
Enantioselective Synthesis of Non-Biaryl Atropisomers

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This thesis is dedicated to my parents, Brian and Helene Fugard.

Declaration

This dissertation describes work carried out in the Chemistry Research Laboratory at the University of Oxford between October 2015 and September 2018. The dissertation is a product of my own work and includes no results obtained through collaboration, except where specifically indicated in the text.

Alison Fugard

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Abbreviations

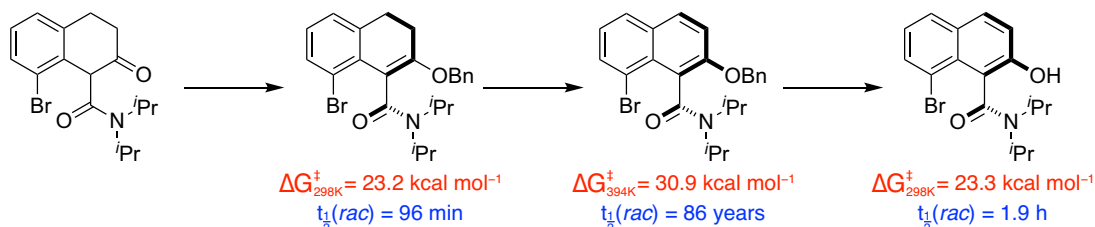
Å	Ångströms
APCI	Atmospheric-Pressure Chemical Ionization
Ar	<i>denotes a generic aromatic system</i>
aq.	aqueous
BINOL	[1,1'-binaphthalene]-2,2'-diol
Bn	benzyl
br	broad
ⁿ Bu	<i>n</i> -butyl
^s Bu	<i>sec</i> -butyl
^t Bu	<i>tert</i> -butyl
°C	degrees Celcius
CI	Chemical Ionisation
CLAmP	<i>N</i> -methoxy- <i>N</i> -methyl-1H-pyrrole-1-carboxamide
compd.	compound
COSY	1H-1H correlation spectroscopy
conc.	concentration <i>or</i> concentrated
Cy	cyclohexyl
DMF	<i>N,N</i> -dimethylformamide
d	doublet
DCE	1,2-dichloroethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
dec.	decomposed
DMF	<i>N,N</i> -dimethylformamide
d.r.	diastereomeric ratio
e.e.	enantiomeric excess
EI	Electron Ionisation
e.r.	enantiomeric ratio

ESI	Electrospray Ionisation
Et	ethyl
eq.	equivalents
FTIR	Fourier-transform infra-red spectroscopy
g	grams
GS	ground state
h	hours
hept	heptet
ⁿ Hex	<i>n</i> -hexyl
HMPA	hexamethylphosphoramide
HPLC	high-performance liquid chromatography
HRMS	high-resolution mass spectrometry
Hz	Hertz
IUPAC	International Union of Pure and Applied Chemistry
<i>J</i>	coupling constant
K	Kelvin
<i>k</i>	rate constant
kcal	kilocalorie
<i>k_{ent}</i>	rate of enantiomerisation
KHMDS	potassium bis(trimethylsilyl)amide
<i>k_{rac}</i>	rate of racemisation
LDA	lithium diisopropylamide
LiHMDS	lithium bis(trimethylsilyl)amide
M	moles per litre
μ	micro-
m	milli-
m	multiplet
<i>m</i> -	meta-
maj.	major
Me	methyl
min	minutes
min.	minor
mol	moles

m.p.	melting point
MTBE	methyl <i>tert</i> -butyl ether
Mukaiyama's reagent	2-chloro-1-methylpyridinium iodide
NBS	<i>N</i> -bromosuccinimide
NMR	nuclear magnetic resonance
<i>o</i> -	ortho-
<i>p</i> -	para-
ⁿ Pen	<i>n</i> -pentyl
Ph	phenyl
PIDA	(diacetoxyiodo)benzene
PNP	4-nitrophenol
ⁱ Pr	isopropyl
ⁿ Pr	<i>n</i> -propyl
q	quartet
quant.	quantitative
R	<i>denotes a generic substituent</i>
rt	room temperature
rac.	racemisation/racemic
S	selectivity factor
s	seconds
t	time
TAA	<i>tert</i> -amyl alcohol
TBAB	tetra- <i>n</i> -butylammonium bromide
TBDMS	<i>tert</i> -butyldimethylsilyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin-layer chromatography
TMEDA	<i>N,N,N',N'</i> -tetramethylethylenediamine
TMS	trimethylsilyl
triglyme	triethylene glycol dimethyl ether
TS	transition state
vs.	versus
w/w	weight for weight

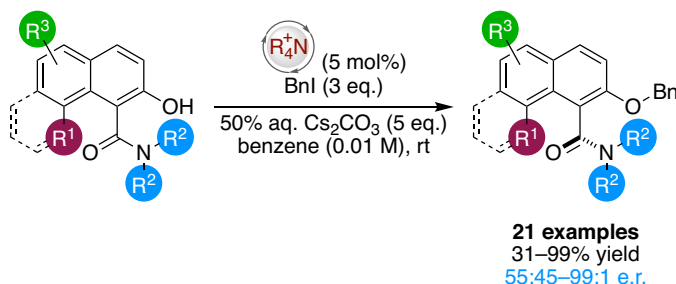
Abstract

This thesis describes the development of novel methods to synthesise non-biaryl atropisomers enantioselectively. In Chapter 1, atropisomerism is defined and explored, with a focus on non-biaryl atropisomers and the literature stereoselective syntheses of chiral naphthamides. Chapter 2 discusses initial attempts to synthesise chiral naphthamides using phase-transfer catalysis, and the barriers to rotation of intermediate enol ethers, and benzylated and debenzylated naphthols are determined (Scheme 1). Chapter 3 concerns investigations into the low barriers to rotation of these debenzylated naphthols.



Scheme 1: Synthesis of benzylated and debenzylated chiral naphthamide *via* enol ether intermediate.

Chapter 4 builds on this work to develop an enantioselective synthesis of benzylated naphthamides *via* a dynamic kinetic resolution of the naphthol starting material (Scheme 2). This reaction was tested on a wide variety of substrates to determine its scope and limitations, and the barriers to rotation of the chiral products were calculated.



Scheme 2: Enantioselective dynamic kinetic resolution of chiral naphthols.

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1 Introduction

1.1 Atropisomerism

Atropisomerism (derived from the Greek *a*, meaning “no” and *tropos*, meaning “turning”) is a molecular property that arises when restricted rotation about a single bond leads to the formation two distinct stereoisomers. This was first discovered by Christie and co-workers during their work on 6,6'-dinitro-2,2'-biphenyldicarboxylic acid (**1**, Figure 1.1).^[1]

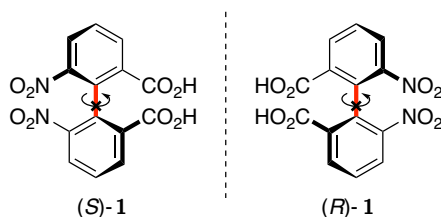


Figure 1.1: Two enantiomers of a biphenyldicarboxylic acid, the first example of atropisomers.

Formally, such isomers are considered atropisomeric at a particular temperature when the half-life to racemisation ($t_{\frac{1}{2}}(rac)$) is over 1000 s at that temperature.^[2] At 298 K this corresponds to a free energy barrier to rotation ($\Delta G_{298K}^\ddagger$) of 22.2 kcal mol⁻¹. This definition means that many molecules can be atropisomeric if the temperature is low enough. For example, butane can exist as two stereoisomers at 53 K,^[3] however this temperature is not practical for separation and handling in a standard laboratory.

The uses and syntheses of biaryl atropisomers have been extensively explored.^[4,5] For example, atropisomerism is present in many natural products such as vancomycin (**2**,

Figure 1.2), a potent antibiotic,^[6] and gossypol (**3**), a vaulted biaryl that has been researched in connection with male contraceptives and cancer treatments.^[7,8] Unfortunately, atropisomerism is often seen as “a lurking menace”^[9,10] leading to modifications to remove atropisomerism by invoking symmetry or enabling facile rotation. Drug compound BMS-207940 (**4**) is a potent endothelin receptor antagonist^[11] but was shown to racemise 25 times faster in blood plasma.^[12] Atropisomers are also useful in organic synthesis to enable other forms of symmetry. For example, bisphosphine BINAP (**5**) is an incredibly useful ligand backbone and has been utilised in numerous asymmetric transformations.^[13]

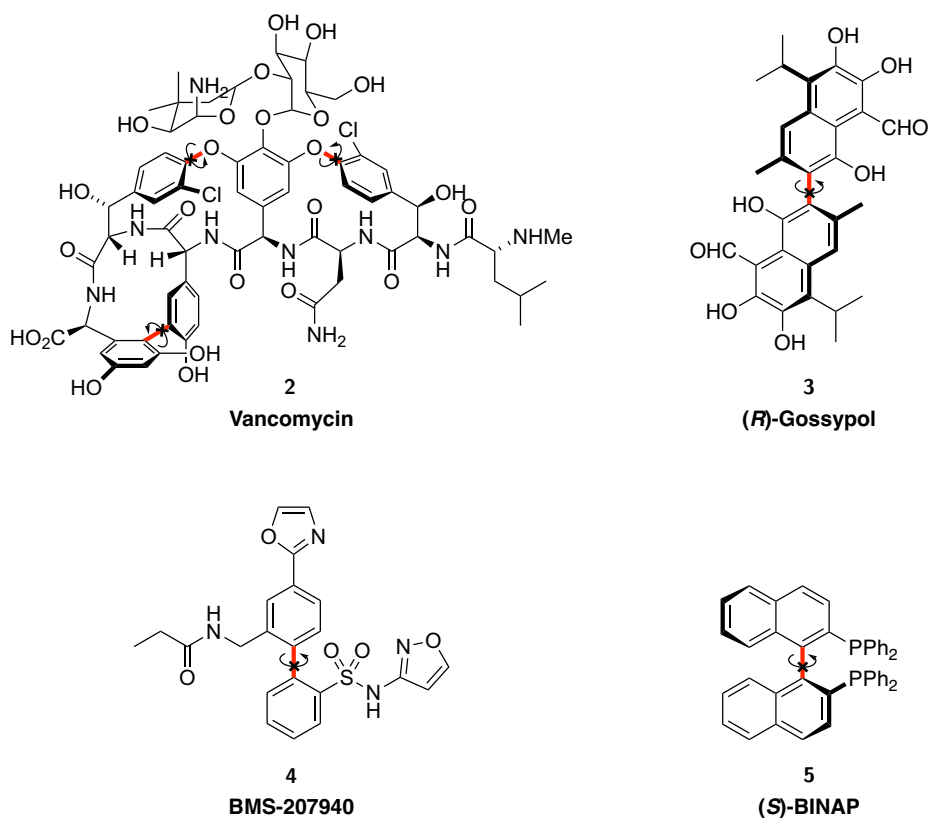


Figure 1.2: Examples of biaryl atropisomeric natural products, drugs, and ligands.

