIR (neat) ν/cm^{-1} = 2956, 1558, 1536, 1508, 1471, 1397, 1366, 1318;

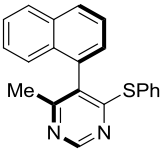
HRMS (ESI^+) calculated for $C_{15}H_{12}ON_2Cl$ = 271.0633, mass found = 271.0629;

Chiral HPLC (Chiralpak ADH, 4 % IPA, 96 % hexane, 1.0 mL/min, λ = 221 nm, 20 μL injection) τ_R = 7.1, 7.5 min.

Kinetic resolution of *rac*-305



305

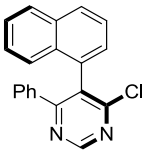


300

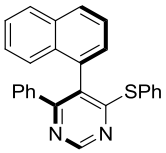
In a 7 mL screw capped vial, *rac*-**305** (50 mg, 0.20 mmol) was dissolved in carbon tetrachloride (2.0 mL) and *N*-benzylquininium chloride (9 mg, 0.02 mmol), thiophenol (12.1 μL, 0.12 mmol) and 50 % aqueous potassium carbonate (135 μL, 0.98 mmol) were added sequentially. The atmosphere was purged with nitrogen, and the biphasic reaction mixture was rapidly stirred at room temperature for 4 days and then saturated aqueous ammonium chloride and dichloromethane were added. The organic layer was separated and the aqueous layer was extracted twice with dichloromethane. The combined organic extracts were dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. Purification of the residue *via* column chromatography eluting with 1:4 ethyl acetate/petrol 40-60 afforded a mixture of recovered starting material **305** and **300** (62 mg). ^{1}H NMR indicated a 93:7 mixture of **305** and **300** to be present (the spectral data for both compounds matched that obtained previously). Analysis of the mixture by chiral HPLC gave **305** (4.8 % e.e. = *c.a.* 52:48 e.r.) and **300** (76.5 % e.e. = c.a. 88:12 e.r.) from which we calculated a conversion of 5.9 % and an S factor of 8.

Chiral HPLC (Chiralpak IC, 2 % IPA, 98 % hexane, 1.0 mL/min, λ = 230 nm, 20 μL injection) τ_R (**305** minor) = 9.5 min, τ_R (**305** major) = 10.0 min, (**300** minor) = 13.2 min, τ_R (**300** major) = 14.3 min.

Kinetic resolution of *rac*-315



315

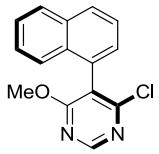


299

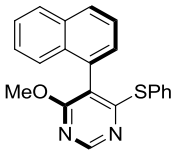
In a 7 mL screw capped vial, *rac*-**315** (62 mg, 0.20 mmol) was dissolved in carbon tetrachloride (2.0 mL) and *N*-benzylquininium chloride (9 mg, 0.02 mmol), thiophenol (12.1 μL, 0.12 mmol) and 50 % aqueous potassium carbonate (135 μL, 0.98 mmol) were added sequentially. The atmosphere was purged with nitrogen, and the biphasic reaction mixture was rapidly stirred at room temperature for 48 hours and then saturated aqueous ammonium chloride and dichloromethane were added. The organic layer was separated and the aqueous layer was extracted twice with dichloromethane. The combined organic extracts were dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. Purification of the residue *via* column chromatography eluting with 1:9 ethyl acetate/petrol 40-60 afforded a mixture of recovered starting material **315** and **299** (64 mg). ^{1}H NMR indicated a 83:17 mixture of **315** and **299** to be present (the spectral data for both compounds matched that obtained previously). Analysis of the mixture by chiral HPLC gave **315** (13.5 % e.e. = *c.a.* 57:43 e.r.) and **299** (77.9 % e.e. = c.a. 89:11 e.r.) from which we calculated a conversion of 14.7 % and an S factor of 9.

Chiral HPLC (Chiralpak ADH, 10 % IPA, 90 % hexane, 1.0 mL/min, λ = 225 nm, 20 μL injection) τ_R (**315** minor) = 6.2 min, τ_R (**315** major) = 8.1 min, (**299** major) = 12.3 min, τ_R (**299** minor) = 13.1 min.

Kinetic resolution of *rac*-316



316

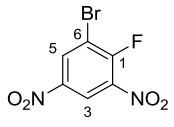


293

In a 7 mL screw capped vial, *rac*-**316** (53 mg, 0.20 mmol) was dissolved in carbon tetrachloride (2.0 mL) and *N*-benzylquininium chloride (9 mg, 0.02 mmol), thiophenol (12.1 μL, 0.12 mmol) and 50 % aqueous potassium carbonate (135 μL, 0.98 mmol) were added sequentially. The atmosphere was purged with nitrogen, and the biphasic reaction mixture was rapidly stirred at room temperature for 48 hours and then saturated aqueous ammonium chloride and dichloromethane were added. The organic layer was separated and the aqueous layer was extracted twice with dichloromethane. The combined organic extracts were dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. Purification of the residue *via* column chromatography eluting with 1:9 ethyl acetate/petrol 40-60 afforded a mixture of recovered starting material **316** and **293** (53 mg). ^{1}H NMR indicated a > 95:5 mixture of **316** and **293** to be present. Analysis of the mixture by chiral HPLC gave **316** (1.0 % e.e. = *c.a.* 50:50 e.r.) and **293** (52.4 % e.e. = c.a. 76:24 e.r.) from which we calculated a conversion of 1.9 % and an S factor of 3.

Chiral HPLC (Chiralpak ADH, 4 % IPA, 96 % hexane, 1.0 mL/min, λ = 230 nm, 20 μL injection) τ_R (**316** minor) = 7.2 min, τ_R (**316** major) = 7.5 min, (**293** major) = 11.4 min, τ_R (**293** minor) = 12.1 min.

1-Bromo-2-fluoro-3,5-dinitrobenzene, 319



This compound was prepared according to a modified literature procedure.[103]

1-Fluoro-2,4-dinitrobenzene (5.00 g, 26.9 mmol) was dissolved in concentrated sulfuric acid (90 mL) and the resulting stirred solution was heated to 60 ^{o}C. *N*-Bromosuccinimide (9.56 g, 53.7 mmol) was added in 1 g portions [caution: bromine vapours are evolved]. The reaction mixture was stirred at 60 ^{o}C for 16 hours, cooled to room temperature and carefully poured onto crushed ice (*c.a.* 1 L) and then allowed to warm to room temperature. The resulting suspension was extracted three times with dichloromethane. The combined organic extracts were dried over anhydrous magnesium sulfate, filtered and the solvent was removed under reduced pressure. Purification of the residue *via* column chromatography eluting with 1:9 ethyl acetate/petrol 40-60 afforded **319** as a pale yellow solid (2.98 g, 42 %).

Melting point: 63-65 ^{o}C (ethyl acetate/petrol 40-60);

^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 8.89 (dd, J = 2.8 Hz, J = 8.0 Hz, 1H, H_3), 8.76 (dd, J = 2.8 Hz, J = 5.0 Hz, 1H, H_5);

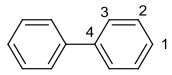
^{13}C NMR (121 MHz, $CDCl_3$) δ_C = 156.1 (d, J = 274.0 Hz, Quat, C_1), 143.2 (d, J = 3.2 Hz, Quat, C_4), 137.8 (d, J = 8.6 Hz, Quat, C_2), 133.4 (d, J = 2.9 Hz, CH, C_5), 121.0 (CH, C_3), 113.5 (d, J = 22.9 Hz, Quat, C_6);

^{19}F NMR (376 MHz, $CDCl_3$) δ_F = -98.9;

FTIR (neat) ν/cm^{-1} = 3100, 1601, 1534, 1465, 1338, 1269, 1159, 1077;

HRMS (FI^+) calculated for $C_6H_2N_2O_4BrF$ = 263.9182, mass found = 263.9187.

Biphenyl, 321



A stirred suspension of aryl bromide **319** (100 mg, 0.38 mmol), phenylboronic acid (92 mg, 0.75 mmol) and tetrakis(triphenylphosphane)palladium(0) (44 mg, 0.038 mmol) in THF (12.7 mL) was sparged with argon for 30 minutes. After this time a degassed solution of aqueous potassium carbonate (2 M, 0.76 mL, 1.g mmol) was added and the resulting biphasic mixture was heated to reflux for 48 hours. After this time, the solution was cooled to room temperature and diluted with diethyl ether and water. The organic layer was separated and the aqueous layer was extracted with diethyl ether. The combined organic extracts were dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. Purification of the residue *via* column chromatography eluting with 1:19 diethyl ether/petrol 40-60 afforded biphenyl **321** as a white solid (12 mg, 21 % based on phenylboronic acid). The spectral data matched that previously reported in the literature.[135]

Melting point: 54-55 ^{o}C (diethyl ether/petrol 40-60);

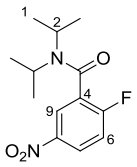
^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 7.63 (d, J = 7.9 Hz, 4H, H_3), 7.47 (t, J = 7.7 Hz, 4H, H_2), 7.38 (t, J = 7.4 Hz, 2H, H_1);

^{13}C NMR (121 MHz, $CDCl_3$) δ_C =141.2 (Quat, C_4), 128.7 (CH, C_2), 127.2 (CH, C_1), 127.2 (CH, C_3);

FTIR (neat) ν/cm^{-1} =3063, 3034, 1569, 1481, 1430;

LRMS (FI^{+}) 154 (M^{+}).

2-Fluoro-*N,N*-diisopropyl-5-nitrobenzamide, 324



To a stirred room temperature suspension of 2-fluoro-5-nitrobenzoic acid **323** (1.00 g, 5.40 mmol) in thionyl chloride (3.0 mL, 41 mmol) was added *N*,*N*-dimethylformamide (2 drops). The resulting suspension was heated to 75 ^{o}C for 2 hours after which time a homogeneous solution had formed. The mixture was cooled to room temperature and concentrated under reduced pressure. The residue was redissolved in anhydrous diethyl ether (15 mL) and the resulting stirred solution was cooled to 0 ^{o}C. A solution of diisopropylamine (3.78 mL, 27.0 mmol) in anhydrous diethyl ether (15 mL) was added. The mixture was warmed to room temperature and stirred for 30 minutes, after which time a white precipitate had formed. 1 M aqueous sodium hydroxide was added. The organic layer was separated and washed with 1 M HCl (x 2) and brine and then dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. Purification of the residue *via* column chromatography eluting with 3:17 ethyl acetate/petrol 40-60 afforded the title compound **324** as a pale yellow solid (347 mg, 20 %).

Melting point: 91-94 ^{o}C (ethyl acetate/petrol 40-60);

^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 8.25 (ddd, J = 9.1, 4.4, 2.8 Hz, 1H, H_7), 8.21 (dd, J = 5.7, 2.8 Hz, H_9), 7.25 (dd, J = 9.3, 7.7 Hz, 1H, H_6), 3.64 (sept., J = 6.7 Hz, 1H, H_2), 7.25 (sept., J = 6.8 Hz, 1H, $H_{2'}$), 1.56 (d, J = 6.9 Hz, 6H, $H_{1'}$), 1.22 (br s, 3H, H_{1A}), 1.15 (br s, 3H, H_{1B});

^{13}C NMR (121 MHz, $CDCl_3$) δ_C = 162.9 (Quat, C_3), 161.4 (d, J = 258.4 Hz, Quat, C_5), 144.4 (d, J = 2.2 Hz, Quat, C_8), 128.0 (d, J = 22.5 Hz, Quat, C_4), 125.9 (d, J = 9.5 Hz, CH, C_7), 124.2 (d,

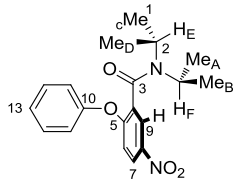
J = 6.7 Hz, CH, C_9), 117.0 (d, J = 24.8 Hz, CH, C_6), 51.5 (CH, C_2), 46.5 (CH, $C_{2'}$), 20.9 (CH_3, C_{1b}), 20.5 (CH_3, C_{1a}), 20.4 (CH_3, $C_{1'a/b}$), 20.2 (CH_3, $C_{1'a/b}$);

^{19}F NMR (377 MHz, $CDCl_3$) δ_F = -106.0 (td, J = 4.6, 9.2 Hz);

FTIR (neat) ν/cm^{-1} = 2976, 1638, 1532, 1452, 1334, 1240, 1118, 1072, 1036;

HRMS (ESI$^+$) calculated for $C_{13}H_{17}FNaNaO_3$ = 291.1115, mass found = 291.1113.

_N,N_-Diisopropyl-5-nitro-2-phenoxybenzamide, 325



To a suspension of **324** (50 mg, 0.19 mmol), phenol (21 mg, 0.22 mmol) and tetrabutylammonium bromide (6 mg, 0.02 mmol) in toluene (3.0 mL) was added cesium hydroxide monohydrate (156 mg, 0.93 mmol). The resulting suspension was stirred rapidly at room temperature for 20 hours. After this time, 1 M HCl (20 mL) and dichloromethane (20 mL) were added. The organic layer was separated and the aqueous layer was extracted twice with dichloromethane. The combined organic extracts were washed with 1 M NaOH, dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. Purification of the residue *via* column chromatography eluting with 3:17 ethyl acetate/petrol 40-60 afforded the title compound **325** as an off white solid (46 mg, 72 %).