1.1.1 Non-Biaryl Atropisomers

Since the discovery of chiral molecules due to restricted rotation, there has been increased interest in non-biaryl atropisomers (Figure 1.3). These have restricted rotation about a

variety of different bonds such as C–C to yield amides (**6**) or styrenes (**7**), C–N to give anilides (**10**), imides (**11**) and ureas (**12**). A chiral axis about a C–S or C–O bond give sulfones (**8** and **9**) and diaryl ethers (**13**) respectively.

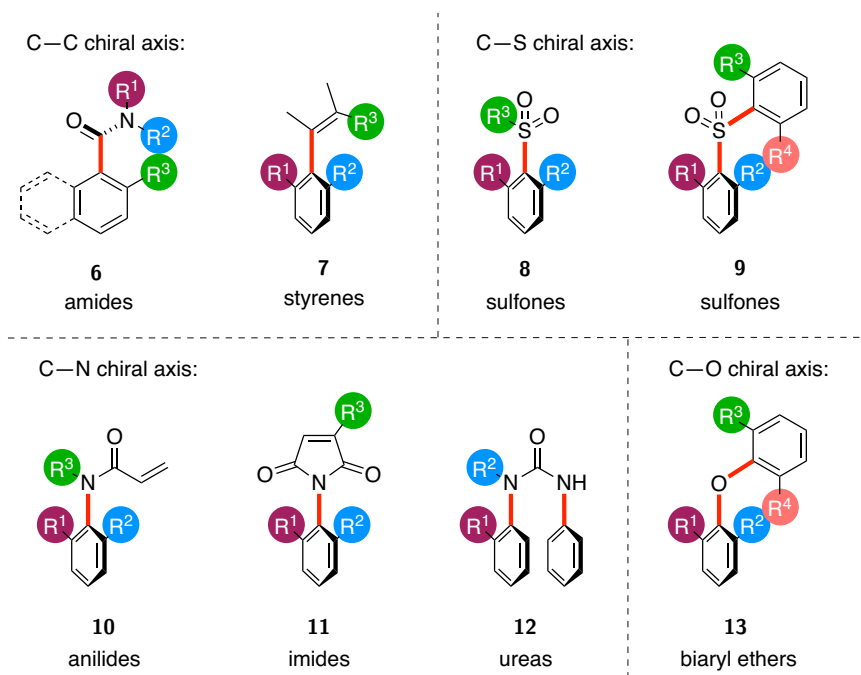


Figure 1.3: Different types of non-biaryl atropisomers.

Just as biaryl atropisomers are prevalent in nature, medicinal chemistry and a synthetic chemist's tool box, so too are non-biaryl atropisomers. For example **14** (Figure 1.4), an indomethacin analog, is a potent cyclooxygenase (COX) inhibitor and therefore has activity as an anti-inflammatory, with restricted rotation about a C–CO bond. Takahashi and co-workers found that the (*R*)-enantiomer was in fact the potent compound and the (*S*)-enantiomer had no activity at 200 μM .^[14] Analogous to a BINAP ligand, **15** has been used as a ligand in the silver-catalysed enantioselective addition of **16** and **17** to yield highly functionalised pyrrolidine derivatives, **18**, with excellent selectivity (Figure 1.4).

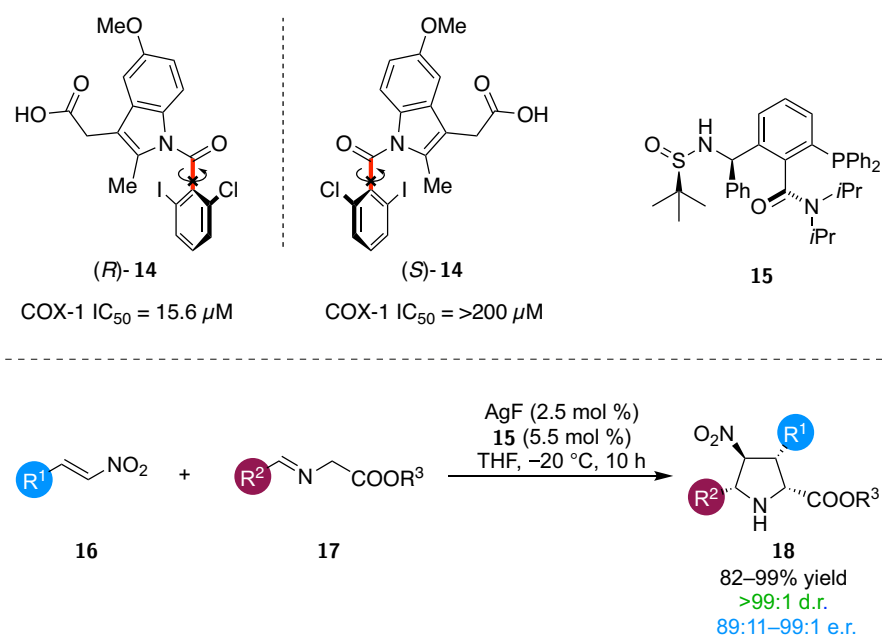


Figure 1.4: Cyclooxygenase inhibitor and silver catalysed enantioselective addition using non-biaryl atropisomeric phosphine ligand.

1.1.2 Barriers to Rotation of Atropisomers

Calculating Barriers to Rotation

The rate of racemisation (k_{rac}) is the rate at which an optically active compound (when e.r. $\neq$ 50:50) is irreversibly converted into a racemic mixture on the macroscopic scale.^[15]

In contrast, the rate of enantiomerisation (k_{ent}) is the rate at which, on a single molecular level, one enantiomer is reversibly transformed into the other.^[15] Therefore:

$$k_{rac} = 2k_{ent} \quad (1.1)$$

This can be calculated from the erosion of the enantiomeric excess (e.e.) of a compound over time at a given temperature.^[16]

$$\ln \left(\frac{100}{\text{e.e.}} \right) = k_{rac} \times t + \ln \left(\frac{100}{\text{e.e.}_{t=0}} \right) \quad (1.2)$$

Therefore a plot of $\ln\left(\frac{100}{e.e.}\right)$ against time will give k_{rac} as the gradient and:

$$t_{\frac{1}{2}}(rac) = \frac{\ln(2)}{k_{rac}} \quad (1.3)$$

k_{rac} can then be used to calculate k_{ent} and the barrier to rotation at a given temperature ($\Delta G_T^\ddagger$) using the Eyring equation.^[17]

$$k_{ent} = \frac{k_B T}{h} e^{\frac{-\Delta G_T^\ddagger}{RT}} \quad (1.4)$$

$$\Delta G_T^\ddagger = \ln\left(\frac{k_B T}{h \times k_{ent}}\right) RT \quad (1.5)$$

Often, to compare barriers to rotation on a more practical level relevant to laboratory work, $t_{\frac{1}{2}}(rac)$ is used. These values are frequently calculated using $\Delta G^\ddagger$ measured at a certain temperature to work out $t_{\frac{1}{2}}(rac)$ at room temperature. This assumes that $\Delta S^\ddagger = 0$ which is not true, however this value is often small in comparison to $\Delta G^\ddagger$ at around 2–20 cal mol⁻¹.^[18–20] For the sake of comparing the scale of $t_{\frac{1}{2}}(rac)$, be it seconds, hours, days or years, this is an accepted and useful practice^[21] as it gives an indication of the extent to which a compound must be kept at cold temperatures, or whether the enantioenrichment of a compound would survive high reaction temperatures.