Melting point: 101-103 ^{o}C (ethyl acetate/petrol 40-60);

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 8.10 (d, J = 2.7 Hz, 1H, H_9), 2.02 (dd, J = 9.0, 2.7 Hz, 1H, H_7), 7.36 (t, J = 7.9 Hz, 2H, H_{12}), 7.18 (t, J = 7.5 Hz, 1H, H_{13}), 7.02 (d, J = 8.1 Hz, 2H, H_{11}), 6.73 (d, J = 9.0 Hz, 1H, H_6), 3.73 (sept, J = 6.6 Hz, 1H, H_{2F}), 3.47 (sept, J = 6.8 Hz, 1H, H_{2E}), 1.50 (d,

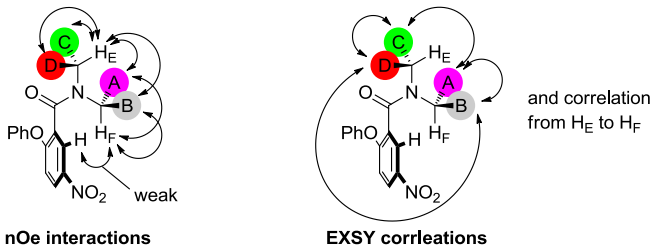
J = 6.8 Hz, 3H, H_{1D}), 1.42 (d, J = 6.8 Hz, 3H, H_{1C}), 1.18 (d, J = 6.6 Hz, 3H, H_{1B}), 1.08 (d, J = 6.8 Hz, 3H, H_{1A}):

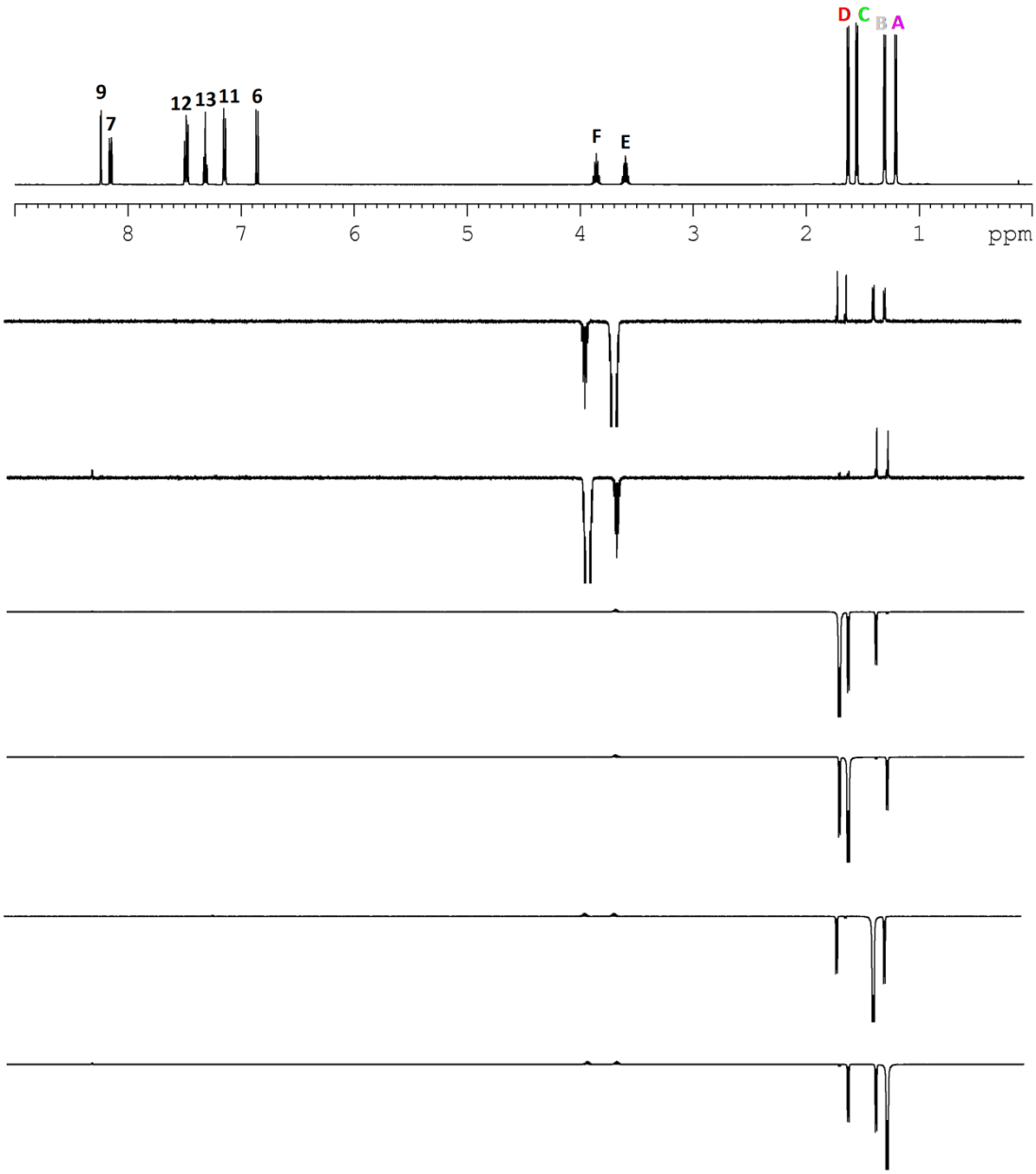
^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 165.1 (Quat, C_3), 158.7 (Quat, C_{Ar}), 154.5 (Quat, C_{Ar}), 142.7 (Quat, C_{Ar}), 130.4 (CH, C_{12}), 130.3 (Quat, C_{Ar}), 125.6 (CH, C_{13}), 125.3 (CH, C_7), 123.6 (CH, C_9), 120.5 (CH, C_{11}), 115.9 (CH, C_6), 51.3 (CH, C_{2F}), 46.2 (CH, C_{2E}), 20.9 (CH_3, C_{1C}), 20.8 (CH_3, C_{1D}), 20.6 (CH_3, C_{1B}), 20.2 (CH_3, C_{1A});

FTIR (neat) ν/cm^{-1} =2971, 1633, 1579, 1523, 1475, 1335, 1247;

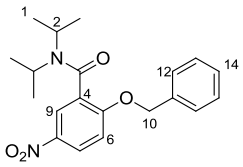
HRMS (ESI^+) calculated for $C_{19}H_{22}N_2NaO_4$ = 365.1472, mass found = 365.1468.

nOe and EXSY correlations for **325** (D_8 = 200 ms):





2-(Benzyloxy)-*N*,*N*-diisopropyl-5-nitrobenzamide, 326



To a suspension of **324** (50 mg, 0.19 mmol), benzyl alcohol (24 mg, 0.22 mmol) and tetrabutylammonium bromide (6 mg, 0.02 mmol) in toluene (3.0 mL) was added cesium hydroxide monohydrate (156 mg, 0.93 mmol). The resulting suspension was stirred rapidly at room temperature for 20 hours. After this time, 1 M HCl (20 mL) and dichloromethane (20 mL) were added. The organic layer was separated and the aqueous layer was extracted twice with dichloromethane. The combined organic extracts were dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. Purification of the residue *via* column chromatography eluting with 1:4 ethyl acetate/petrol 40-60 afforded the title compound **326** as an off white solid (57 mg, 86 %).

Melting point: 181-183 ^{o}C (ethyl acetate/petrol 40-60);

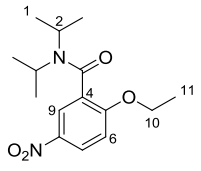
^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 8.22 (dd, J = 9.1, 2.8 Hz, 1H, H_7), 8.10 (d, J = 2.8 Hz, 1H, H_9), 7.43-7.32 (m, 5H, H_{12}, H_{13} and H_{14}), 7.04 (d, J = 9.1 Hz, 1H, H_6), 5.22 (d, J = 11.7 Hz, 1H, H_{10a}), 5.17 (d, J = 11.7 Hz, 1H, H_{10b}), 3.62 (sept, J = 6.7 Hz, 1H, H_2), 3.47 (sept, J = 6.8 Hz, 1H, $H_{2'}$), 1.56 (d, J = 6.6 Hz, 3H, $H_{1'a}$), 1.46 (d, J = 6.6 Hz, 3H, $H_{1'b}$), 1.08 (d, J = 6.6 Hz, 3H, H_{1a}), 1.04 (d, J = 6.9 Hz, 3H, H_{1b}):

^{13}C NMR (121 MHz, $CDCl_3$) δ_C = 165.5 (Quat, C_3), 159.1 (Quat), 141.6 (Quat), 135.1 (Quat), 129.6 (Quat), 128.6 (CH, $C_{12/13}$), 128.4 (CH, C_{14}), 127.2 (CH, $C_{12/13}$), 125.7 (CH, C_7), 122.9 (CH, C_9), 111.9 (CH, C_6), 71.0 (CH_2, C_{10}), 51.1 (CH, C_2), 46.0 (CH, $C_{2'}$), 20.8 (CH_3, C_{1a}), 20.6 (CH_3, $C_{1'a}$), 20.5 (CH_3, C_{1b}), 20.0 (CH_3, $C_{1'b}$);

FTIR (neat) ν/cm^{-1} = 2971, 1630, 1588, 1519, 1453, 1337, 1271;

HRMS (ESI$^+$) calculated for $C_{20}H_{24}N_2NaO_4$ = 379.1628, mass found = 379.1623.

2-Ethoxy-*N*,*N*-diisopropyl-5-nitrobenzamide, 328



To a solution of **324** (50 mg, 0.19 mmol), diethyl methylmalonate (28 mg, 0.16 mmol) and tetrabutylammonium bromide (5 mg, 0.01 mmol) in toluene (3.0 mL) was added cesium hydroxide monohydrate (123 mg, 0.73 mmol). The resulting suspension was stirred rapidly at room temperature for 72 hours. After this time, saturated aqueous ammonium chloride (20 mL) and dichloromethane (20 mL) were added. The organic layer was separated and the aqueous layer was extracted twice with dichloromethane. The combined organic extracts were dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. Purification of the residue *via* column chromatography eluting with 1:4 ethyl acetate/petrol 40-60 afforded the title compound **328** as an off white solid (34 mg, 72 %).

Melting point: 145-149 ^oC (ethyl acetate/petrol 40-60);

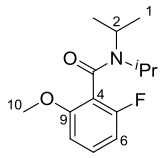
^1H NMR (500 MHz, $CDCl_3$) δ_H = 8.19 (dd, J = 9.1, 2.8 Hz, 1H, H_7), 8.06 (d, J = 2.8 Hz, 1H, H_9), 6.94 (d, J = 9.1 Hz, 1H, H_6), 4.21-4.09 (m, 2H, H_{10a} and H_{10b}), 3.59 (sept, J = 6.7 Hz, 1H, H_2), 3.52 (sept, J = 6.8 Hz, 1H, $H_{2'}$), 1.55 (d, J = 6.9 Hz, 3H, $H_{1'a}$), 1.53 (d, J = 6.9 Hz, 3H, $H_{1'b}$), 1.43 (t, J = 7.1 Hz, 3H, H_{11}), 1.18 (d, J = 6.6 Hz, 3H, H_{1a}), 1.08 (d, J = 6.6 Hz, 3H, H_{1b});

^{13}C NMR (121 MHz, $CDCl_3$) δ_C = 165.7 (Quat, C_3), 159.4 (Quat), 141.2 (Quat), 129.2 (Quat), 125.7 (CH, C_7), 122.8 (CH, C_9), 111.2 (CH, C_6), 64.9 (CH_2, C_{10}), 51.1 (CH, C_2), 46.0 (CH, $C_{2'}$), 20.8 (CH_3, C_{1b}), 20.6 (CH_3, $C_{1'a}$), 20.4 (CH_3, C_{1a}), 20.0 (CH_3, $C_{1'b}$), 14.4 (CH_3, C_{11});

FTIR (neat) ν/cm^{-1} = 2979, 1626, 1589, 1519, 1455, 1334, 1270, 1144, 1112, 1073, 1036;

HRMS (ESI$^+$) calculated for $C_{15}H_{22}N_2NaO_4$ = 317.1472, mass found = 317.1469.

2-Fluoro-*N*,*N*-diisopropyl-6-methoxybenzamide, 330



A stirred suspension of 2-fluoro-6-methoxybenzoic acid (2.00 g, 11.8 mmol) in thionyl chloride (5.0 mL, 130 mmol) was heated to 90 ^{o}C for 1 hour. The resulting homogeneous solution was cooled to room temperature and concentrated under reduced pressure. The residue was redissolved in anhydrous diethyl ether (30 mL) and cooled to 0 ^{o}C. A solution of diisopropylamine (8.3 mL, 59 mmol) in anhydrous diethyl ether (30 mL) was added. The mixture was warmed to room temperature and stirred for 30 minutes. After this time, water was added. The organic layer was separated and washed with 1 M HCl and brine and then dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. Purification of the residue *via* recrystallization from boiling ethyl acetate/petrol 60-80 afforded the title compound **330** as a white solid (2.51 g, 84 %).

Melting point: 128-132 ^{o}C (ethyl acetate/petrol 60-80);

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.20 (td, J = 8.4, 6.7 Hz, 1H, H_7), 6.70-6.63 (m, 2H, H_6 and H_8), 3.79 (s, 3H, H_{10}), 3.68 (sept, J = 6.7 Hz, 1H, H_2), 3.49 (sept, J = 6.8 Hz, 1H, $H_{2'}$), 1.53 (d, J = 6.8 Hz, 3H, $H_{1'A}$), 1.53 (d, J = 6.6 Hz, 3H, $H_{1'B}$), 1.10 (d, J = 6.6 Hz, 3H, H_{1A}), 1.09 (d, J = 6.6 Hz, 3H, H_{1B});

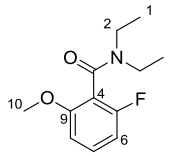
^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 163.2 (Quat, C_3), 158.9 (d, J = 245.0 Hz, Quat, C_5), 156.8 (d, J = 8.6 Hz, Quat, C_9), 129.6 (d, J = 9.8 Hz, CH, C_7), 116.5 (d, J = 22.3 Hz, Quat, C_4), 108.2 (d, J = 21.9 Hz, CH, C_6), 106.6 (d, J = 2.8 Hz, CH, C_8), 56.0 (CH_3, C_{10}), 51.2 (CH, C_2), 46.0 (CH, $C_{2'}$), 20.7 (CH_3, C_{1A}), 20.7 (CH_3, C_{1B}), 20.5 (CH_3, $C_{1'A}$), 20.5 (CH_3, $C_{1'B}$);

^{19}F NMR (377 MHz, $CDCl_3$) δ_F = -116.9;

FTIR (neat) ν/cm^{-1} =2973, 1626, 1470, 1439, 1371, 1341, 1274, 1240, 1215, 1256, 1079, 1037;

HRMS (ESI^+) calculated for $C_{14}H_{21}FNO_2$ = 254.1551, mass found = 254.1558.

***N*,*N*-Diethyl-2-fluoro-6-methoxybenzamide, 331**



A stirred suspension of 2-fluoro-6-methoxybenzoic acid (1.00 g, 5.88 mmol) in thionyl chloride (2.5 mL, 64 mmol) was heated to 90 ^oC for 1 hour. The resulting homogeneous solution was cooled to room temperature and concentrated under reduced pressure. The residue was redissolved in anhydrous diethyl ether (15 mL) and cooled to 0 ^oC. A solution of diethylamine (3.0 mL, 29 mmol) in anhydrous diethyl ether (15 mL) was added. The mixture was warmed to room temperature and stirred for 30 minutes. After this time, water was added. The organic layer was separated and washed with 1 M HCl and brine and then dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. Purification of the residue *via* column chromatography eluting with 1:1 ethyl acetate/petrol 40-60 afforded the title compound **331** as a colourless oil (1.26 g, 95 %).

^1H NMR (400 MHz, $CDCl_3$) δ_H = 7.23 (td, J = 8.4, 6.6 Hz, 1H, H_7), 6.67 (td, J = 8.4, 0.7 Hz, 1H, H_6), 6.67 (d, J = 8.6 Hz, 1H, H_8), 3.79 (s, 3H, H_{10}), 3.59 (dq, J = 14.2, 6.9 Hz, 1H, H_{2A}), 3.51 (dq, J = 14.2, 6.9 Hz, 1H, H_{2B}), 3.13 (q, J = 7.2 Hz, 2H, $H_{2'}$), 1.21 (t, J = 7.1 Hz, 3H, $H_{1'}$), 1.02 (t, J = 7.2 Hz, 3H, H_1);

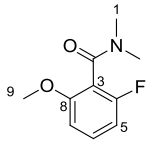
^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 163.6 (Quat, C_3), 159.0 (d, J = 245.6 Hz, Quat, C_5), 156.9 (d, J = 8.3 Hz, Quat, C_9), 130.2 (d, J = 9.5 Hz, CH, C_7), 115.1 (d, J = 22.3 Hz, Quat, C_4), 108.2 (d, J = 21.5 Hz, CH, C_6), 106.7 (d, J = 2.9 Hz, CH, C_8), 56.0 (CH_3, C_{10}), 42.9 (CH_2, $C_{2'}$), 39.0 (CH_2, C_2), 13.9 (CH_3, $C_{1'}$), 12.8 (CH_3, C_1);

^{19}F NMR (377 MHz, $CDCl_3$) δ_F = -116.1;

FTIR (neat) ν/cm^{-1} = 2977, 1634, 1614, 1469, 1430, 1284, 1240, 1079;

HRMS (ESI^+) calculated for $C_{12}H_{17}FNO_2$ = 226.1238; mass found = 226.1246.