Mechanism of Rotation

The major mechanism for racemisation of atropisomers is rotation about the chiral axis bond. There are a number of factors which determine how quickly this occurs including temperature, solvent, and electronics. However, one of the major factors is sterics, as has been studied extensively in biaryl systems by Adams and co-workers.^[22] Seminal work by

Clayden and co-workers investigated factors affecting barriers to rotation of substituted naphthamides **19** (Figure 1.5a).^[21]

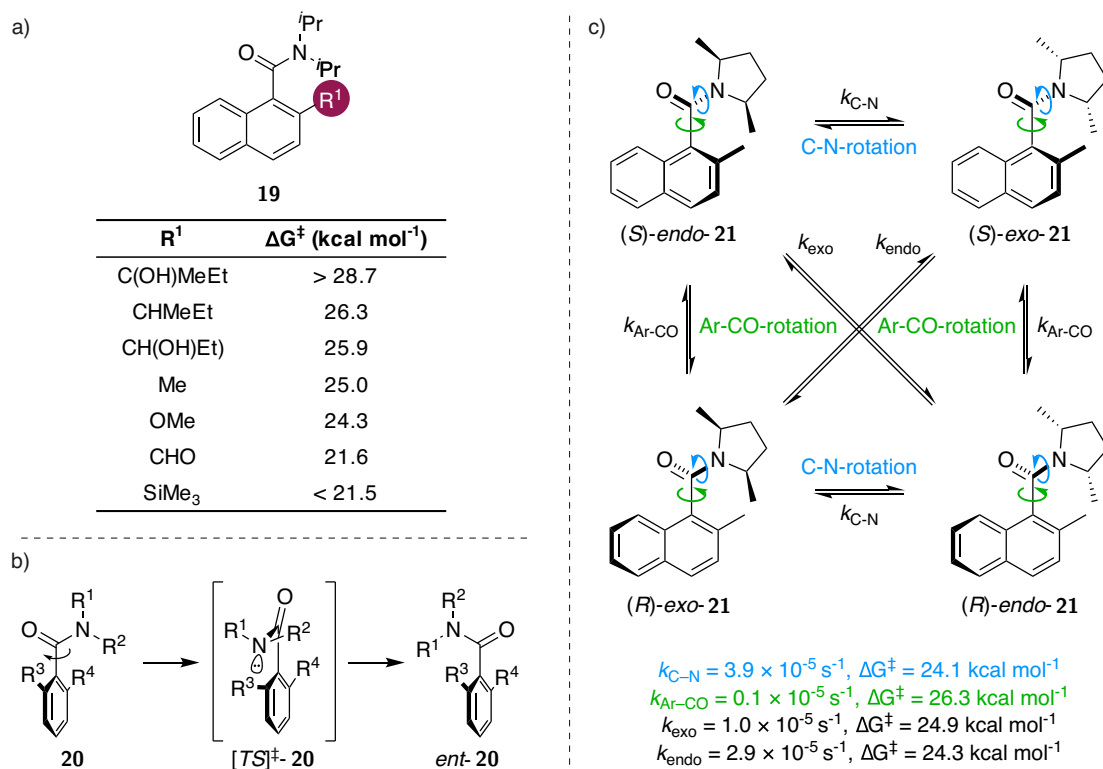


Figure 1.5: a) Barriers of naphthamides. b) Mechanisms of racemisation of benzamides. c) Stereoisomers and interconversions of **21**

Several fundamental observations came from research into naphthamides **19**. First, when $R^3 \neq H$ the barrier of **19** was heavily dependent on the size of the 2-substituent, R^3 , and less so on the size of the amide substituents. This is in contrast to when $R^3 = H$, where there is a strong dependence of barrier on the smaller amide substituent. In fact, when $R^3 = H$, the barrier to rotation is so low that the compound is not atropisomeric at room temperature ($t_{\frac{1}{2}}(rac) < 1 \text{ s}$).

The second important observation from this work was that polar solvents, such as methanol, gave a small but consistent increase in the barrier to rotation of 0.5–0.7 kcal mol⁻¹. These two observations led to a proposed mechanism of racemisation through transi-

tion state [TS][‡]**20** (Figure 1.5b) whereby the nitrogen becomes sp³ hybridised, out of planarity with the carbonyl, so the lone pair, the smallest group on nitrogen, is able to move past R³. This explains why methanol slows down racemisation; in the ground state the amide is in resonance with the carbonyl and this is stabilised in polar solvents. Breaking planarity to rotate about the Ar–CO bond then requires a larger energetic cost and is therefore less favourable. This mechanism also suggests that Ar–CO bond rotation and C–N bond rotation are concerted, as can be seen in the rotation of **20** to *ent*-**20**. Further studies of both Ar–CO rotation and C–N bond rotation of **21** (Figure 1.5c) shows this is indeed the case, as concerted bond rotation rates, k_{exo} and k_{endo} , are notably faster than k_{Ar-CO} alone.^[23]

However, not all observations can be explained solely by steric factors. Investigations into 8-substituted naphthamides showed that the electronic properties, rather than steric properties, of the 8-substituent of naphthamides is an important factor in determining the barrier to rotation of naphthamides.^[24] A crystal structure of **22** (Figure 1.6a) shows the two substituents are pulled together by bonding interactions, rather than repelled by sterics. Consequently, a shorter bond length is observed compared to when no such bonding interaction can take place, such as in dimethylnaphthyl **23**.^[25] This effect has also been observed by Dunitz and co-workers in 1,8-naphthyl compounds containing one carbonyl and one nucleophilic substituent.^[26] The result of this bonding interaction is an increase in the barrier to rotation of the amide. Substituents which enable incipient bonding (R² = NMe₂, OMe), have a higher barrier to rotation than substituents which cannot form an interaction with the amide carbonyl (R² = CH₂NMe₂) (Figure 1.6c).

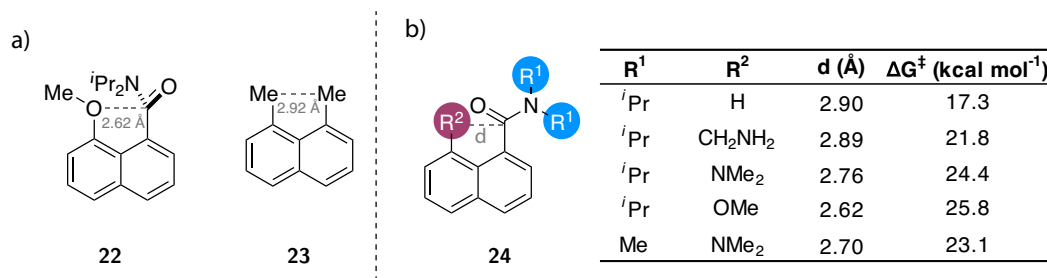


Figure 1.6: Effect of 8-substituent on barrier to rotation of naphthamides.

However, the sterics of the amide substituents still have an important impact on the barrier to rotation. Changing the amide substituents from *i*Pr to Me, decreases the bulk of the amide, enabling the R² group to get closer to the carbonyl. The length between R² and the carbonyl decreases from 2.76 Å (R¹ = *i*Pr) to 2.70 Å (R¹ = Me) but the barrier also decreases by 1.3 kcal mol⁻¹ despite this interaction.

Factors affecting the barrier to rotation are very dependent on the structure of the molecule. For instance, in **25** (Figure 1.7a) substituting X = O for X = S increases the barrier, as one might expect from steric effects.^[27] Sulfur has a Van de Waals radius of 1.85 Å and is therefore larger than oxygen, with a radius of 1.52 Å.^[28] However, in **26** (Figure 1.7b) this substitution has the opposite effect and pyrimidinethione (X = S) has a lower barrier to rotation than pyrimidinone (X = O).^[29]

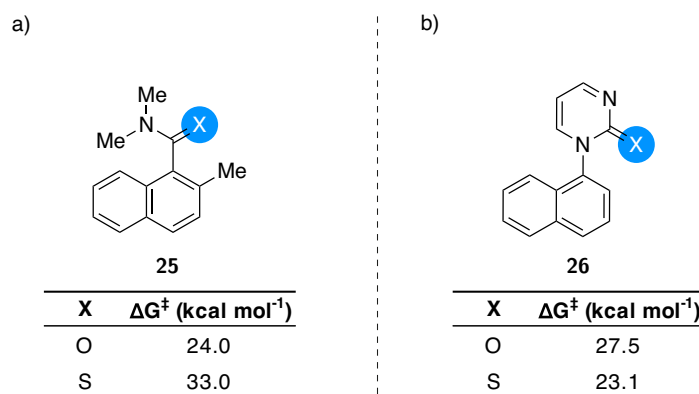


Figure 1.7: a) Effect of X on barrier of naphthamides. b) Barriers of pyrimidinone and pyrimidinethione.

There are a few hypotheses as to the reason behind this. Kashima and co-workers postulated that the C=S bond is able to bend more due to a higher degree of single bond character,^[30] decreasing the repulsive interactions with the aryl ring.^[28] Roussel and co-workers suggested a 3,3-electrocyclic ring-opening of **27** (Figure 1.8a) gives achiral intermediate **28**, facilitated by a weak C–N bond, which will then close unselectively to give racemic **27**.^[31] However, more recent computational calculations of **29** (Figure 1.8b) by Schirok and co-workers predict a deplanarisation of the pyridinone ring, facilitating racemisation by pushing the phenyl ring and carbonyl in opposite directions, opening up the molecule and providing less resistance to rotation.

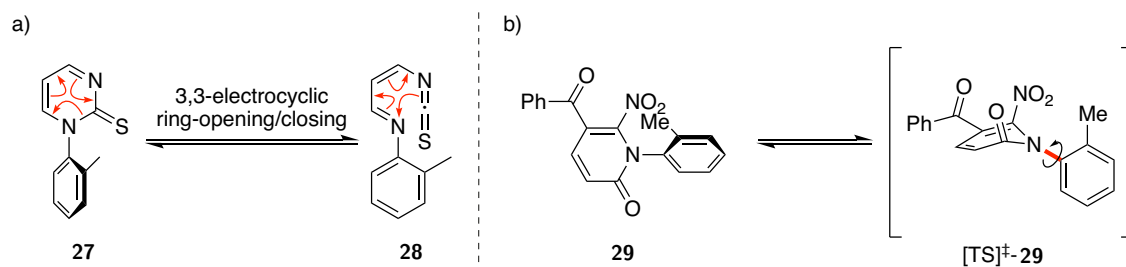


Figure 1.8: a) Racemisation by electrocyclic ring-opening. b) Racemisation by deplanarisation of pyridinone.

In some cases, racemisation can be facilitated by guest molecules or protonation. As mentioned previously, the molecule must pass through a planar transition state in order to racemise. Conditions that stabilise this transition state will lower the barrier to rotation and speed up racemisation. Guest molecules such as acetate^[32] (Figure 1.9a), or protonation^[33] (Figure 1.9b) can, in these cases, lower the barrier to rotation by 9.3 kcal mol^{−1} and 3.1–4.6 kcal mol^{−1} respectively. Another example of “proton grease” for rotation is in the racemisation of **32** (Figure 1.9c).^[34] Protonation of the nitrogen on the chiral axis results in a change of hybridisation from trigonal planar sp² to tetrahedral sp³ so the aryl rings are tilted away from each other, enabling less hindered rotation.

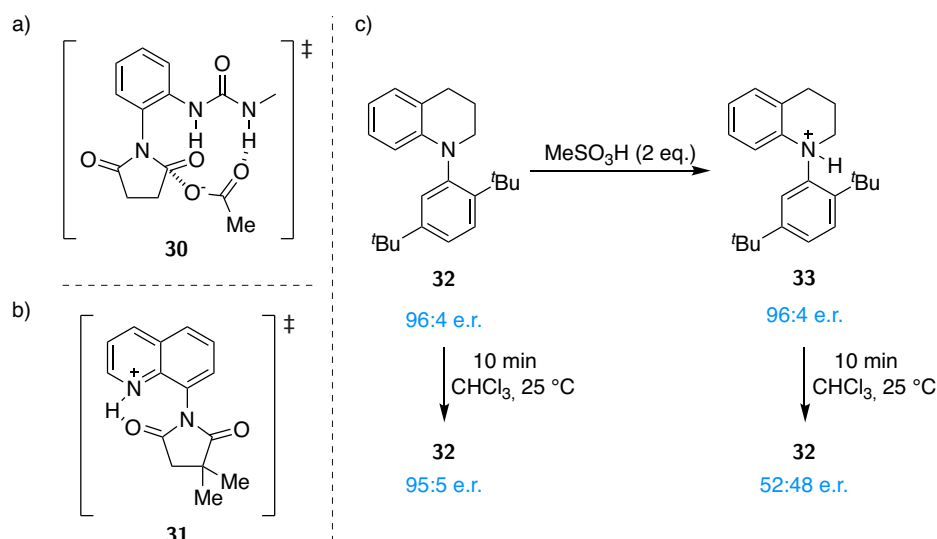


Figure 1.9: Decreased barrier to rotation by stabilisation of TS by guest molecules or protons.

Protons can also act as “brakes” to hinder racemisation. Kitagawa and co-workers found that electron withdrawing groups on the phenyl ring of **34** (Figure 1.10) led to higher barriers to rotation.^[35] Electron withdrawing groups favour planarity of the aryl ring with the nitrogen by resonance stabilisation of the nitrogen lone pair into the aromatic ring, which is enabled by this geometry.

However, computational calculations show this aryl ring must twist out of planarity with nitrogen in order to racemise. Therefore, breaking the planar configuration stabilised by electron withdrawing groups, is energetically unfavourable, and the barrier to this, and thus to rotation will be higher. When $\text{R}^1 = \text{NH}_2$ (**35**), a strong electron donating group, racemisation occurs at 30°C (99:1 to 73:27 e.r. in 24 h). Protonation of **35** turns R^1 into a strongly electron withdrawing group ($^+\text{NH}_3$) in compound **36**. Racemisation then proceeds at a significantly slower rate (99:1 to 98:2 e.r. in 24 h).

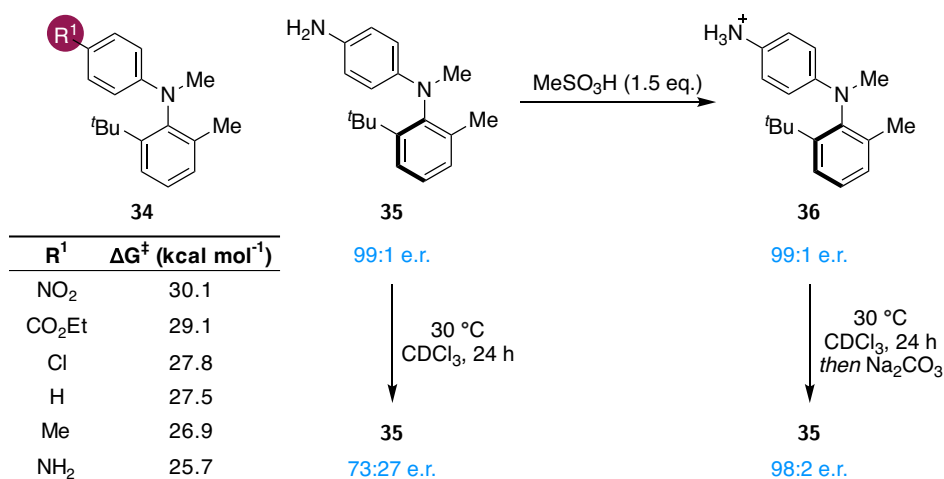


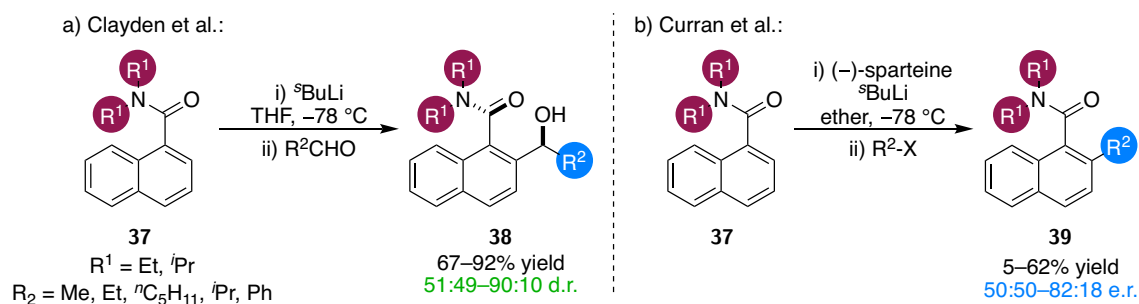
Figure 1.10: Electronic effect on barrier to rotation.

1.1.3 Stereoselective Synthesis of Amide Atropisomers

As this thesis is concerned with the synthesis of amide atropisomers, only literature pertaining to the development and success of methodologies to create molecules with restricted rotation about a C–(CO)NR₂ bond will be discussed here.

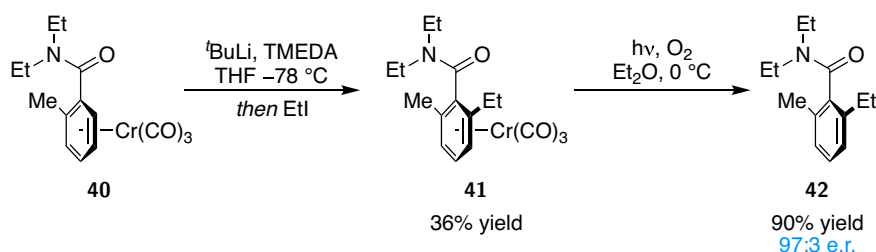
First Stereoselective Syntheses

The atropisomerism of amides was first exploited by Clayden and co-workers in 1994 (Scheme 1.1a).^[36,37] Amide **37** rotates too fast at room temperature to be considered atropisomeric. When subjected to *ortho*-lithiation, followed by quenching with various electrophiles, sufficient steric bulk is added to prevent rapid racemisation, and the compound is now considered atropisomeric. When quenched with an aldehyde, a new stereo-centre is created and the chiral axis of the amide acts as an auxiliary to generate **38** diastereoselectivity. Curran and co-workers employed a similar strategy, using (–)-sparteine as a stoichiometric chiral ligand, to create amides **39**, with moderate enantioselectivity (Scheme 1.1b).^[38]



Scheme 1.1: First use and stereoselective synthesis of atropisomeric amides.

Uemura and co-workers used a planar chiral auxiliary in **40** (Scheme 1.2) to trap the amide in one configuration and generate benzamides **42** in high enantioselectivity following removal of chromium (Scheme 1.2).^[39] It was found that the dialkylamino group of **40** was positioned on the opposite face of the ring to the chromium atom due to steric factors. Then, once the ethyl group is added and the chromium removed, the barrier to rotation of **42** is high enough to prevent rapid racemisation. This methodology was later coupled with the use of a chiral lithium amide in a similar reaction involving desymmetrisation of chromium complexes, which proceeded in high enantioselectivity (93:7 e.r.).^[40]

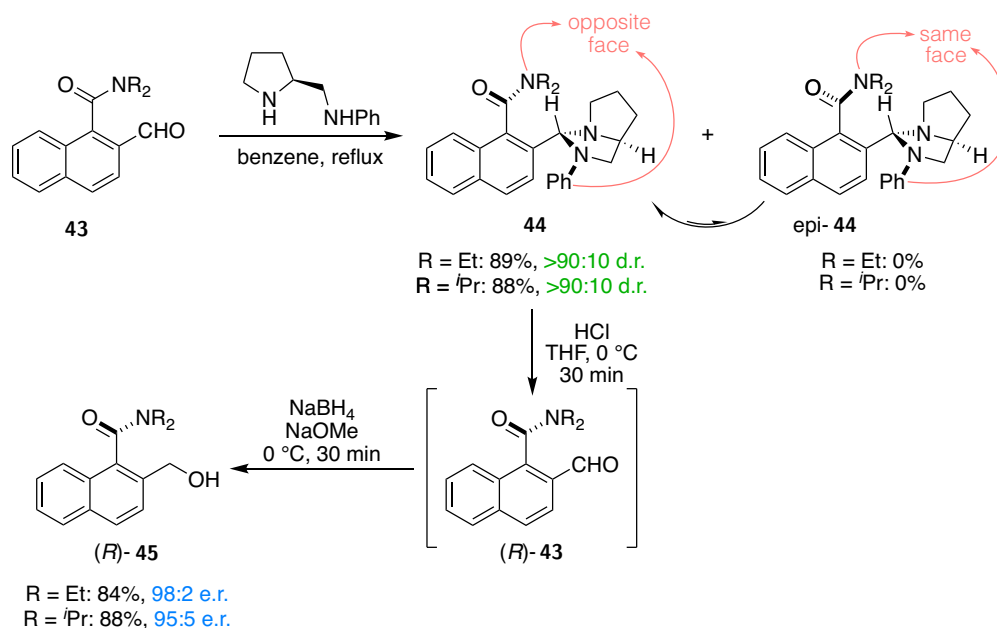


Scheme 1.2: Enantioselective synthesis using planar chiral auxiliary.