_N_,_N_-Dimethyl-2-fluoro-6-methoxybenzamide, 332



A stirred suspension of 2-fluoro-6-methoxybenzoic acid (1.00 g, 5.88 mmol) in thionyl chloride (2.5 mL, 64 mmol) was heated to 90 ^{o}C for 1 hour. The resulting homogeneous solution was cooled to room temperature and concentrated under reduced pressure. The residue was redissolved in anhydrous diethyl ether (15 mL) and cooled to 0 ^{o}C. A solution of dimethylamine (7.9 M in MeOH, 3.7 mL, 29 mmol) in anhydrous diethyl ether (15 mL) was added. The mixture was warmed to room temperature and stirred for 30 minutes. After this time, water was added. The organic layer was separated and washed with 1 M HCl and brine and then dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. Purification of the residue *via* column chromatography eluting with 2:3 ethyl acetate/petrol 40-60 afforded the title compound **332** as a colourless oil (983 mg, 85 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.24 (td, J = 8.4. 6.8 Hz, 1H, H_6), 6.67 (td, J = 8.4, 0.6 Hz, 1H, H_5), 6.67 (d, J = 8.6 Hz, 1H, H_7), 3.79 (s, 3H, H_9), 3.09 (s, 3H, H_1), 2.84 (s, 3H, $H_{1'}$);

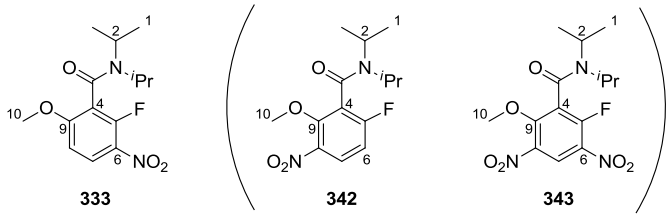
^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 164.4 (Quat, C_2), 159.0 (d, J = 246.1 Hz, Quat, C_4), 156.9 (d, J = 8.4 Hz, Quat, C_8), 130.6 (d, J = 9.5 Hz, CH, C_6), 114.4 (d, J = 22.0 Hz, Quat, C_3), 108.1 (d, J = 21.5 Hz, CH, C_5), 106.8 (d, J = 2.9 Hz, CH, C_7), 56.1 (CH_3, C_9), 37.8 (CH_3, $C_{1'}$), 34.5 (CH_3, C_1);

^{19}F NMR (377 MHz, $CDCl_3$) δ_F = -115.9;

FTIR (neat) ν/cm^{-1} = 2936, 1638, 1614 1469, 1440, 1397, 1277, 1240, 1077, 1059;

HRMS (ESI^+) calculated for $C_{10}H_{13}FNO_2$ = 198.0925, mass found = 198.0919.

2-Fluoro-*N*,*N*-diisopropyl-6-methoxy-3-nitrobenzamide, 333



Concentrated sulfuric acid (9 mL) was stirred at 0 °C and concentrated nitric acid (3 mL) was added. **330** (500 mg, 1.97 mmol) was added in one portion and the resulting solution was stirred at 0 °C for 15 minutes. After this time, the reaction mixture was poured onto crushed ice (c.a. 30 g) and then allowed to warm to room temperature. The resulting heterogeneous mixture was extracted three times with dichloromethane. The combined organic extracts were dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. Purification of the residue *via* column chromatography eluting with a gradient from 1:9 ethyl acetate/petrol 40-60 to 2:3 ethyl acetate/petrol 40-60 afforded the title compound **333** as a white solid (293 mg, 50 %) along with a 1.6:1.0 inseparable mixture of **342** and **343** as a yellow oil (257 mg, 41 %). An analytical quantity of enantioenriched **333** (98:2 e.r.) was obtained by semi-preparative HPLC (Chiralpak ADH, 20 % IPA, 80 % hexane, 1.0 mL/min).

<u>Data for 333</u>:

Melting point: 144-146 °C (ethyl acetate/petrol 40-60);

^1H NMR (500 MHz, $CDCl_3$) δ_H = 8.12 (t, J = 8.8 Hz, 1H, H_7), 6.79 (dd, J = 9.3, 0.7 Hz, 1H, H_8), 3.94 (s, 3H, H_{10}), 3.63 (sept, J = 6.7 Hz, 1H, H_2), 3.54 (sept, J = 6.8 Hz, 1H, $H_{2'}$), 1.55 (d, J = 6.9 Hz, 6H, $H_{1'}$), 1.16 (d, J = 6.9 Hz, 3H, H_{1A}), 1.15 (d, J = 6.6 Hz, 3H, H_{1B});

^{13}C NMR (126 MHz, $CDCl_3$) δ_C = 161.0 (d, J = 9.2 Hz, Quat, C_9), 160.5 (d, J = 1.5 Hz, Quat, C_3), 152.7 (d, J = 263.1 Hz, Quat, C_5), 131.1 (d, J = 7.6 Hz, Quat, C_6), 127.3 (CH, C_7), 118.4 (d, J = 22.9 Hz, Quat, C_4), 106.5 (d, J = 3.3 Hz, CH, C_8), 56.8 (CH_3, C_{10}), 51.5 (CH, C_2), 46.4 (CH, $C_{2'}$), 20.8 (CH_3, C_{1A}), 20.8 (CH_3, C_{1B}), 20.3 (CH_3, $C_{1'A}$), 20.3 (CH_3, $C_{1'B}$);

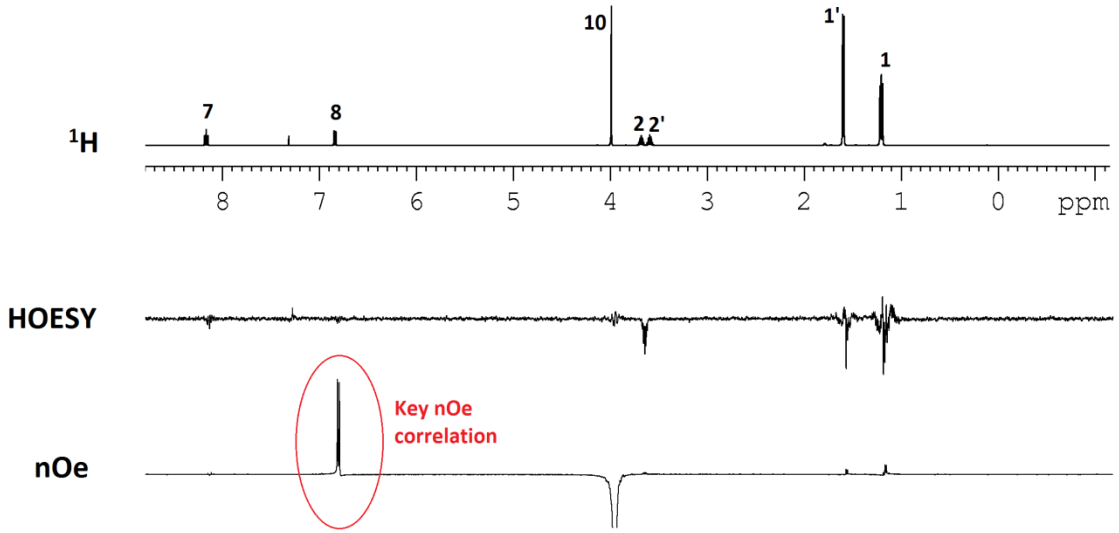
^{19}F NMR (470 MHz, $CDCl_3$) δ_F = -118.9;

FTIR (neat) ν/cm^{-1} = 2975, 1639, 1596, 1524, 1485, 1439, 1330, 1289, 1084;

HRMS (ESI$^+$) calculated for $C_{14}H_{19}FN_2NaO_4$ = 321.1221, mass found = 321.1214;

Chiral HPLC (Chiralpak ADH, 20 % IPA, 80 % hexane, 1.0 mL/min, λ = 245 nm, 20 µL injection) τ_R = 14.1, 15.6 min.

^{1}H, HOESY and nOe spectra of **333** (298 K, key ^{1}H-^{1}H correlation in red):



Data for 342

^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 7.91 (dd, J = 9.1, 6.0 Hz, 1H, H_7), 6.98 (dd, J = 9.1, 7.3 Hz, 1H, H_6), 4.02 (s, 3H, H_{10}), 3.65-3.51 (m, 2H, H_2 and $H_{2'}$), 1.59 (d, J = 6.9 Hz, 6H, H_1), 1.18 (d, J = 63.6 Hz, 3H, $H_{1'A}$), 1.14 (d, J = 6.6 Hz, 3H, $H_{1'B}$);

^{13}C NMR (126 MHz, $CDCl_3$) δ_C = 160.8 (d, J = 257.0 Hz, Quat, C_5), 160.7 (Quat, C_3), 151.9 (d, J = 8.6 Hz, Quat, C_9), 140.4 (d, J = 3.2 Hz, Quat), 126.5 (d, J = 11.0 Hz, CH, C_7), 124.3 (d, J = 22.5 Hz, Quat), 111.9 (d, J = 23.8 Hz, CH, C_6), 64.0 (CH_3, C_{10}), 51.7 (CH, C_2), 46.3 (CH, $C_{2'}$), 20.7 (CH_3, $C_{1'}$), 20.3 (CH_3, C_{1A}), 20.1 (CH_3, C_{1B});

^{19}F NMR (470 MHz, $CDCl_3$) δ_F = -105.7;

HRMS (ESI^+) calculated for $C_{14}H_{19}FN_2NaO_4$ = 321.1221, mass found = 321.1223.

Data for 343

^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 8.68 (d, J = 7.6 Hz, 1H, H_7), 4.11 (s, 3H, H_{10}), 3.65-3.51 (m, 2H, H_2 and $H_{2'}$), 1.57 (d, J = 6.6 Hz, 6H, H_1), 1.21 (d, J = 6.6 Hz, 3H, $H_{1'A}$), 1.21 (d, J = 6.6 Hz, 3H, $H_{1'B}$);

^{13}C NMR (126 MHz, $CDCl_3$) δ_C = 158.5 (Quat, C_3), 155.2 (Quat, C_9), 154.2 (d, J = 282.4 Hz, Quat, C_5), 139.0 (d, J = 2.7 Hz, Quat, C_{Ar}), 132.2 (d, J = 9.5 Hz, Quat, C_{Ar}), 126.0 (d, J = 22.7 Hz, Quat, C_{Ar}), 132.2 (CH, C_7), 64.2 (CH_3, C_{10}), 52.1 (CH, C_2), 46.8 (CH, $C_{2'}$), 20.8 (CH_3, $C_{1'A}$), 20.7 (CH_3, $C_{1'B}$), 20.3 (CH_3, C_{1A}), 19.9 (CH_3, C_{1B});

^{19}F NMR (470 MHz, $CDCl_3$) δ_F = -110.0;

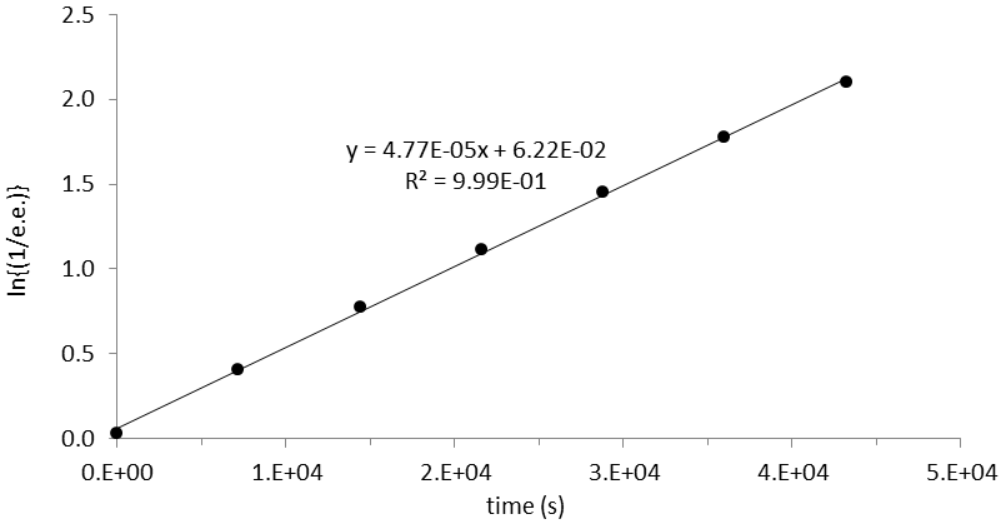
HRMS (ESI^+) calculated for $C_{14}H_{18}FN_3NaO_6$ = 366.1072, mass found = 366.1082.

Experiment to determine the rate of racemization of 333

A solution of **333** (98:2 e.r.) in 1:4 IPA:hexane was allowed to stand at room temperature. 50 μL aliquots were removed over the course of 12 h and the enantioenrichment was analysed by chiral HPLC (Chiralpak ADH, 20 % IPA, 80 % hexane, 1.0 mL/min, λ= 221 nm).

time / h	t / s	% major ent.	% minor ent.	ln{1/e.e.}
0.00	0	98.47	1.53	0.031
2.00	7200	83.22	16.78	0.409
4.00	14400	73.13	26.87	0.771
6.00	21600	66.38	33.62	1.116
8.00	28800	61.72	38.28	1.451
10.00	36000	58.47	41.53	1.775
12.00	43200	56.11	43.89	2.102

A plot of ln(1/e.e.) *vs* time resulted in a straight line with a gradient of 4.77 x 10^{-5} s^{-1}.



$$ln\left\{\frac{1}{e.e.}\right\} = 2k_{ent}t + C$$

$k_{rac} = 2k_{ent} = 4.77 \times 10^{-5}\ s^{-1}$

$t_{1/2}^{rac} = \ln 2 / k_{rac} = 4.0$ h

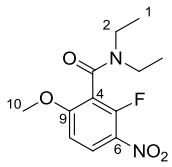
Employing the Eyring equation:

$$\Delta G^{\ddagger} = -RT\ ln\left\{\frac{k_{ent} \times h}{k_B \times T}\right\}$$

= 9.94 x 10^4 J mol^{-1} (at 298 K)

= 23.8 kcal mol^{-1} (at 298 K)

***N*,*N*-diethyl-2-fluoro-6-methoxy-3-nitrobenzamide, 334**



Concentrated sulfuric acid (10 mL) was stirred at 0 °C and concentrated nitric acid (3.3 mL) was added. **331** (500 mg, 2.22 mmol) was added in one portion and the resulting solution was stirred at 0 °C for 15 minutes. After this time, the reaction mixture was poured onto crushed ice (c.a. 30 g) and then allowed to warm to room temperature. The resulting heterogeneous mixture was extracted three times with dichloromethane. The combined organic extracts were dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. Purification of the residue *via* column chromatography eluting with 1:1 ethyl acetate/petrol 40-60 afforded the title compound **334** as yellow oil (321 mg, 54 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 8.12 (t, J = 8.9 Hz, 1H, H_7), 6.81 (dd, J = 9.4, 1.1 Hz, 1H, H_8), 3.92 (s, 3H, H_{10}), 3.61 (dq, J = 14.2, 6.9 Hz, 1H, H_{2A}), 3.50 (dq, J = 14.2, 6.9 Hz, 1H, H_{2B}), 3.14 (q, J = 7.2 Hz, 2H, $H_{2'}$), 1.22 (t, J = 7.1 Hz, 3H, H_1), 1.05 (t, J = 7.2 Hz, 3H, $H_{1'}$);

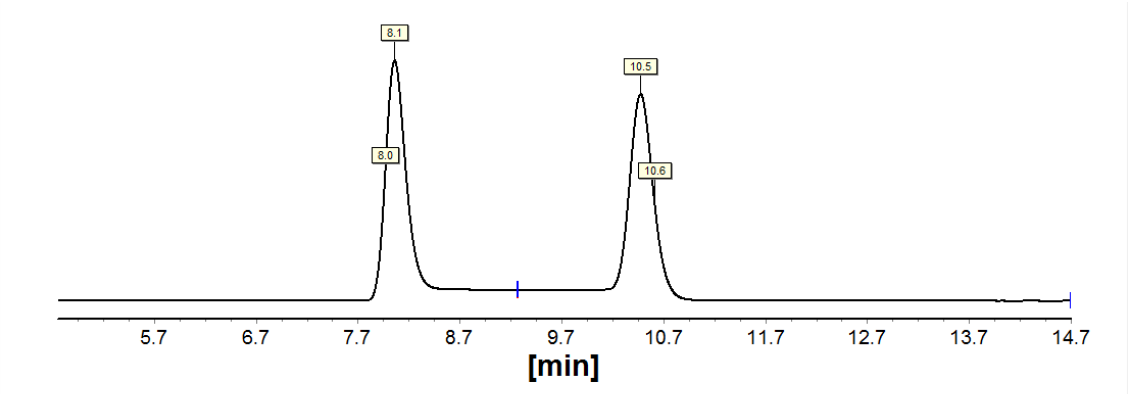
^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 161.1 (d, J = 8.7 Hz, Quat, C_9), 161.0 (d, J = 1.6 Hz, Quat, C_3), 152.8 (d, J = 263.8 Hz, Quat, C_5), 131.1 (d, J = 7.2 Hz, Quat, C_6), 127.9 (CH, C_7), 117.0 (d, J = 22.3 Hz, Quat, C_4), 106.7 (d, J = 3.2 Hz, CH, C_8), 56.9 (CH_3, C_{10}), 43.1 (CH_2, C_2), 39.4 (CH_2, $C_{2'}$), 14.0 (CH_3, $C_{1'}$), 12.7 (CH_3, C_1);

^{19}F NMR (377 MHz, $CDCl_3$) δ_F = -118.3;

FTIR (neat) ν/cm^{-1} = 2980, 1640, 1607, 1597, 1524, 1485, 1461, 1434, 1349, 1294, 1084;

HRMS (ESI^+) calculated for $C_{12}H_{15}FN_2NaO_4$ = 293.0908, mass found = 293.0895.

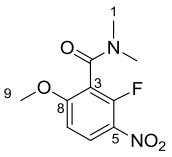
Chiral HPLC (Chiralpak ADH, 20 % IPA, 80 % hexane, 1.0 mL/min, λ = 245 nm, 20 μL injection) τ_R = 8.1, 10.5 min. The raw data was analysed using DCXplotter to obtain thermodynamic parameters shown below.



tR1 [min]	tR2 [min]	wh1 [s]	wh2 [s]	h1 [%]	hp [%]	h2 [%]	A1	A2
8.073	10.487	11.6	16.0	100.00	4.49	86.14	49.79	50.21

k1 [1/s]
4.910E-0004

2-Fluoro-6-methoxy-*N*,*N*-dimethyl-3-nitrobenzamide, 335



Concentrated sulfuric acid (10 mL) was stirred at 0 °C and concentrated nitric acid (3.3 mL) was added. **332** (500 mg, 2.54 mmol) was added in one portion and the resulting solution was stirred at 0 °C for 15 minutes. After this time, the reaction mixture was poured onto crushed ice (c.a. 30 g) and then allowed to warm to room temperature. The resulting heterogeneous mixture was extracted three times with dichloromethane. The combined organic extracts were dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. Purification of the residue *via* column chromatography eluting with 1:1 ethyl acetate/petrol 40-60 afforded the title compound **335** as yellow oil which solidified upon standing to form a yellow solid (294 mg, 48 %).

Melting point: 139-141 ^{o}C (ethyl acetate/petrol 40-60);

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 8.09 (t, J = 8.9 Hz, 1H, H_6), 6.78 (dd, J = 9.4, 1.1 Hz, 1H, H_7), 3.90 (s, 3H, H_9), 3.08 (s, 3H, H_1), 2.84 (s, 3H, $H_{1'}$);

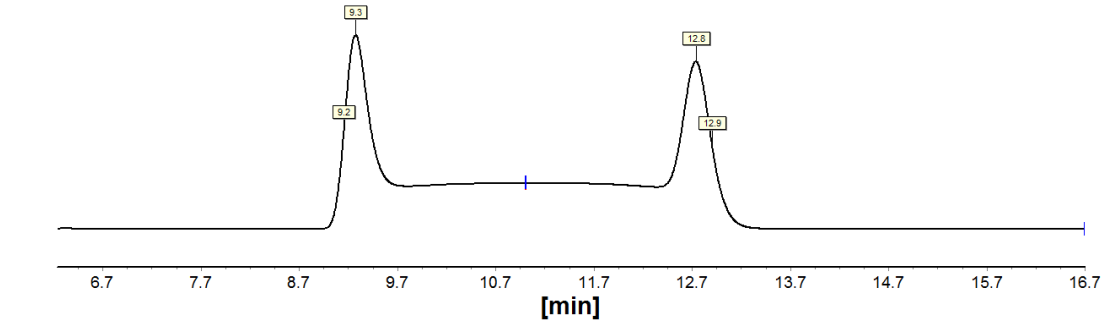
^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 161.8 (d, J = 1.6 Hz, Quat, C_2), 161.2 (d, J = 8.7 Hz, Quat, C_8), 152.9 (d, J = 263.8 Hz, Quat, C_4), 131.1 (d, J = 7.9 Hz, Quat, C_5), 128.1 (CH, C_6), 116.5 (d, J = 22.3 Hz, Quat, C_3), 106.7 (d, J = 3.2 Hz, CH, C_7), 57.0 (CH_3, C_9), 37.7 (CH_3, $C_{1'}$), 34.7 (CH_3, C_1);

^{19}F NMR (377 MHz, $CDCl_3$) δ_F = -118.0;

FTIR (neat) ν/cm^{-1} = 2945, 1645, 1597, 1524, 1485, 1401, 1349, 1293, 1230, 1106, 1081;

HRMS (ESI$^+$) calculated for $C_{10}H_{11}FN_2NaO_4$ = 265.0595, mass found = 265.0603.

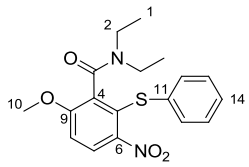
Chiral HPLC (Chiralpak ADH, 20 % IPA, 80 % hexane, 1.0 mL/min, λ = 245 nm, 20 µL injection) τ_R = 9.3, 12.8 min. The raw data was analysed using DCXplotter to obtain thermodynamic parameters shown below.



tR1 [min]	tR2 [min]	wh1 [s]	wh2 [s]	h1 [%]	hp [%]	h2 [%]	A1	A2
9.320	12.783	14.8	20.0	100.00	23.68	86.43	49.35	50.65

k1 [1/s]
1.807E-0003

***N*,*N*-Diethyl-6-methoxy-3-nitro-2-(phenylthio)benzamide, 336**



Asymmetric: According to **General Procedure E** with **334** (50 mg, 0.19 mmol), carbon tetrachloride (1.9 mL), *N*-benzylquininium chloride (8 mg, 0.019 mmol), thiophenol (20.9 μL, 0.20 mmol), 33 % w/w aqueous potassium carbonate (127 μL, 0.93 mmol) at room temperature for 24 hours. The crude residue was dissolved in $CDCl_3$ (0.6 mL) and dibenzyl ether (37 mg, 0.19 mmol) was added as an internal standard. ^{1}H NMR of this solution indicated the title compound **336** was present in 47 % NMR yield along with 42 % NMR yield of recovered **334**. An analytical HPLC sample of a mixture of **336** and **334** was obtained by small scale preparative TLC (1:1 ethyl acetate/petrol 40-60) which indicated both **336** and **334** to be racemic.

Racemic: According to **General Procedure F** with **334** (50 mg, 0.19 mmol), toluene (1.9 mL), tetrabutylammonium bromide (6 mg, 0.019 mmol), thiophenol (20.9 μL, 0.20 mmol), 50 % w/w aqueous potassium hydroxide (0.05 mL, 0.93 mmol) at room temperature for 16 hours. Purification *via* column chromatography eluting with 3:2 ethyl acetate/petrol 40-60 afforded the title compound *rac*-**336** as a yellow solid (54 mg, 81 %). An analytical quantity of enantioenriched **336** (99:1 e.r.) was obtained by semi-preparative HPLC (Chiralpak ADH, 20 % IPA, 80 % hexane, 0.5 mL/min).

Melting point: 122-123 ^{o}C (ethyl acetate/petrol 40-60);

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 7.89 (d, J = 9.0 Hz, 1H, H_7), 7.22-7.18 (m, 2H, H_{12}), 7.17-7.07 (m, 3H, H_{13} and H_{14}), 6.91 (d, J = 9.0 Hz, 1H, H_8), 3.84 (s, 3H, H_{10}), 3.64 (dq, J = 14.2, 6.9 Hz, 1H, H_{2A}),

3.35 (dq, J = 14.2, 6.9 Hz, 1H, H_{2B}), 3.03 (dq, J = 14.4, 7.2 Hz, 1H, $H_{2'A}$), 2.91 (dq, J = 14.4, 7.2 Hz, 1H, $H_{2'B}$), 1.15 (t, J = 7.1 Hz, 3H, H_1), 0.97 (t, J = 7.2 Hz, 3H, $H_{1'}$);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 164.4 (Quat, C_3), 158.3 (Quat, C_{Ar}), 146.1 (Quat, C_{Ar}), 134.3 (Quat, C_{Ar}), 133.6 (Quat, C_{Ar}), 129.9 (CH, C_{12}), 129.0 (CH, C_{13}), 127.2 (CH, C_{14}), 127.0 (Quat, C_{Ar}), 127.0 (CH, C_7), 111.0 (CH, C_8), 56.4 (CH, C_{10}), 42.7 (CH, $C_{2'}$), 38.8 (CH, C_2), 13.8 (CH, $C_{1'}$), 12.5 (CH, C_1);

FTIR (neat) ν/cm^{-1} = 2978, 2938, 1632, 1569, 1523, 1459, 1431, 1345, 1268;

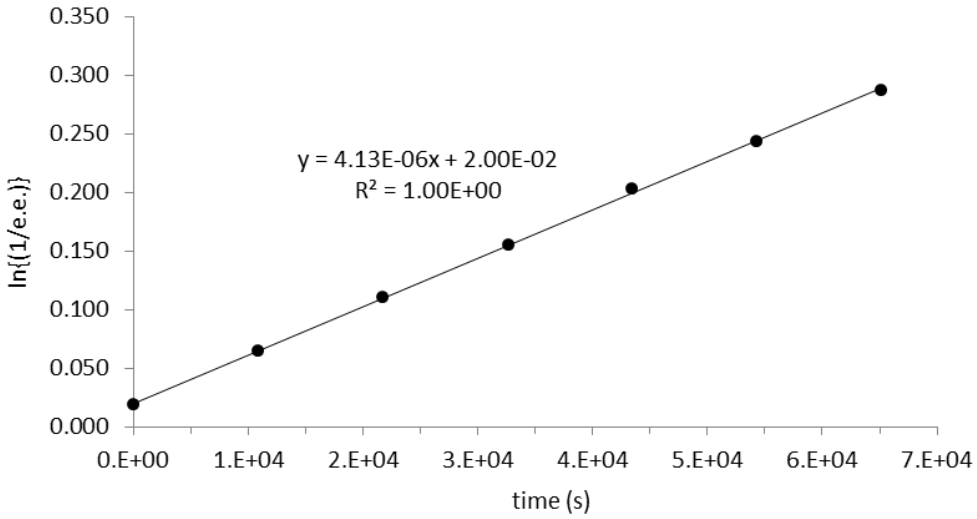
HRMS (ESI^+) calculated for $C_{12}H_{15}FN_2NaO_4$ = 293.0908, mass found = 293.0895.

Scheme 5.17 – Experiment to determine the rate of racemization of 336

A solution of **336** (99:1 e.r.) in 1:8 IPA/hexane was allowed to stand at room temperature. 50 μL aliquots were removed over the course of 18 h and the enantioenrichment was analysed by chiral HPLC (Chiralpak ADH, 20 % IPA, 80 % hexane, 1.0 mL/min, λ = 254 nm, 50 μL injection, τ_R = 19.9, 21.8 min).

time / h	t / s	% major ent.	% minor ent.	ln{1/e.e.}
0.00	0	99.08	0.92	0.019
3.02	10878	96.86	3.14	0.065
6.05	21774	94.79	5.21	0.110
9.07	32652	92.80	7.20	0.155
12.07	43452	90.81	9.19	0.203
15.10	54348	89.20	10.80	0.243
18.10	65154	87.53	12.47	0.287

A plot of ln(1/e.e.) *vs* time resulted in a straight line with a gradient of 4.13×10^{-6} s^{-1}.



$$ln\left\{\frac{1}{e.e.}\right\} = 2k_{ent}t + C$$

$k_{rac} = 2k_{ent} = 4.13 \times 10^{-6}\ s^{-1}$

$t_{1/2}^{rac} = \ln 2 / k_{rac} = 46.6$ h

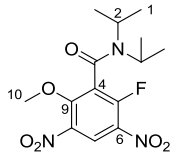
Employing the Eyring equation:

$$\Delta G^{\ddagger} = -RT\ ln\left\{\frac{k_{ent} \times h}{k_B \times T}\right\}$$

$= 1.05 \times 10^{5}$ j mol^{-1} (at 298 K)

$= 25.2$ kcal mol^{-1} (at 298 K)

2-Fluoro-*N*,*N*-diisopropyl-6-methoxy-3,5-dinitrobenzamide, 337



Preparation from 333: Concentrated sulfuric acid (1.8 mL) was stirred at 0 °C and concentrated nitric acid (0.60 mL) was added. **333** (100 mg, 0.34 mmol) was added in one portion and the resulting solution was warmed to room temperature and stirred for 1 hour. After this time, the reaction mixture was poured onto crushed ice (c.a. 5 g) and then allowed

to warm to room temperature. The resulting heterogeneous mixture was extracted three times with dichloromethane. The combined organic extracts were dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. Purification of the residue *via* column chromatography eluting with 3:7 ethyl acetate/petrol 40-60 afforded the title compound **337** as colourless oil (134 mg, quant). An analytical quantity of enantioenriched **337** (98:2 e.r.) was obtained by semi-preparative HPLC (Chiralpak ADH, 10 % IPA, 90 % hexane, 1 mL/min).