Thermodynamic Resolution

Clayden and co-workers exploited certain naphthamides able to rotate rapidly at elevated temperatures (named “near-atropisomers”) to resolve enantiomers using a thermodynamic resolution (Scheme 1.3).^[41] Reaction of a chiral proline derivative with aldehyde **43** forms an amina in a mixture of diastereomers **44** and *epi*-**44**. The high temperature of the

reaction enables rotation about the Ar–CO bond, and the minor diastereomer, *epi*-**44**, converts to the thermodynamically more stable isomer **44**. This ensures the bulky amide substituents are on the opposite face to the phenyl group. **44** is isolated, deprotected, and reduced at 0 °C (to prevent racemisation of the aldehyde) to yield highly enantioenriched alcohol **45**.

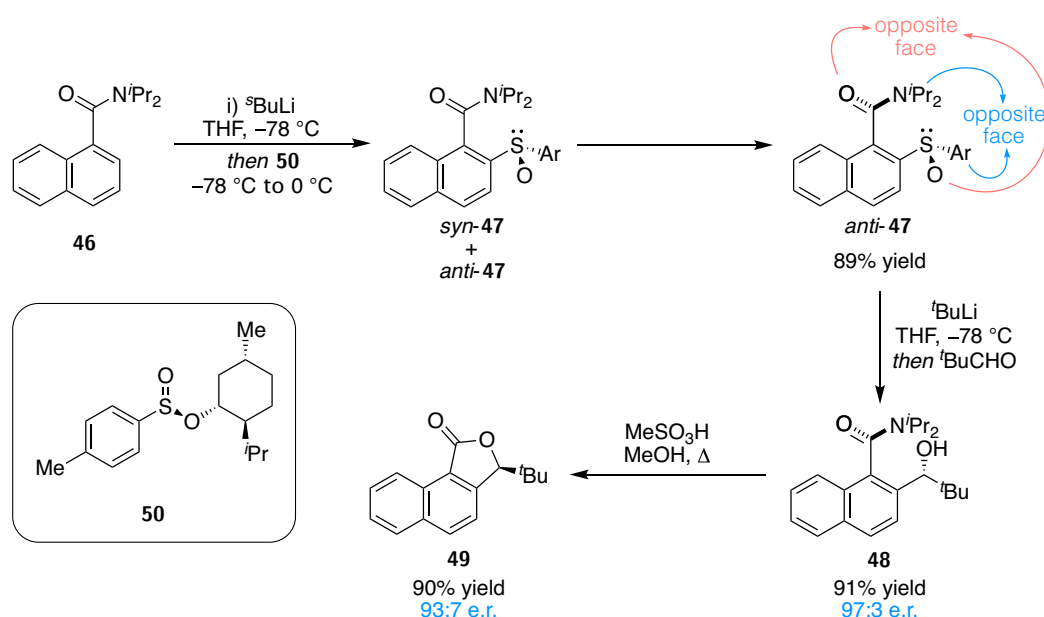


Scheme 1.3: Thermodynamic resolution of naphthamides using a chiral aminal auxiliary.

Later, ephedrine, was employed to enable the same transformation *via* oxazolidines.^[42] As a cheap, commercially available auxiliary, this was a preferable method and both enantiomers of **45** could be isolated depending on whether ephedrine or pseudoephedrine was used. However, the drawback to this method in general, is that 8-substituents are not tolerated, as the barriers to rotation of the oxazolidine or aminal are too high for facile racemisation to the more stable diastereomer.^[43]

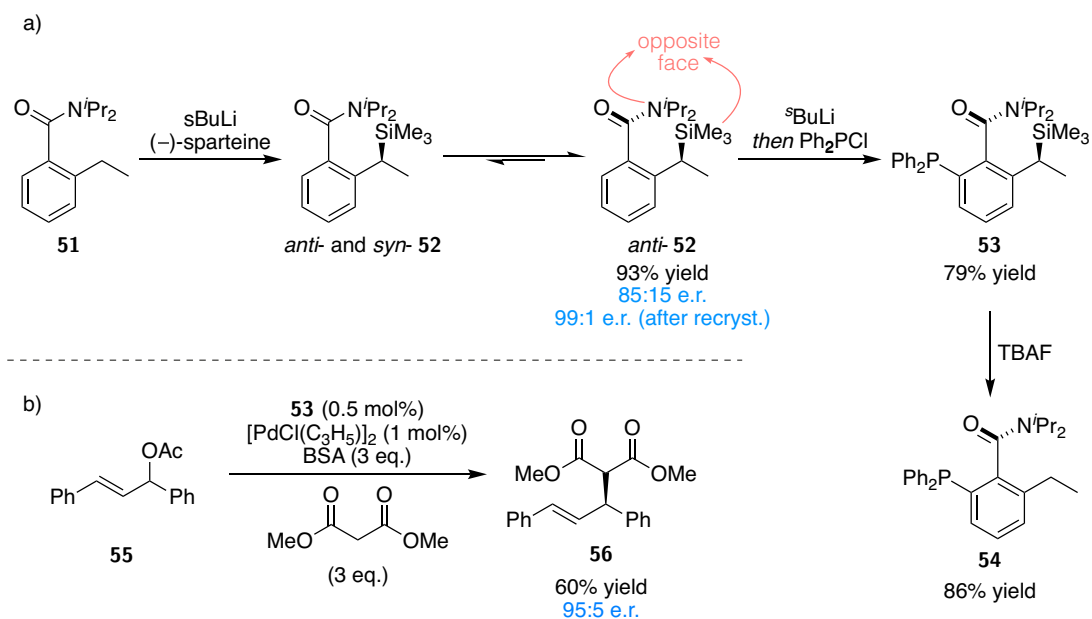
Clayden and co-workers employed a similar resolution strategy using sulfoxides (Scheme 1.4).^[44] Sulfoxides **47** have a low barrier to rotation due to a lack of steric bulk where the lone pair is situated. However, they will equilibrate to the more stable

anti-diastereomer, in which the the C–O dipole is opposite the S–O dipole (*anti*-**47**).^[45] At $-78\text{ }^{\circ}\text{C}$, $t\text{BuLi}$ removes the sulfoxides from the enantiopure compounds and the lithiated species (rotationally stable at this temperature) can be quenched with various electrophiles. When quenched with an aldehyde to give **48**, these compounds can undergo axial to point chirality transfer followed by lactonisation to yield benzofuran **49** in high enantioselectivity.



Scheme 1.4: Thermodynamic resolution of naphthamides using sulfoxide auxiliary.

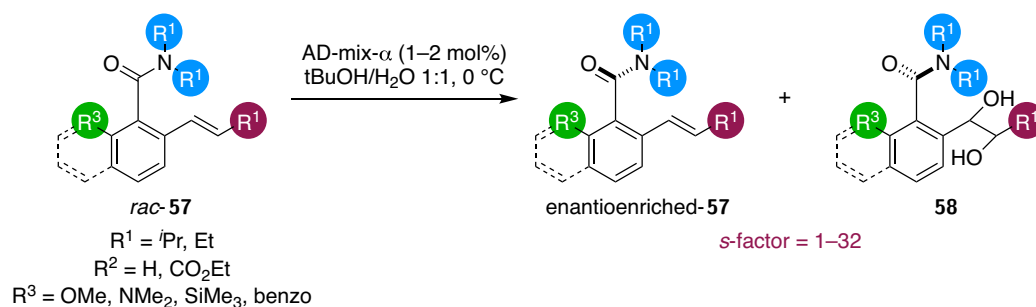
Another use of near-atropisomers with low barriers to rotation is the enantioselective silylation directed by sparteine (Scheme 1.5).^[46,47] Once **51** is silylated, amide **52** can rotate so that the bulky amide substituents are opposite the large silyl group (*anti*-**52**). Then, after *ortho*-lithiation, a variety of electrophiles can be added to raise the barrier to rotation so the compound is stable to racemisation. Quenching with Ph_2PCl resulted in chiral phosphine **53**, which can be used to effect the enantioselective allylic substitution of **55** in high selectivity. Interestingly, use of desilylated ligand **54** gave racemic **56**. It was discovered that adding palladium decreased the barrier to rotation of **54** from $26.1\text{ kcal mol}^{-1}$ ($t_{\frac{1}{2}}(\text{rac}) = 2\text{ days}$) to $21.0\text{ kcal mol}^{-1}$ ($t_{\frac{1}{2}}(\text{rac}) = 5\text{ min}$).



Scheme 1.5: a) Synthesis of axially chiral phosphorous ligand. b) Asymmetric allylic substitution using **53**.

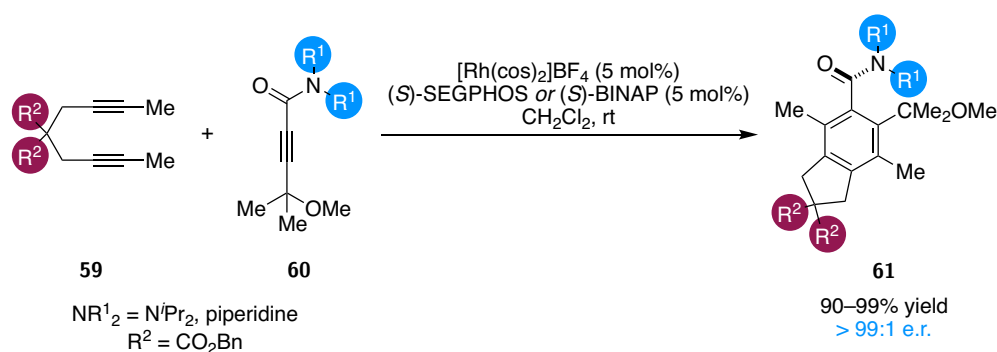
Catalytic Enantioselective Syntheses

A catalytic kinetic resolution of atropisomeric amides was first carried out by Walsh and co-workers (Scheme 1.6).^[48] Low loadings of AD-mix- α achieved a Sharpless asymmetric dihydroxylation with high selectivity factors (s up to 32), enabling isolation of highly enantioenriched **57** (up to 97:3 e.r.).



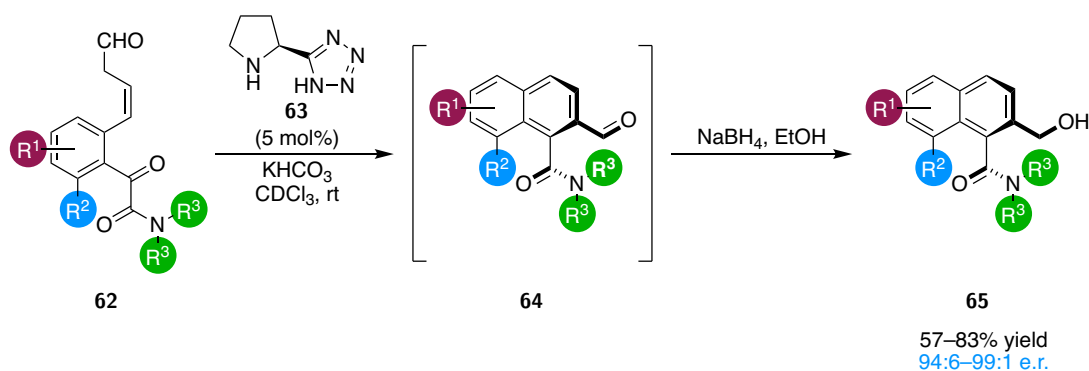
Scheme 1.6: Kinetic resolution of benzamides.

The first complete catalytic, enantioselective synthesis of axially chiral amides was achieved by Tanaka and co-workers *via* a rhodium catalysed [2+2+2] cycloaddition (Scheme 1.7).^[49] This novel aromatisation approach yielded dialkylbenzamides **61** in excellent enantioselectivity using a BINAP or SEGPHOS ligand. A similar approach can be used to generate atropisomers with restricted rotation about a C–N bond.^[50]



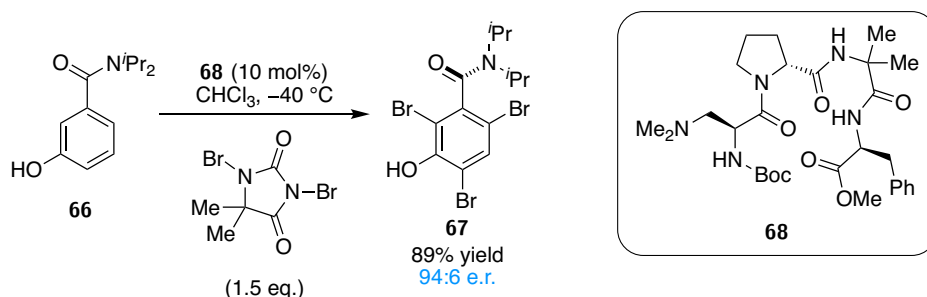
Scheme 1.7: Enantioselective [2+2+2]-cycloaddition.

Recent work by Sparr and co-workers also created atropisomers through enantioselective formation of an arene ring (Scheme 1.8). Using proline derived **63** as a catalytic auxiliary, **62** underwent an aldol condensation to give aldehyde intermediate **64**. As this possesses a low barrier to rotation, it is reduced *in situ* to give rotationally stable alcohol **65** in excellent enantioselectivity.



Scheme 1.8: Enantioselective aldol condensation.

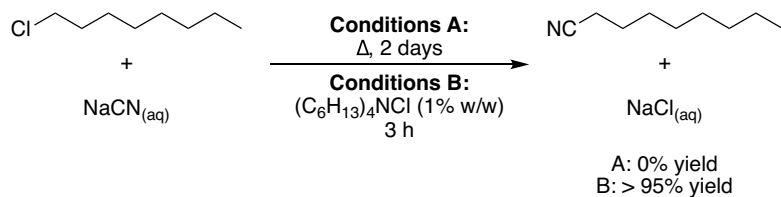
Chiral benzamides have also been synthesised catalytically by peptide-catalysed bromination (Scheme 1.9).^[51,52] Bromination of **66** (which has a very low barrier to racemisation) leads to conformationally stable **67** using peptide catalyst **68**. Miller shows bromination between the hydroxy and amide group occurs first and determines the stereochemistry of the chiral axis.



Scheme 1.9: Enantioselective bromination to generate an atropisomer.

1.2 Phase-Transfer Catalysis

Phase-transfer catalysis is a powerful method in organic chemistry which enables the interaction of two molecules that are separated by a phase boundary. In this way, cheap and mild conditions can be used to promote reactivity between compounds that would otherwise be inert. The capability of this methodology was exemplified by the work of Starks on the reaction of 1-chlorooctane and aqueous sodium cyanide (Scheme 1.10).^[53] Heating these compounds to reflux for over 2 days gave no reaction (Conditions A). However, on addition of a catalytic amount of a chiral ammonium salt catalyst, the reaction proceeded to completion in under 3 hours (Conditions B).



Scheme 1.10: Reaction of 1-chlorooctane with and without a phase transfer catalyst.

This reaction follows an extractive mechanism, first proposed by Starks^[54] (Figure 1.11a). The phase-transfer catalyst (Q^+Y^-), present in both the aqueous and organic phase, undergoes a counter-ion metathesis in the aqueous phase to give (Q^+X^-). The anion can then escort the reactive cation X^- across the phase boundary interface into the organic layer where it can react with substrate $\text{R}-\text{Y}$ to give the product, $\text{R}-\text{X}$ and return catalyst Q^+Y^- which extracts Y^- into the aqueous phase once more. This mechanism has since been modified in the event that the catalyst is very lipophilic and not soluble in the aqueous phase and therefore counter-ion metathesis occurs in the interface.^[55]

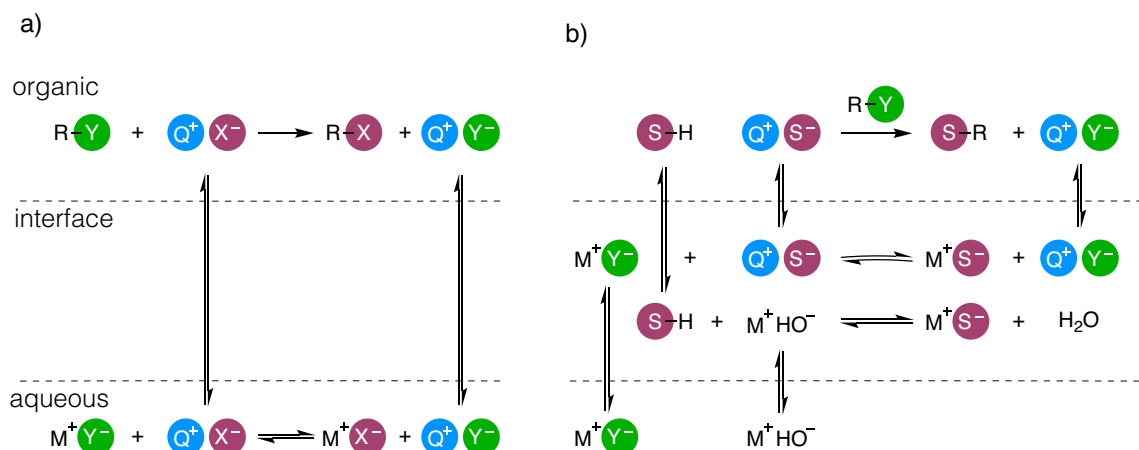


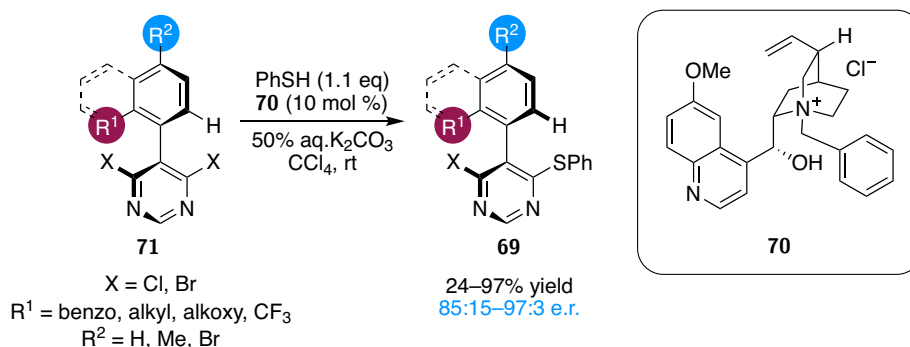
Figure 1.11: a) Starks' extractive mechanism. b) Markoza's interfacial mechanism.

Makosza has suggested a second plausible mechanism, the interfacial mechanism (Figure 1.11b) where substrate $\text{S}-\text{H}$ is deprotonated at the interface and forms an ion pair

with the catalyst anion Q^+ to give Q^+S^- . This ion pair moves into the organic phase, where the substrate reacts with $R-Y$ to give the product $S-R$ and reform the catalyst Q^+Y^- .