Preparation from 330: Concentrated sulfuric acid (1.8 mL) was stirred at 0 ^{o}C and concentrated nitric acid (0.60 mL) was added. **330** (100 mg, 0.39 mmol) was added in one portion and the resulting solution stirred at 0 ^{o}C for 5 minutes and then warmed to room temperature and stirred for 1 hour. After this time, the reaction mixture was poured onto crushed ice (c.a. 5 g) and then allowed to warm to room temperature. The resulting heterogeneous mixture was extracted three times with dichloromethane. The combined organic extracts were dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. Purification of the residue *via* column chromatography eluting with 2:8 ethyl acetate/petrol 40-60 afforded the title compound **337** as colourless oil (110 mg, 81 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 8.67 (d, J = 7.8 Hz, 1H, H_7), 4.01 (s, 3H, H_{10}), 3.67-3.51 (m, 2H, H_2 and $H_{2'}$), 1.51 (d, J = 6.8 Hz, 6H, H_1), 1.18 (d, J = 6.4 Hz, 3H, $H_{1'A}$), 1.16 (d, J = 5.9 Hz, 3H, $H_{1'B}$);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 160.1 (Quat, C_3), 155.5 (d, J = 7.9 Hz, Quat, C_9), 154.1 (d, J = 274.2 Hz, Quat, C_5), 138.6 (d, J = 2.4 Hz, Quat, C_{Ar}), 132.2 (d, J = 7.9 Hz, Quat, C_{Ar}), 124.4 (CH, C_7), 124.3 (d, J = 22.6 Hz, Quat, C_{Ar}), 64.3 (CH_3, C_{10}), 52.9 (CH, $C_{2'}$), 47.7 (CH, C_2), 20.6 (CH_3, $C_{1'A}$), 20.5 (CH_3, $C_{1'B}$), 19.9 (CH_3, C_{1A}), 19.8 (CH_3, C_{1B});

^{19}F NMR (376 MHz, $CDCl_3$) δ_F = -109.7 (d, J = 8.0 Hz);

FTIR (neat) ν/cm^{-1} = 2978, 1599, 1538, 1473, 1331, 1288, 1076;

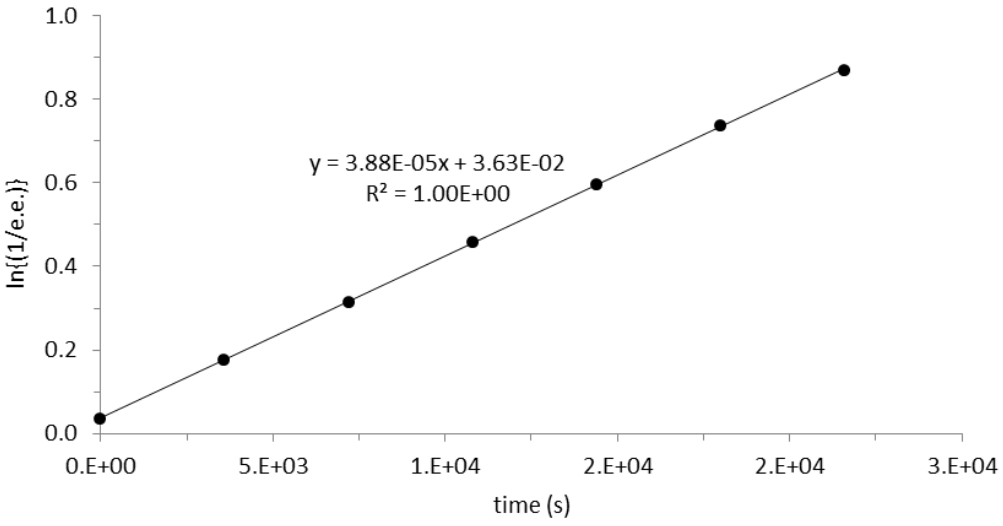
HRMS (ESI^+) calculated for $C_{14}H_{19}O_6N_3F$ = 344.1258, mass found = 344.1253.

Experiment to determine the rate of racemization of 337

A solution of **337** (98:2 e.r.) in 1:9 IPA/hexane was allowed to stand at room temperature. 50 μL aliquots were removed over the course of 6 h and the enantioenrichment was analysed by chiral HPLC (Chiralpak ADH, 10 % IPA, 90 % hexane, 1.0 mL/min, λ = 254 nm, 50 μL injection, τ_R = 8.1, 9.3 min).

time / h	t / s	% major ent.	% minor ent.	ln{1/e.e.}
0.00	0	98.32	1.68	0.034
1.00	3.60E+03	91.94	8.06	0.176
2.00	7.20E+03	86.50	13.50	0.315
3.00	1.08E+04	81.62	18.38	0.458
4.00	1.44E+04	77.57	22.43	0.595
5.00	1.80E+04	73.94	26.06	0.736
6.00	2.16E+04	70.97	29.03	0.869

A plot of ln(1/e.e.) *vs* time resulted in a straight line with a gradient of 3.88 x 10^{-5} s^{-1}.



$$ln\left\{\frac{1}{e.e.}\right\} = 2k_{ent}t + C$$

$k_{rac} = 2k_{ent} = 3.88 \times 10^{-5}\ s^{-1}$

$t_{1/2}^{rac} = \ln 2 / k_{rac} = 4.97$ h

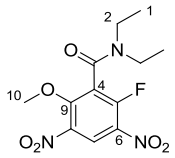
Employing the Eyring equation:

$$\Delta G^{\ddagger} = -RT\ ln\left\{\frac{k_{ent} \times h}{k_B \times T}\right\}$$

$= 9.99 \times 10^{4}$ J mol^{-1} (at 298 K)

= 23.9 kcal mol^{-1} (at 298 K)

_N_,_N_-Diethyl-2-fluoro-6-methoxy-3,5-dinitrobenzamide, 338



Concentrated sulfuric acid (1.3 mL) was stirred at 0 ^{o}C and concentrated nitric acid (0.43 mL) was added. **334** (72 mg, 0.27 mmol) was added in one portion and the resulting solution was warmed to room temperature and stirred for 1 hour. After this time, the reaction mixture was poured onto crushed ice (c.a. 5 g) and then allowed to warm to room temperature. The resulting heterogeneous mixture was extracted three times with dichloromethane. The combined organic extracts were dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. Purification of the residue *via* column chromatography eluting with 3:7 ethyl acetate/petrol 40-60 afforded the title compound **338** as colourless oil (73 mg, 87 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 8.63 (d, J = 7.8 Hz, 1H, H_7), 4.01 (s, 3H, H_{10}), 3.61 (dq, J = 14.4, 6.9 Hz, 1H, H_{2A}), 3.49 (dq, J = 14.2, 6.9 Hz, 1H, H_{2B}), 3.14 (q, J = 7.3 Hz, 2H, $H_{2'}$), 1.22 (t, J = 7.1 Hz, 3H, H_1), 1.09 (t, J = 7.2 Hz, 3H, $H_{1'}$);

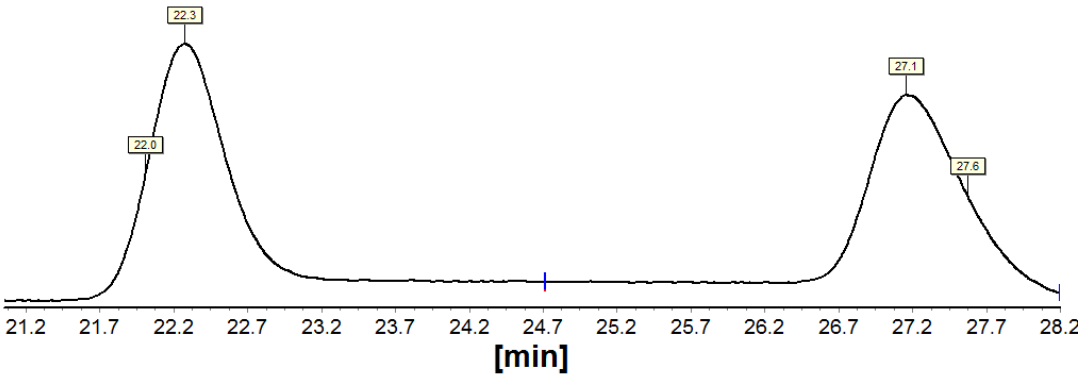
^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 159.2 (Quat, C_3), 155.4 (d, J = 8.7 Hz, Quat, C_9), 154.3 (d, J = 273.4 Hz, Quat, C_5), 138.8 (Quat, C_{Ar}), 132.1 (d, J = 11.1 Hz, Quat, C_{Ar}), 124.4 (d, J = 22.3 Hz, Quat, C_{Ar}), 123.7 (CH, C_7), 63.9 (CH_3, C_{10}), 43.4 (CH_2, $C_{2'}$), 39.8 (CH_2, C_2), 13.9 (CH_3, $C_{1'}$), 12.5 (CH_3, C_1);

^{19}F NMR (376 MHz, $CDCl_3$) δ_F = -109.0 (d, J = 6.9 Hz);

FTIR (neat) ν/cm^{-1} = 2980, 1644, 1600, 1537, 1475, 1461, 1437, 1340, 1315, 1295, 1075;

HRMS (ESI$^+$) calculated for $C_{12}H_{15}O_6N_3F$ = 316.0945, mass found = 316.0940.

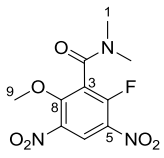
Chiral HPLC (Chiralpak IC, 30 % IPA, 70 % hexane, 1.0 mL/min, λ = 254 nm, 10 µL injection) τ_R = 22.3, 27.1 min. The raw data was analysed using DCXplotter to obtain thermodynamic parameters shown below.



tR1 [min]	tR2 [min]	wh1 [s]	wh2 [s]	h1 [%]	hp [%]	h2 [%]	A1	A2
22.263	27.143	31.6	50.0	100.00	5.76	78.17	51.73	48.27

k1 [1/s]
1.775E-0004

2-Fluoro-6-methoxy-*N*,*N*-dimethyl-3,5-dinitrobenzamide, 339



Concentrated sulfuric acid (0.9 mL) was stirred at 0 °C and concentrated nitric acid (0.3 mL) was added. **335** (50 mg, 0.21 mmol) was added in one portion and the resulting solution was warmed to room temperature and stirred for 1 hour. After this time, the reaction mixture was poured onto crushed ice (c.a. 5 g) and then allowed to warm to room temperature. The resulting heterogeneous mixture was extracted three times with dichloromethane. The combined organic extracts were dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. Purification of the residue *via* column chromatography eluting with 1:1 ethyl acetate/petrol 40-60 afforded the title compound **339** as yellow oil (46 mg, 78 %).

Melting point: 96-98 °C (ethyl acetate/petrol 40-60);

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 8.63 (d, J = 7.8 Hz, 1H, H_6), 4.00 (s, 3H, H_9), 3.13 (s, 3H, H_1), 2.91 (s, 3H, $H_{1'}$);

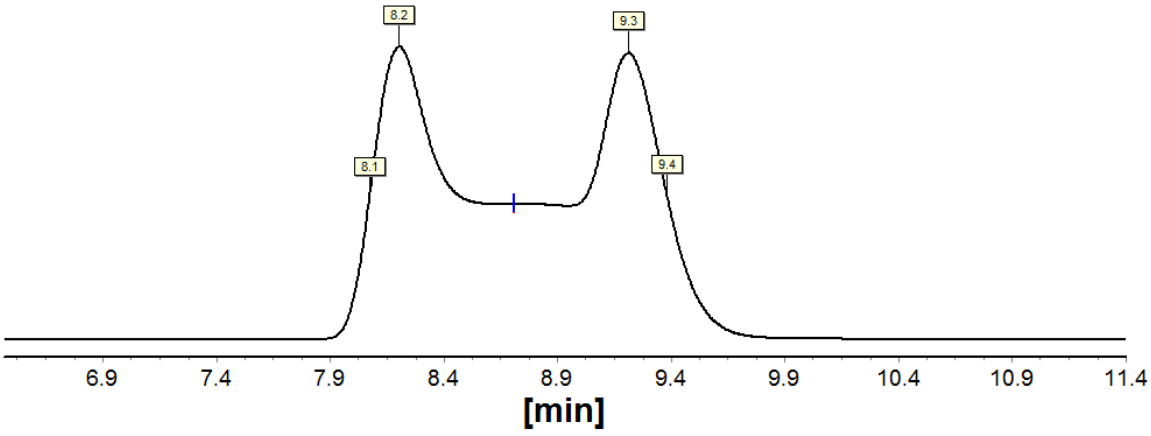
^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 160.0 (Quat, C_2), 155.5 (d, J = 8.4 Hz, Quat, C_8), 154.3 (d, J = 273.3 Hz, Quat, C_4), 138.7 (Quat, C_{Ar}), 131.9 (d, J = 9.1 Hz, Quat, C_{Ar}), 124.0 (CH, C_6), 123.4 (d, J = 22.0 Hz, Quat, C_{Ar}), 63.6 (CH_3, C_9), 38.0 (CH_3, C_1), 35.1 (CH_3, $C_{1'}$);

^{19}F NMR (376 MHz, $CDCl_3$) δ_F = -109.0 (d, J = 6.9 Hz);

FTIR (neat) ν/cm^{-1} = 2940.1, 1651, 1599, 1536, 1414, 1339, 1291, 1076;

HRMS (ESI^+) calculated for $C_{12}H_{15}FN_2NaO_4$ = 288.0632, mass found = 288.0627.

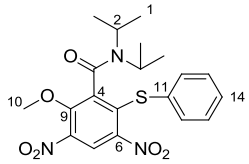
Chiral HPLC (Chiralpak ADH, 20 % IPA, 80 % hexane, 1.0 mL/min, λ = 254 nm, 10 μL injection) τ_R = 8.2, 9.3 min. The raw data was analysed using DCXplotter to obtain thermodynamic parameters shown below.



tR1 [min]	tR2 [min]	wh1 [s]	wh2 [s]	h1 [%]	hp [%]	h2 [%]	A1	A2
8.247	9.257	15.6	20.4	100.00	46.29	97.81	47.87	52.13

k1 [1/s]
1.439E-0003

***N*,*N*-Diisopropyl-2-methoxy-3,5-dinitro-6-(phenylthio)benzamide, 340**



Asymmetric (stoichiometric in thiophenol): According to **General Procedure E** with **337** (50 mg, 0.15 mmol), carbon tetrachloride (1.5 mL), *N*-benzylquininium chloride (7 mg, 0.015 mmol), thiophenol (16.5 μL, 0.16 mmol), 33 % w/w aqueous potassium carbonate (100 μL, 0.73 mmol) at room temperature for 1 hour. Purification *via* column chromatography eluting with 1:4 ethyl acetate/petrol 40-60 afforded the title compound **340** as a yellow solid (47 mg, 74 %, 50:50 e.r.).