1.2.1 Asymmetric Phase-Transfer Catalysis

By using a chiral phase-transfer catalyst, this methodology can be used to synthesise chiral compounds with high enantioselectivity. This approach has previously been used by the Smith group to make atropisomeric compounds such as biaryl **69** *via* a nucleophilic aromatic substitution (S_NAr) using cinchona alkaloid derived catalyst **70** (Scheme 1.11).^[56] The thiophenolate and quaternary ammonium anion of **70** form a chiral pair which selectively reacts with dichloropyrimidine **71** in a desymmetrisation reaction.

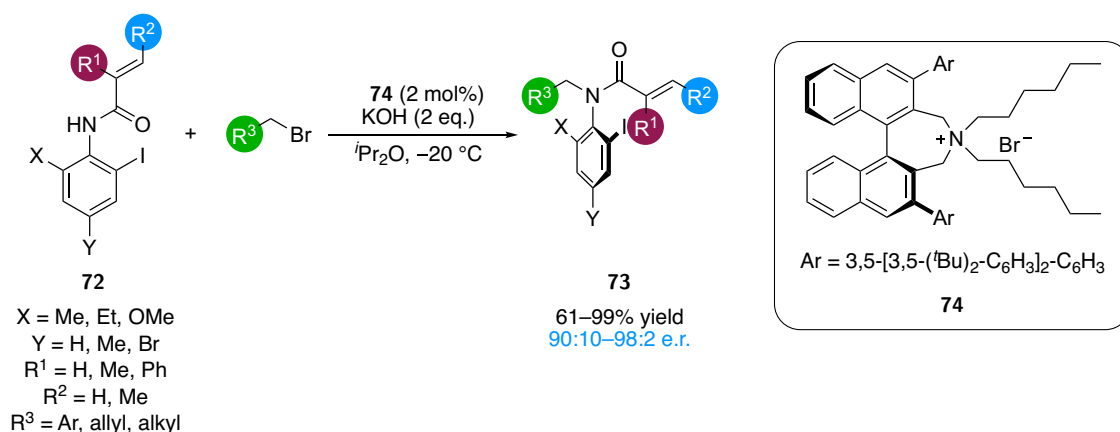


Scheme 1.11: Phase-transfer catalysed desymmetrisation.

The enantioenrichment of **69** is enhanced by a kinetic resolution by which the undesired enantiomer reacts faster with another molecule of thiophenol to give the achiral disubstituted product which can be separated from desired **69**.

Maruoka and co-workers have successfully used phase-transfer catalysis to synthesise non-biaryl atropisomers **73** (Scheme 1.12) with high enantioselectivity.^[57] Starting material

72, a non-atropisomeric anilide, is selectively alkylated using binaphthyl derived chiral ammonium salt **74**. Due to an increased barrier to rotation, **73** is now fixed as an enantioenriched stereoisomer.

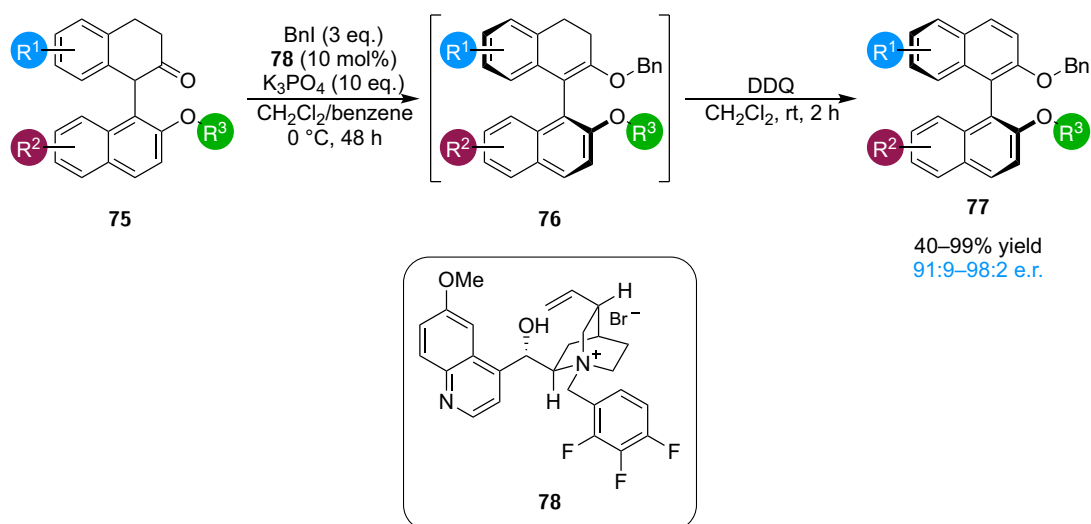


Scheme 1.12: Phase-transfer catalysed formation of atropisomeric anilides.

1.3 Project

1.3.1 Project Background

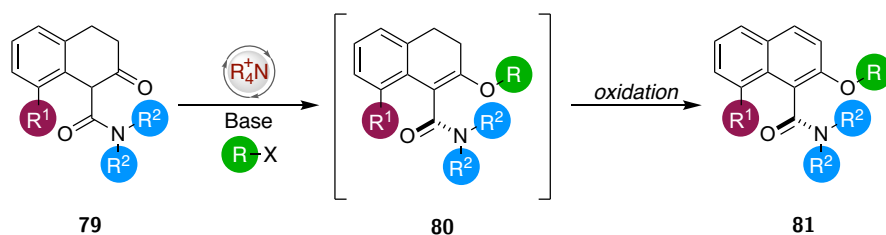
Recent work in the Smith group has concerned the synthesis of atropisomers *via* enantioselective *O*-alkylation using phase-transfer catalysis.^[58] This has been used to make atropisomeric BINOL derivatives **77** (Scheme 1.13). Under phase-transfer conditions, chiral but racemic β -tetralone **75** is deprotonated and alkylated exclusively on oxygen to give chiral enol ether **76** in high selectivity. This is then oxidised using DDQ to give the fully aromatic product **77**.



Scheme 1.13: Catalytic enantioselective synthesis of BINOL derivatives.

1.3.2 Project Aims

It was thought the above strategy could be used to make non-biaryl atropisomers, in particular, naphthamides (Scheme 1.14). Starting from racemic β -tetralone **79**, the above reaction should occur, in a similar manner, to give the chiral enol ether **80** and once again, this can be oxidised to give the aromatic naphthamide **81**. These naphthamides should have a sufficient barrier to rotation to prevent racemisation at room temperature.^[21,59] However it was unknown if intermediate **80** would possess a sufficient barrier to rotation to resist racemisation for the duration of the reaction. Therefore, the barrier of **80** would need to be determined during racemic studies of this reaction before investigation of any enantioselective reactivity.



Scheme 1.14: Strategy for catalytic enantioselective synthesis of naphthamides.

2 Alkylation of β -Tetralones

2.1 Substrate Selection and Synthesis

For the desired *O*-alkylation to be successful, the enol ether must have a sufficient barrier to rotation to resist racemisation at room temperature for the duration of the enantioselective reaction (24–48 h). In the BINOL derivatives project shown in Scheme 1.13, two compounds were tested for rotation at room temperature (Figure 2.1).^[60] Enol ether **82** was found to racemise at room temperature with a barrier of 25.0 kcal mol⁻¹. Enol ether **83**, however, with an additional *ortho*-substituent, required higher temperatures for any observable racemisation, and had a high barrier to rotation of 32.0 kcal mol⁻¹. Enol ether **83** was therefore able to withstand the long reaction times before oxidation was initiated.

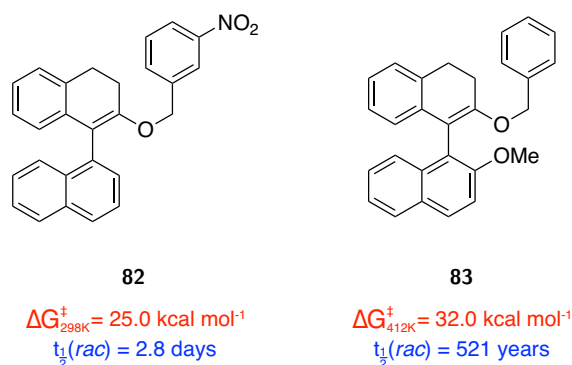


Figure 2.1: Barriers to rotation of naphthyl enol ethers.

Non-biaryl atropisomers such as amides typically have lower barriers to rotation than binaphthyl derivatives. Consequently, synthesis of atropisomeric amides **84** (Figure 2.2) *via* enol ether **85** would require large groups at the 8-position of the naphthalene ring (R^1 ,

Figure 2.2) and on the amide (R^2). For initial tests of this reaction, Br was chosen as a suitable 8-substituent, and isopropyl and cyclohexyl groups (**86** and **87**) were selected as appropriate amide substituents, as both have been observed in numerous atropisomers of this kind.^[61]

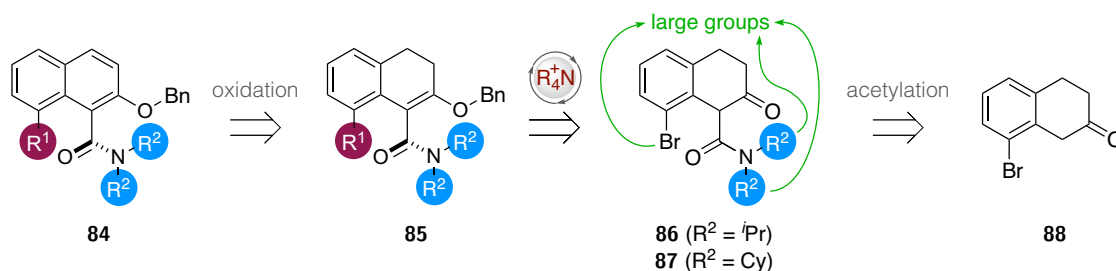


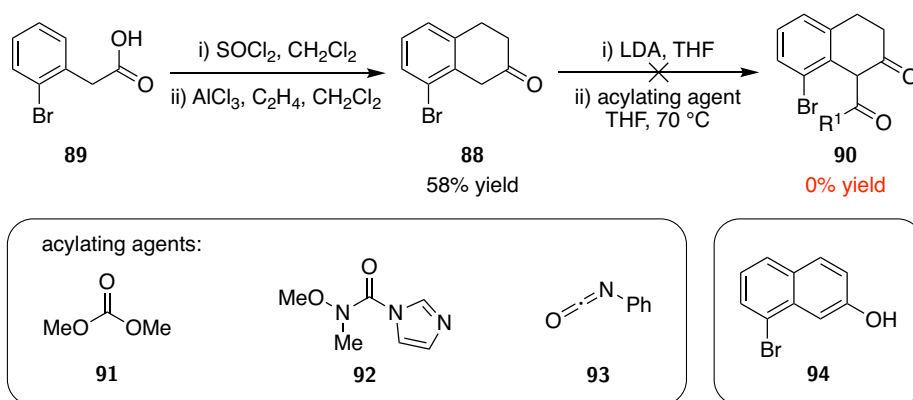
Figure 2.2: Suitable substrates for enantioselective *O*-alkylation.