Asymmetric (sub-stoichiometric in thiophenol): According to **General Procedure E** with **337** (50 mg, 0.15 mmol), carbon tetrachloride (1.5 mL), *N*-benzylquininium chloride (7 mg, 0.015 mmol), thiophenol (7.5 μL, 0.073 mmol), 33 % w/w aqueous potassium carbonate

(100 μL, 0.73 mmol) at room temperature for 1 hour. The crude residue was dissolved in $CDCl_3$ (0.6 mL) and dibenzyl ether (29 mg, 0.15 mmol) was added as an internal standard. ^{1}H NMR of this solution indicated the title compound **340** was present in 42 % NMR yield along with 38 % NMR yield of recovered **337**. An analytical HPLC sample of a mixture of **337** and **340** was obtained by small scale preparative TLC (1:4 ethyl acetate/petrol 40-60) which indicated both **337** and **340** to be racemic.

Racemic: According to **General Procedure F** with **337** (79 mg, 0.23 mmol), toluene (2.0 mL), tetrabutylammonium bromide (7 mg, 0.02 mmol), thiophenol (23.0 μL, 0.22 mmol), 50 % w/w aqueous potassium hydroxide (57 μL, 1.0 mmol) at room temperature for 2 hours. Purification *via* column chromatography eluting with 1:4 ethyl acetate/petrol 40-60 afforded the title compound *rac*-**340** as a yellow solid (93 mg, 93 %). An analytical quantity of enantioenriched **340** (> 99:1 e.r.) was obtained by semi-preparative HPLC (Chiralpak ADH, 10 % IPA, 90 % hexane, 1 mL/min).

Melting point: 182-184 ^{o}C (ethyl acetate/petrol 40-60);

^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 8.17 (s, 1H, H_7), 7.30-7.16 (m, 5H, H_{12}, H_{13} and H_{14}), 4.00 (s, 3H, H_{10}), 3.59-3.46 (m, 2H, H_2 and $H_{2'}$), 1.53 (d, J = 6.6 Hz, 3H, H_{1A}), 1.51 (d, J = 6.8 Hz, 3H, H_{1B}), 1.15 (d, J = 6.6 Hz, 6H, $H_{1'}$);

^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 162.3 (Quat, C_3), 151.8 (Quat, C_{Ar}), 146.6 (Quat, C_{Ar}), 142.1 (Quat, C_{Ar}), 141.9 (Quat, C_{Ar}), 134.2 (Quat, C_{Ar}), 131.8 (Quat, C_{Ar}), 131.3 (CH, C_{12}), 129.5 (CH, C_{13}), 128.7 (CH, C_{14}), 122.1 (CH, C_7), 64.6 (CH_3, C_{10}), 52.1 (CH, $C_{2'}$), 46.6 (CH, C_2), 21.0 (CH_3, $C_{1'A}$), 20.9 (CH_3, $C_{1'B}$), 20.3 (CH_3, C_{1A}), 20.0 (CH_3, C_{1B});

FTIR (neat) ν/cm^{-1} = 2976, 1635, 1578, 1534, 1452, 1322, 1249;

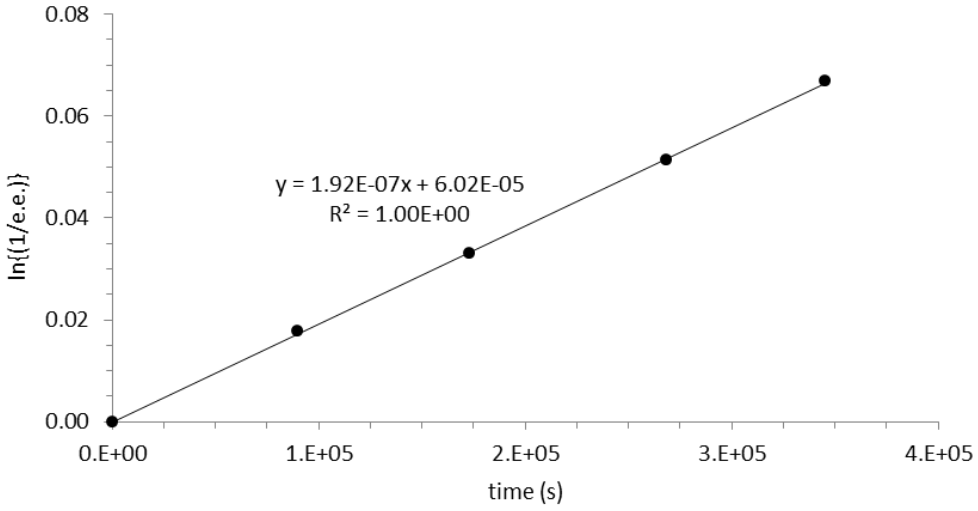
HRMS (ESI$^+$) calculated for $C_{20}H_{23}O_6N_3NaS$ = 456.1200, mass found = 456.1195.

Experiment to determine the rate of racemization of 340

A solution of **340** (> 99:1 e.r.) in IPA was allowed to stand at room temperature. 50 μL aliquots were removed over the course of 4 days and the enantioenrichment was analysed by chiral HPLC (Chiralpak ADH, 10 % IPA, 90 % hexane, 1.0 mL/min, λ = 254 nm, 50 μL injection, τ_R = 7.5, 15.9 min).

time / h	t / s	% major ent.	% minor ent.	ln{1/e.e.}
0.00	0.00E+00	100.00	0.00	0.000
25.00	9.00E+04	99.12	0.88	0.018
48.00	1.73E+05	98.38	1.62	0.033
74.50	2.68E+05	97.50	2.50	0.051
96.00	3.46E+05	96.77	3.23	0.067

A plot of ln(1/e.e.) *vs* time resulted in a straight line with a gradient of 1.92 x 10^{-7} s^{-1}.



$$ln\left\{\frac{1}{e.e.}\right\} = 2k_{ent}t + C$$

k_{rac} = 1.92 x 10^{-7} s^{-1}

$t_{1/2}^{rac}$ = ln2/ k_{rac} = 41.7 d

Employing the Eyring equation:

$$\Delta G^{\ddagger} = -RT\ ln\left\{\frac{k_{ent} \times h}{k_B \times T}\right\}$$

= 1.13 x 10^5 J mol^{-1} (at 298 K)

= 27.0 kcal mol^{-1} (at 298 K)

8. References

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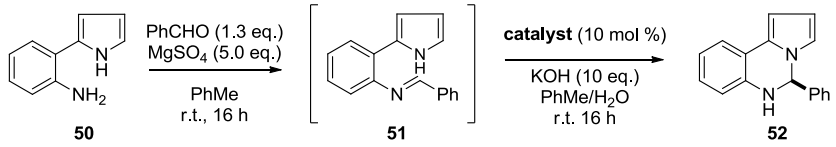
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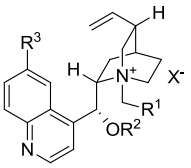
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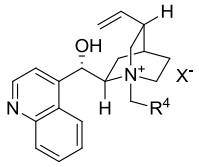
9. Appendix

Appendix A – Catalyst optimization

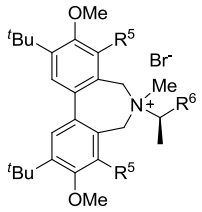




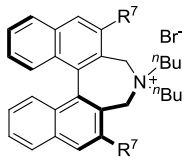
18: R^1 = Ph; R^2 = H; R^3 = H; X = Cl: **32:68 e.r.**
53: R^1 = Ph; R^2 = allyl; R^3 = H; X = Br: **47:53 e.r.**
54: R^1 = 9-Anth; R^2 = Me; R^3 = H; X = Br: **51:49 e.r.**
55: R^1 = Ph; R^2 = H; R^3 = OMe; X = Cl: **34:66 e.r.**
56: R^1 = 4-NO_2-C_6H_4; R^2 = H; R^3 = H; X = Br: **27:73 e.r.**
57: R^1 = 3-F-C_6H_4; R^2 = H; R^3 = H; X = Br: **30:70 e.r.**
58: R^1 = 1-naphthyl; R^2 = H; R^3 = H; X = Br: **34:66 e.r.**
59: R^1 = 2-naphthyl; R^2 = H; R^3 = H; X = Br: **34:66 e.r.**
362: R^1 = 4-CF_3-C_6H_4; R^2 = H; R^3 = H; X = Br: **29:71 e.r.**
363: R^1 = 9-Anth; R^2 = H; R^3 = H; X = Cl: **23:77 e.r.**
364: R^1 = Ph; R^2 = Bn; R^3 = OH; X = Br: **48:52 e.r.**



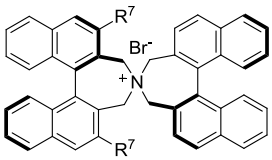
60: R^4 = Ph; X = Cl: **80:20 e.r.**
61: R^4 = 4-NO_2-C_6H_4; X = Br: **78:22 e.r.**
12: R^4 = 4-CF_3-C_6H_4; X = Br: **74:26 e.r.**
62: R^4 = 3,5-$(CF_3)_2$-C_6H_3; X = Br: **64:36 e.r.**
63: R^4 = 4-F-C_6H_4; X = Br: **76:24 e.r.**
64: R^4 = 3-F-C_6H_4; X = Br: **76:24 e.r.**
65: R^4 = 2,3,4-F_3-C_6H_2; X = Br: **74:26 e.r.**
365: R^4 = C_6F_5; X = Br: **56:44 e.r.**



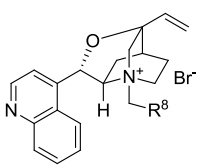
66: R^5 = 3,5-$(CF_3)_2$-C_6H_3; R^6 = 2-naphthyl: **23:77 e.r.**



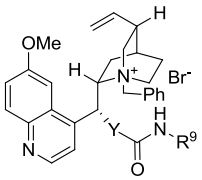
67: R^7 = 3,4,5-F_3-Ph: **29:71 e.r.**



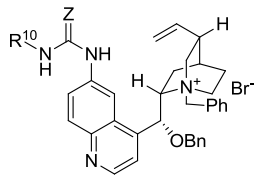
366: R^7 = 3,4,5-F_3-Ph: **52:48 e.r.**



367: R^8 = Ph: **46:54 e.r.**
368: R^8 = 4-NO_2-Ph: **46:54 e.r.**

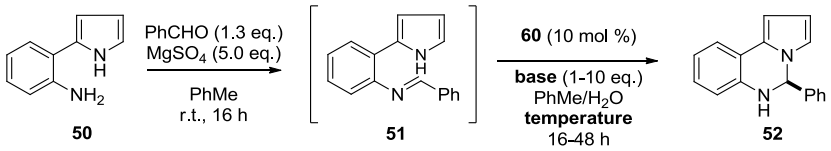


369: Y = O; R^9 = 4-NO_2-C_6H_4: **31:69 e.r.**
370: Y = NH; R^9 = 3,5-$(CF_3)_2C_6H_3$: **54:46 e.r.**



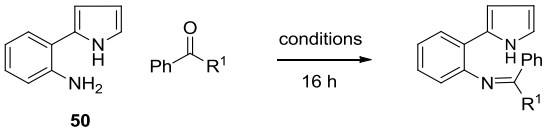
371: Z = O; R^{10} = 4-$NO_2C_6H_4$: **51:49 e.r.**
372: Z = S; R^{10} = 3,5-$(CF_3)_2C_6H_3$: **49:51 e.r.**

Appendix B – Base and temperature optimization



Entry	Temp. / °C	Base [eq.]	Time	Ratio **52**:**51** (^{1}H NMR)	e.r.
1	r.t.	KOH (50 % aq.) [10]	16 h	> 95:5	80:20
2	r.t.	KOH (s) [1]	16 h	> 95:5	56:44
3	r.t.	CsOH (50 % aq.) [10]	16 h	> 95:5	80:20
4	r.t.	$CsOH.H_2O$ (s) [1]	16 h	> 95:5	56:44
5	r.t.	K_2CO_3 (33 % aq.) [10]	16 h	> 95:5	80:20
6	r.t.	K_2CO_3 (s) [1]	16 h	< 5:95	n.d.
7	-15 °C	KOH (50 % aq.) [10]	48 h	> 95:5	86:14
8	-15 °C	KOH (s) [1]	48 h	> 95:5	55:45
9	-15 °C	CsOH (50 % aq.) [10]	48 h	> 95:5	85:15
10	-15 °C	$CsOH.H_2O$ (s) [1]	48 h	> 95:5	51:49
11	-15 °C	K_2CO_3 (33 % aq.) [10]	48 h	< 5:95	n.d.
12	-15 °C	K_2CO_3 (s) [1]	48 h	< 5:95	n.d.
13	-30 °C	KOH (50 % aq.) [10]	48 h	< 5:95	n.d.
14	-30 °C	KOH (s) [1]	48 h	36:64	52:48
15	-30 °C	CsOH (50 % aq.) [10]	48 h	> 95:5	85:15
16	-30 °C	$CsOH.H_2O$ (s) [1]	48 h	26:74	51:49

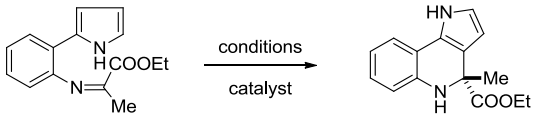
Appendix C – Attempted conditions for imine formation with aromatic ketones



50

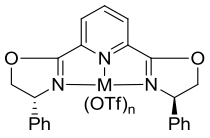
Entry	Ketone [eq.]	conditions	Result
1	PhC(O)Me [1.3]	$MgSO_4$ (5.0 eq.), PhMe, r.t.	No reaction
2	$PhC(O)CF_3$ [5]	$MgSO_4$ (5 eq.), PhMe, r.t.	No reaction
3	$PhC(O)CF_3$ [20]	$MgSO_4$ (20 eq.), PhMe, r.t.	No reaction
4	$PhC(O)CF_3$ [5]	$MgSO_4$ (5 eq.), PhMe, 50 ^oC	No reaction
5	$PhC(O)CF_3$ [5]	$MgSO_4$ (5 eq.), 3 Å MS, (200 % w/w), PhMe, r.t.	No reaction
6	$PhC(O)CF_3$ [5]	cat. AcOH, 3 Å MS (200 % w/w), CH_2Cl_2, r.t.	No reaction
7	$PhC(O)CF_3$ [5]	$AlMe_3$ (10 mol %), CH_2Cl_2, r.t.	Decomposed
8	$PhC(O)CF_3$ [5]	3 Å MS (600 % w/w), CH_2Cl_2, 60 ^oC	No reaction

Appendix D – Investigation of asymmetric cyclization of 101

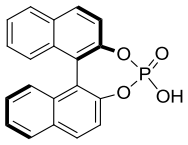


101 **102**

Entry	Catalyst [mol %]	Conditions	e.r.
1	**117** [10]	1:1 THF/PhMe, r.t., 1 h	50:50
2	**373** [10]	1:1 THF/PhMe, r.t., 1 h	50:50
3	**374** [10]	1:1 THF/PhMe, r.t., 1 h	50:50
4	**117** [10]	MeCN, r.t., 1 h	50:50
5	**117** [10]	CH_2Cl_2, r.t., 1 h	51:49
6	(*R*)-TRIP [5]	CH_2Cl_2, r.t., 1 h	49:51
7	(*R*)-TRIP [5]	PhMe, r.t., 1 h	50:50

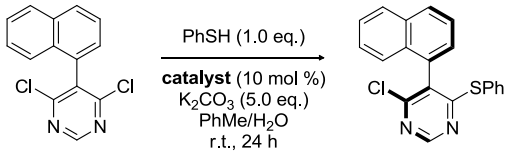


117; M = Sc(III)
373; M = Cu(II)
374; M = Zn(II)

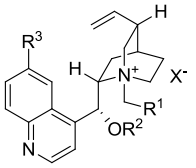


(*R*)-TRIP

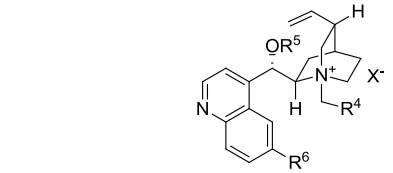
Appendix E – Catalyst optimization for desymmetrizing S_NAr reaction



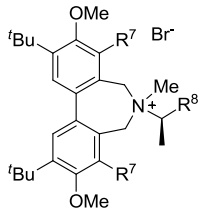
201 **203**



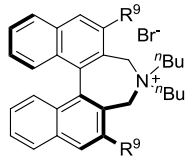
18: R^1 = Ph; R^2 = H; R^3 = H; X = Cl: **58:42 e.r.**
53: R^1 = Ph; R^2 = Allyl; R^3 = H; X = Br: **48:52 e.r.**
55: R^1 = Ph; R^2 = H; R^3 = OMe; X = Cl: **87:13 e.r.**
207: R^1 = 4-NO_2-C_6H_4; R^2 = H; R^3 = OMe; X = Br: **39:61 e.r.**
208: R^1 = 3,5-$(CF_3)_2$-C_6H_3; R^2 = H; R^3 = OMe; X = Br: **46:54 e.r.**
209: R^1 = 2,3,4-F_3-C_6H_2; R^2 = H; R^3 = OMe; X = Br: **43:57 e.r.**
210: R^1 = 3-Me-C_6H_4; R^2 = H; R^3 = OMe; X = Br: **43:57 e.r.**
211: R^1 = 2-Me-C_6H_4; R^2 = H; R^3 = OMe; X = Br: **45:55 e.r.**
212: R^1 = 2-naphthyl; R^2 = H; R^3 = OMe; X = Br: **43:57 e.r.**
375: R^1 = 4-F-C_6H_4; R^2 = H; R^3 = OMe; X = Br: **49:51 e.r.**
376: R^1 = 9-anth; R^2 = H; R^3 = OMe; X = Cl: **47:53 e.r.**
377: R^1 = Ph; R^2 = H; R^3 = O^{i}Pr; X = Cl: **57:43 e.r.**
378: R^1 = Ph; R^2 = H; R^3 = O^{n}Hex; X = Cl: **46:54 e.r.**
363: R^1 = 9-anth; R^2 = H; R^3 = H; X = Cl: **55:45 e.r.**
362: R^1 = 4-CF_3-C_6H_4; R^2 = H; R^3 = H; X = Br: **32:68 e.r.**
379: R^1 = Ph; R^2 = OBz; R^3 = H; X = Cl: **48:52 e.r.**
57: R^1 = 3-F-C_6H_4; R^2 = H; R^3 = H; X = Br: **41:59 e.r.**
56: R^1 = 4-NO_2-C_6H_4; R^2 = H; R^3 = H; X = Br: **50:50 e.r.**
59: R^1 = 2-naphthyl; R^2 = H; R^3 = H; X = Br: **47:53 e.r.**
380: R^1 = 9-anth; R^2 = Allyl; R^3 = H; X = Br: **49:51 e.r.**



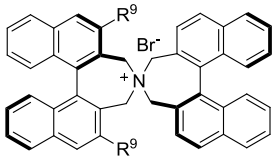
60: R^4 = Ph; R^5 = H; R^6 = H; X = Cl: **61:39 e.r.**
206: R^4 = Ph; R^5 = H; R^6 = OMe; X = Cl: **55:45 e.r.**
65: R^4 = 2,3,4-F_3-C_6H_2; R^5 = H; R^6 = H; X = Br: **52:48 e.r.**
64: R^4 = 3-F-C_6H_4; R^5 = H; R^6 = H; X = Br: **56:44 e.r.**
63: R^4 = 4-F-C_6H_4; R^5 = H; R^6 = H; X = Br: **59:41 e.r.**
61: R^4 = 4-NO_2-C_6H_4; R^5 = H; R^6 = H; X = Br: **52:48 e.r.**
365: R^4 = C_6F_5; R^5 = H; R^6 = H; X = Br: **67:33 e.r.**
12: R^4 = 4-CF_3-C_6H_4; R^5 = H; R^6 = H; X = Br: **77:23 e.r.**



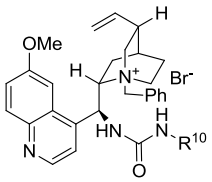
66: R^7 = 3,5-$(CF_3)_2$-C_6H_3; R^8 = 2-naphthyl: n.r.



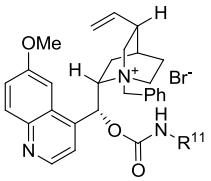
67: R^9 = 3,4,5-F_3-Ph: n.r.



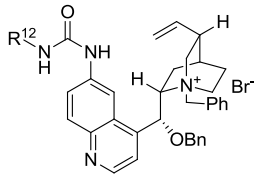
366: R^9 = 3,4,5-F_3-Ph: n.r.



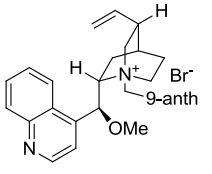
370: R^{10} = 3,5-$(CF_3)_2$-C_6H_3: **38:62 e.r.**



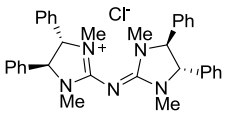
369: R^{11} = 4-$NO_2C_6H_4$: **47:53 e.r.**



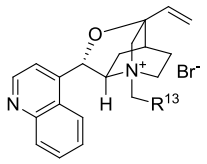
371: R^{12} = 4-$NO_2C_6H_4$: **41:59 e.r.**



381: 51:49 e.r.



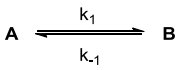
382: 46:54 e.r.



367: R^{13} = Ph: **51:49 e.r.**
368: R^{13} = 4-NO_2-Ph: **52:48 e.r.**

Appendix F – Origin of rate of racemization equation

For an enantioenriched sample undergoing racemization with a major enantiomer **A** and minor enantiomer **B**, the kinetic scenario is shown below:



The rate of change of [**A**] can would then be:

$$\frac{d[A]}{dt} = -k_1[A] + k_{-1}[B]$$

This can be simplified for an enantiomerization process, since it is necessary that k_1=k_{-1}=k.

Therefore:

$$\frac{d[A]}{dt} = -k[A] + k[B]$$

We know the initial concentrations of A and B are $[A_o]$ and $[B_o]$ respectively. It must be true that $[A_o] + [B_o] = [A] + [B]$. Substitution into the rate equation gives the following:

$$\frac{d[A]}{dt} = -k[A] + k([A_o] + [B_o] - [A])$$

Following rearrangement and integration up to a concentration of A at time t we obtain:

$$\int_{[A_o]}^{[A]} \frac{d[A]}{[A_o] + [B_o] - 2[A]} = \int_0^t k\,.\,dt$$

Evaluating this integral leads to:

$$\left[-\frac{1}{2}ln([A_o] + [B_o] - 2[A])\right]_{[A_o]}^{[A]} = [kt]_o^t$$

$$\left(-\frac{1}{2}ln([A_o] + [B_o] - 2[A])\right) - \left(-\frac{1}{2}ln([A_o] + [B_o] - 2[A_o])\right) = kt$$

Rearrangement of this expression gives:

$$ln\left(\frac{[B_o]-[A_o]}{[A_o]+[B_o]-2[A]}\right)=2kt$$

Thus substituting $[A_o] + [B_o] = [A] + [B]$:

$$ln\left(\frac{[B_o]-[A_o]}{[B]-[A]}\right)=2kt$$

Multiplication of both the numerator and denominator of this fraction by [A] + [B]:

$$ln\left(\frac{[B_o]-[A_o]}{[A]+[B]}\times\frac{[A]+[B]}{[B]-[A]}\right)=2kt$$

Separating the logarithms:

$$ln\left(\frac{[B_o]-[A_o]}{[A]+[B]}\right)+ln\left(\frac{[A]+[B]}{[B]-[A]}\right)=2kt$$

Substitution of $[A] + [B] = [A_o] + [B_o]$ gives:

$$ln\left(\frac{[B_o]-[A_o]}{[A_o]+[B_o]}\right)+ln\left(\frac{[A]+[B]}{[B]-[A]}\right)=2kt$$

And since the term on the right is a constant, the expression can be written in the form of a straight line:

$$ln\left(\frac{[A]+[B]}{[B]-[A]}\right)=2kt+ln\left(\frac{[A_o]+[B_o]}{[B_o]-[A_o]}\right)$$

Or if preferred, this can be rearranged to the following format in which e.e. refers to the enantiomeric excess of A and $e.e._0$ is the enantiomeric excess of A at t = 0:

$$ln\left(\frac{1}{e.e.}\right)=2kt+ln\left(\frac{1}{e.e_o}\right)$$

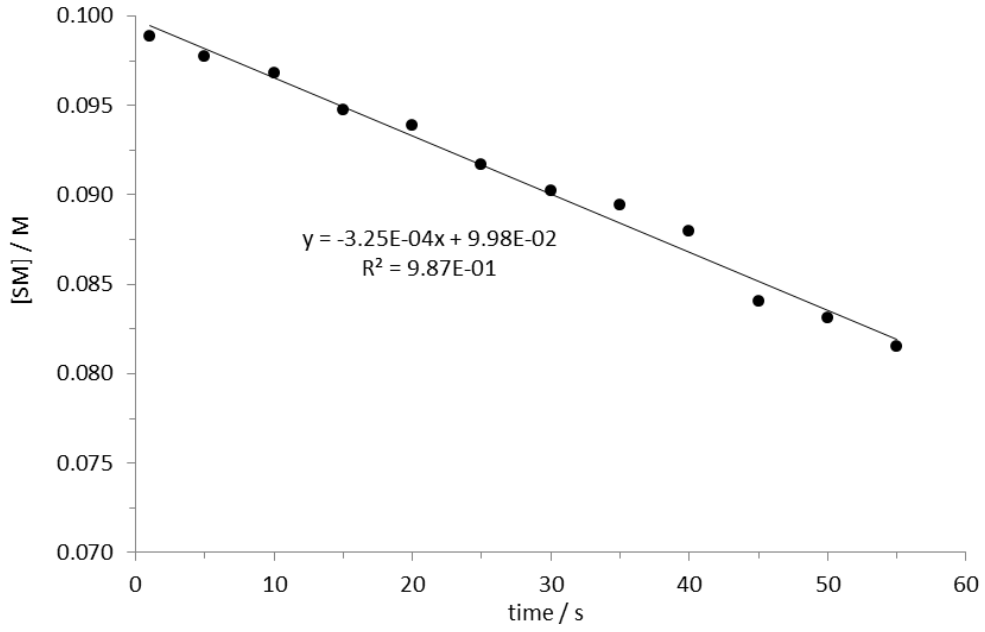
Appendix G – Data and calculations for 1st, 2nd and 3rd order plots

t / min	[**201**] / %	[**201**] / M	ln[**201**] / [**201**] in M	1/[**201**] / M^{-1}
1	98.89	0.099	-2.31	10.11
5	97.57	0.098	-2.33	10.25
10	96.68	0.097	-2.34	10.34
15	94.90	0.095	-2.35	10.54
20	93.33	0.093	-2.37	10.72
25	91.55	0.092	-2.39	10.92
30	90.13	0.090	-2.41	11.10
35	88.89	0.089	-2.42	11.25
40	86.58	0.087	-2.45	11.55
45	85.87	0.086	-2.45	11.65
50	84.12	0.084	-2.48	11.89
55	82.56	0.083	-2.49	12.11
60	82.12	0.082	-2.50	12.18
65	80.39	0.080	-2.52	12.44
70	78.49	0.078	-2.54	12.74
75	78.52	0.079	-2.54	12.74
80	76.79	0.077	-2.57	13.02
85	75.43	0.075	-2.58	13.26
90	75.78	0.076	-2.58	13.20
100	72.58	0.073	-2.62	13.78
110	69.32	0.069	-2.67	14.43
120	68.23	0.068	-2.68	14.66
150	62.24	0.062	-2.78	16.07
187	57.32	0.057	-2.86	17.45
248	47.89	0.048	-3.04	20.88
330	38.00	0.038	-3.27	26.32
465	23.99	0.024	-3.73	41.68
690	12.16	0.012	-4.41	82.24
1245	2.04	0.002	-6.19	490.20

Appendix H – data for initial rates plot

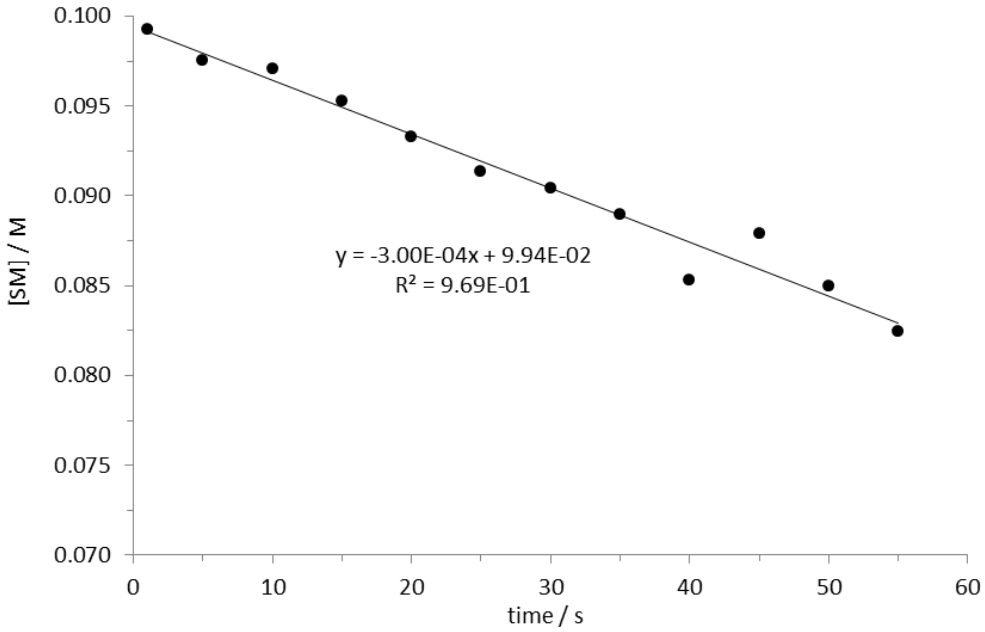
Run 1: **201** (1.0 eq., 0.1 M), **55** (0.1 eq.), PhSH (1.1 eq.), 50 % aq. K_2CO_3 (5.0 eq.):

time / min	[**201**] / %	[*ent*-**203**] / %	[**203**] / %	[**204**] / %	[**201**] / M
1	98.90	0.53	0.57	0.00	0.0989
5	97.71	0.89	1.40	0.00	0.0977
10	96.82	0.93	2.25	0.00	0.0968
15	94.73	1.36	3.91	0.00	0.0947
20	93.88	1.33	4.73	0.06	0.0939
25	91.69	1.47	6.76	0.08	0.0917
30	90.22	1.42	8.27	0.09	0.0902
35	89.44	1.36	9.09	0.11	0.0894
40	87.97	1.52	10.40	0.11	0.0880
45	84.05	1.90	13.94	0.11	0.0841
50	83.09	1.88	14.91	0.12	0.0831
55	81.54	2.00	16.33	0.12	0.0815



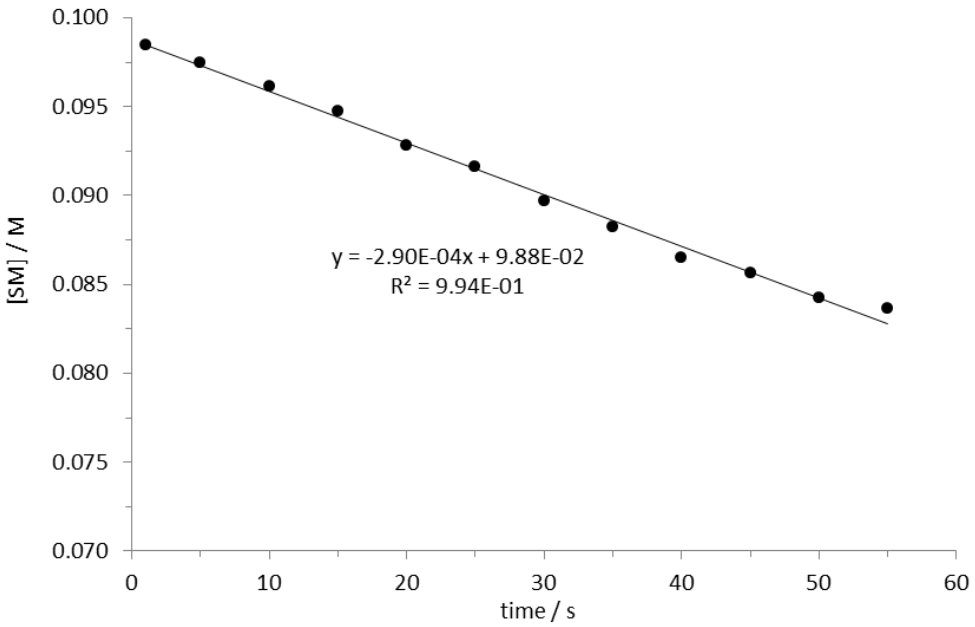
Run 2: **201** (1.0 eq., 0.1 M), **55** (0.1 eq.), PhSH (1.1 eq.), 50 % aq. K_2CO_3 (5.0 eq.):

time / min	[**201**] / %	[*ent*-**203**] / %	[**203**] / %	[**204**] / %	[**201**] / M
1	99.28	0.35	0.37	0.00	0.0993
5	97.51	0.91	1.54	0.05	0.0975
10	97.06	0.86	2.04	0.05	0.0971
15	95.25	1.23	3.44	0.08	0.0953
20	93.28	1.57	5.08	0.07	0.0933
25	91.36	1.81	6.74	0.08	0.0914
30	90.45	1.87	7.59	0.10	0.0905
35	88.97	1.95	8.97	0.11	0.0890
40	85.30	2.54	12.07	0.10	0.0853
45	87.90	1.76	10.23	0.11	0.0879
50	85.00	2.18	12.70	0.12	0.0850
55	82.47	2.42	14.99	0.12	0.0825



Run 3: **201** (1.0 eq., 0.1 M), **55** (0.1 eq.), PhSH (1.1 eq.), 50 % aq. K_2CO_3 (5.0 eq.):

time / min	[**201**] / %	[*ent*-**203**] / %	[**203**] / %	[**204**] / %	[**201**] / M
1	98.49	0.68	0.83	0.00	0.0985
5	97.48	0.87	1.61	0.04	0.0975
10	96.17	1.13	2.64	0.06	0.0962
15	94.73	1.30	3.90	0.06	0.0947
20	92.82	1.73	5.38	0.06	0.0928
25	91.60	1.74	6.59	0.07	0.0916
30	89.72	2.01	8.18	0.10	0.0897
35	88.27	2.19	9.45	0.09	0.0883
40	86.48	2.42	11.00	0.09	0.0865
45	85.67	2.36	11.88	0.10	0.0857
50	84.28	2.28	13.30	0.13	0.0843
55	83.67	2.23	13.98	0.12	0.0837

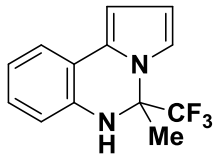


Averaged data used to plot Figure 4.3

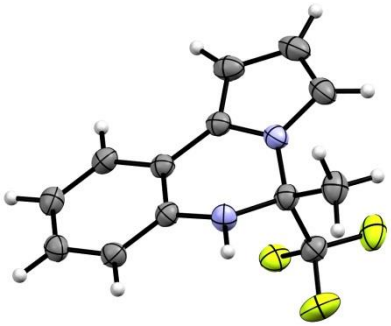
time / min	[**201**] / M				
	run 1	run 2	run 3	average	st. dev.
1	0.0989	0.0993	0.0985	0.0989	0.00040
5	0.0977	0.0975	0.0975	0.0976	0.00013
10	0.0968	0.0971	0.0962	0.0967	0.00046
15	0.0947	0.0953	0.0947	0.0949	0.00030
20	0.0939	0.0933	0.0928	0.0933	0.00053
25	0.0917	0.0914	0.0916	0.0916	0.00017
30	0.0902	0.0905	0.0897	0.0901	0.00037
35	0.0894	0.0890	0.0883	0.0889	0.00059
40	0.0880	0.0853	0.0865	0.0866	0.00134
45	0.0841	0.0879	0.0857	0.0859	0.00193
50	0.0831	0.0850	0.0843	0.0841	0.00096
55	0.0815	0.0825	0.0837	0.0826	0.00107

Appendix I – X-ray crystallography data

X-ray crystallographic data and structure refinement for compound **99**, 037RWD12

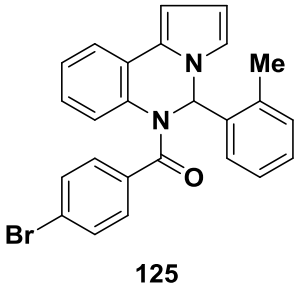


99

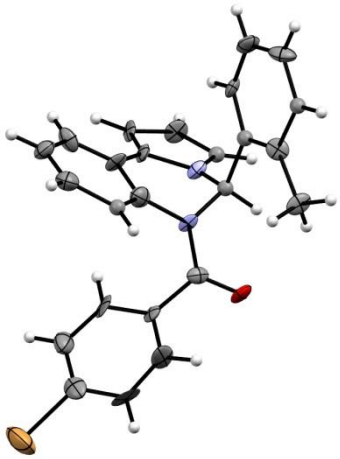


Identification code	037RWD12	
Empirical formula	$C_{13}H_{11}F_3N_2$	
Formula weight	252.24	
Temperature	150 K	
Wavelength	0.71073 Å	
Crystal system	orthorhombic	
Space group	P 2_1 2_1 2_1	
Unit cell dimensions	a = 7.1443 Å	α = 90°
	b = 10.9909 Å	β = 90°
	c = 14.7465 Å	γ = 90°
Volume	1157.93 $Å^3$	
Z,Z’	Z: 4 Z': 0	
Density (calculated)	1.447 g m^{-3}	
Absorption coefficient	0.121 mm^{-1}	
F(000)	520.0	
Crystal size	0.10 x 0.26 x 0.40mm ^{3}	
Theta range for data collection	5.366° to 27.874°	
Reflections collected	2743	
Independent reflections	1590	
Absorption correction	Multi-scan	
Refinement method	Full-matrix least squares on F^2	
Goodness-of-fit on F^2	0.977	
Final R indices [I>2σ(I)]	R^1 = 0.0305, wR^2 = 0.0707	
R indices (all data)	R^1 = 0.0335, wR^2 = 0.0748	

X-ray crystallographic data and structure refinement for compound **125**, 124RWD13

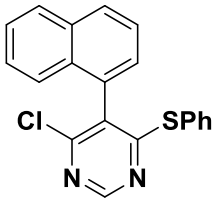


125

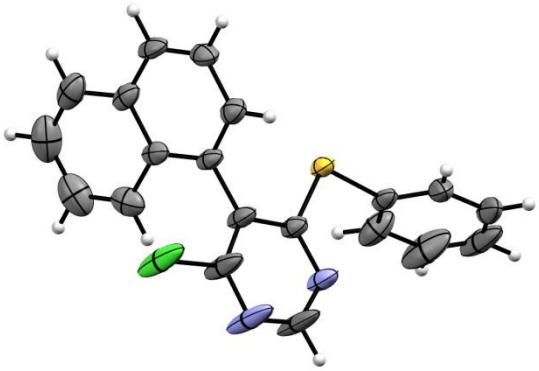


Identification code	124RWD13	
Empirical formula	$C_{25}H_{19}BrN_2O$	
Formula weight	443.32	
Temperature	150 K	
Wavelength	1.54180 Å	
Crystal system	hexagonal	
Space group	P 6_1 2 2	
Unit cell dimensions	a = 8.4400 Å	α = 90°
	b = 8.4400 Å	β = 90°
	c = 111.400 Å	γ = 120°
Volume	6872.3 $Å^3$	
Z,Z'	Z: 12 Z': 0	
Density (calculated)	1.285 g cm^{-3}	
Absorption coefficient	2.569 mm^{-1}	
F(000)	2712.0	
Crystal size	0.05 x 0.05 x 0.09 mm^3	
Theta range for data collection	4.763 ° to 78.060 °	
Reflections collected	19451	
Independent reflections	4864	
Absorption correction	Multi-scan	
Refinement method	Full-matrix least squares on F^2	
Goodness-of-fit on F^2	3.109	
Final R indices [I>2σ(I)]	R^1 = 0.1579, wR^2 = 0.5156	
R indices (all data)	R^1 = 0.1585, wR^2 = 0.5167	

X-ray crystallographic data and structure refinement for compound **203**, 180RWD14

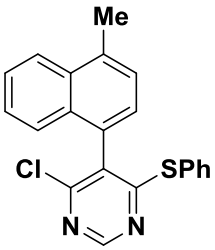


203

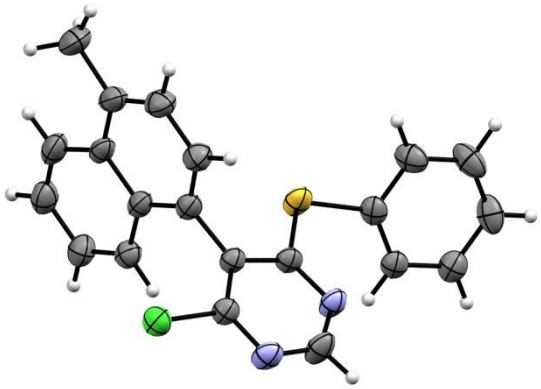


Identification code	180RWD14	
Empirical formula	$C_{20}H_{13}ClN_2S$	
Formula weight	348.83	
Temperature	149 K	
Wavelength	1.54184 Å	
Crystal system	orthorhombic	
Space group	P 2_1 2_1 2_1	
Unit cell dimensions	a = 7.71601 Å	α = 90°
	b = 8.77660 Å	β = 90°
	c = 24.9002 Å	γ = 90°
Volume	1686.25 $Å^3$	
Z,Z'	Z: 4 Z': 0	
Density (calculated)	1.374 g cm^{-3}	
Absorption coefficient	3.170 mm^{-1}	
F(000)	720.0	
Crystal size	0.05 x 0.06 x 0.10 mm^3	
Theta range for data collection	3.550° to 76.107°	
Reflections collected	32781	
Independent reflections	3513	
Absorption correction	none	
Refinement method	Full-matrix least squares on F^2	
Goodness-of-fit on F^2	1.023	
Final R indices [I>2σ(I)]	R^1 = 0.0662, wR^2 = 0.1400	
R indices (all data)	R^1 = 0.0672, wR^2 = 0.1408	

X-ray crystallographic data and structure refinement for compound **263**, 016PCK14

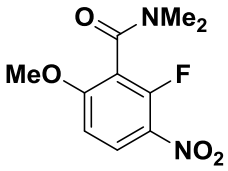


263

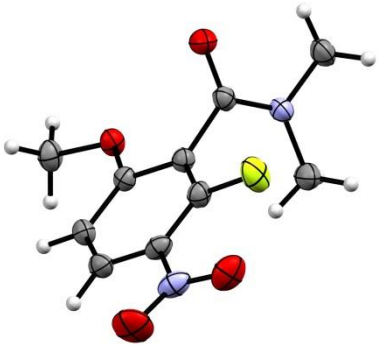


Identification code	016PCK14	
Empirical formula	$C_{21}H_{15}ClN_2S$	
Formula weight	362.86	
Temperature	150 K	
Wavelength	0.71073 Å	
Crystal system	monoclinic	
Space group	P 2_1 1 1	
Unit cell dimensions	a = 7.6005 Å	α = 86.3764°
	b = 14.3158 Å	β = 90°
	c = 16.2551 Å	γ = 90°
Volume	1765.14 $Å^3$	
Z,Z'	Z: 4 Z': 0	
Density (calculated)	1.365 g cm^{-3}	
Absorption coefficient	0.340 mm^{-1}	
F(000)	752.0	
Crystal size	0.10 x 0.16 x 0.28 mm^3	
Theta range for data collection	5.138° to 27.546°	
Reflections collected	28660	
Independent reflections	7429	
Absorption correction	Multi-scan	
Refinement method	Full-matrix least squares on F^2	
Goodness-of-fit on F^2	0.904	
Final R indices [I>2σ(I)]	R^1 = 0.0435, wR^2 = 0.0959	
R indices (all data)	R^1 = 0.0542, wR^2 = 0.1049	

X-ray crystallographic data and structure refinement for compound **335**, 031JDJ15



335



Identification code	031JDJ15	
Empirical formula	$C_{10}H_{11}FN_2O_4$	
Formula weight	242.21	
Temperature	150 K	
Wavelength	0.71073 Å	
Crystal system	orthorhombic	
Space group	P b c a	
Unit cell dimensions	a = 8.5848 Å	α = 90°
	b = 11.2416 Å	β = 90°
	c = 22.3028 Å	γ = 90°
Volume	2152.37 $Å^3$	
Z,Z'	Z: 8 Z': 0	
Density (calculated)	1.495 g cm^{-3}	
Absorption coefficient	0.127 mm^{-1}	
F(000)	1008.0	
Crystal size	0.32 x 0.38 x 0.38 mm^3	
Theta range for data collection	5.130° to 27.493°	
Reflections collected	4572	
Independent reflections	2454	
Absorption correction	Multi-scan	
Refinement method	Full-matrix least squares on F^2	
Goodness-of-fit on F^2	0.938	
Final R indices [I>2σ(I)]	R^1 = 0.0394, wR^2 = 0.0945	
R indices (all data)	R^1 = 0.0530, wR^2 = 0.1102	