2.1.1 Synthesis 1: β -Tetralone Acylation

A convenient divergent synthesis to β -tetralones **86** and **87** was an acylation of **88** (Figure 2.2). Ketones can be acylated using dimethyl carbonate (**91**, Scheme 2.1)^[62] or imidazole based reagents such as **92**.^[63] This would enable further functionalisation *via* an addition-elimination with different amines to afford the desired amide tetralones. Alternatively, the reaction of β -tetralone **88** with an isocyanate such as **93** would generate the amide in one step.^[64]

β -tetralone **88** was readily prepared by forming the acid chloride of 2-bromophenylacetic acid (**89**, Scheme 2.1) using thionyl chloride, followed by a reaction with aluminium chloride and ethylene.^[65]

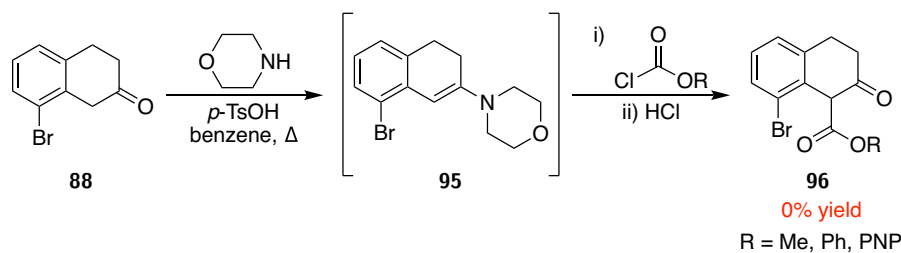
Various acylating conditions were then attempted. The use of dimethylcarbonate (**91**) or CLAmP (**92**) led to no product formation and merely returned starting material. Quenching the lithium enolate with isocyanate **93**, to form an amide, gave no product, and only



Scheme 2.1: Attempted acylation of **88**.

a small amount of oxidised starting material, 8-bromonaphthalen-2-ol (**94**), was isolated. The reaction of **88** with LDA, followed by quenching with D₂O yielded the deuterated compound, proving enolate formation was proceeding, however, the subsequent acylation did not seem to be possible. This could be due to the steric crowding around the site of acylation, as compounds without an 8-substituent were functionalisable under similar acylating conditions.^[62] Due to these specific requirements, it seemed this approach was not going to succeed in giving the required amide tetralone.

Acylation was also attempted *via* enamine **95** (Scheme 2.2) which was formed using morpholine and catalytic *p*-toluenesulfonic acid. The formation of **95** was confirmed by ¹H NMR analysis of crude reaction mixture. Different chloroformates were added followed by hydrolysis of the resulting iminium products by acidic work up. However, no tetralone **96** was observed under these conditions.

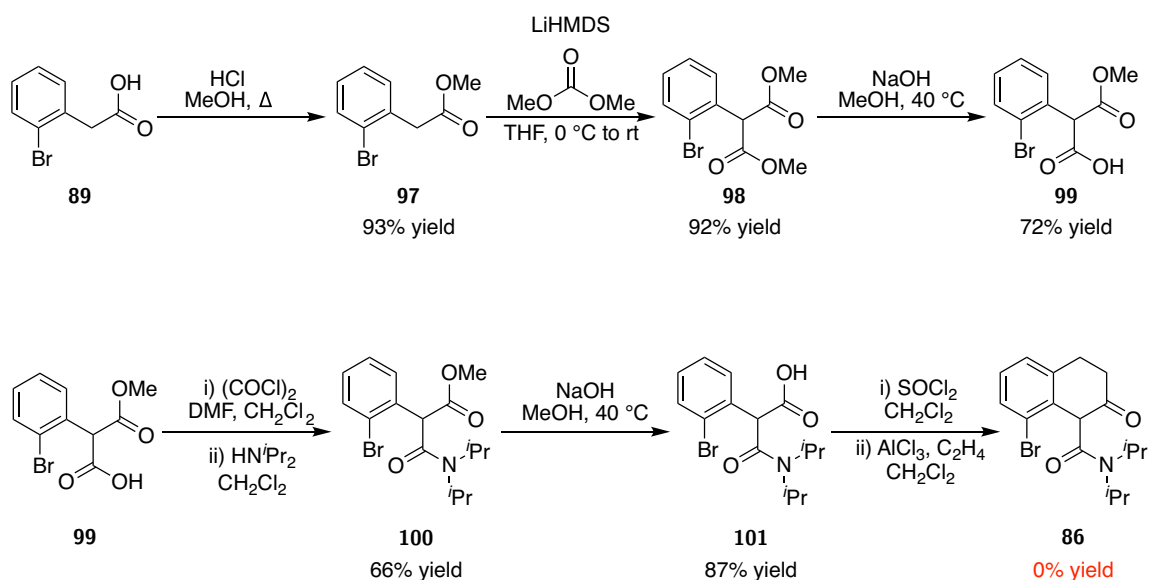


Scheme 2.2: Attempted acylation of **88** *via* enamine **95**.

The difficulties associated with acylation of β -tetralone **88** using standard methods, prompted a new approach to β -tetralone **86** and **87**.

2.1.2 Synthesis 2: Final Step Formation of β -Tetralone

The electrophilic aromatic substitution of 2-bromophenylacetic acid with ethylene was an effective way to form β -tetralones (Scheme 2.1). This method could also be used to form the desired β -tetralones **86** and **87** with the amide moieties already in place (Scheme 2.3).

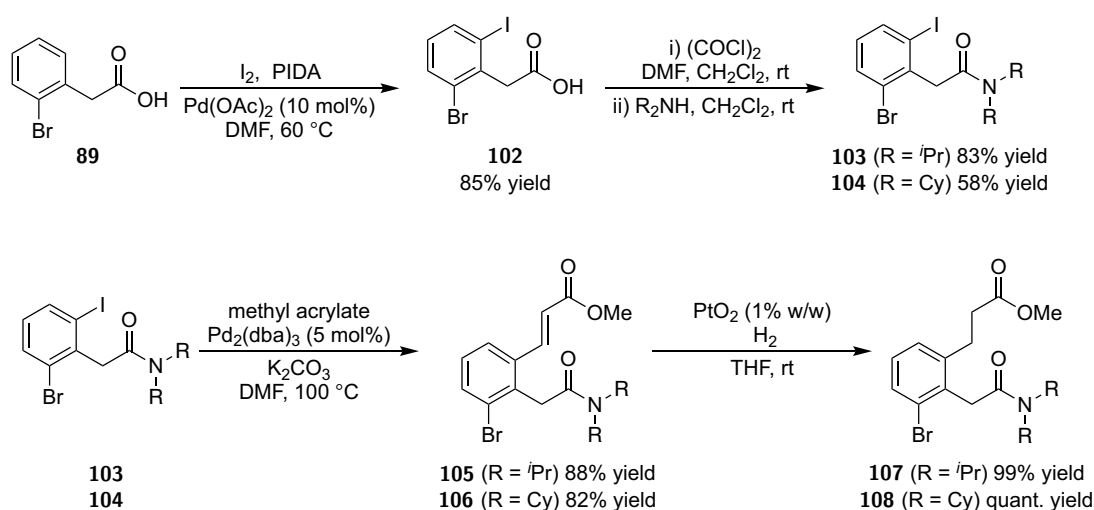


Scheme 2.3: Attempts to form β -tetralone by reaction with ethylene.

Synthesis of precursor **101** was straightforward using simple procedures. 2-Bromophenylacetic acid was esterified in methanol to give **97**, before reaction with dimethyl carbonate to give 1,3-diester **98**. A mono-ester hydrolysis yielded **99** which was coupled to diisopropylamine *via* the acyl chloride to give **100**. Hydrolysis of **100** revealed acid **101**, on which the aromatic substitution reaction was tested. Unfortunately, the reaction of the acyl chloride of **101** and ethylene in the presence of aluminium chloride gave no product. Once again, another direction was necessary.

2.1.3 Synthesis 3: Dieckmann Condensation

The third attempt at synthesising a plausible starting material concerned the formation of the β -tetralone by a Dieckmann cyclisation. Construction of the cyclisation precursor began with an iodination of 2-bromophenylacetic acid (**89**, Scheme 2.4) using a modified procedure from Yu.^[66] An amide coupling of **102** (*via* the acyl chloride) and diisopropylamine or dicyclohexylamine yielded amides **103** and **104**, respectively. These underwent a Heck reaction where the amide reacted with methyl acrylate exclusively at the C–I bond to yield **105** and **106**. Hydrogenation of **105** using palladium on carbon led to competing reduction of the C–Br bond. Fortunately, the use of platinum oxide in a hydrogen atmosphere led to hydrogenation product **107**. These conditions were repeated on **106** to give **108** in quantitative yield.

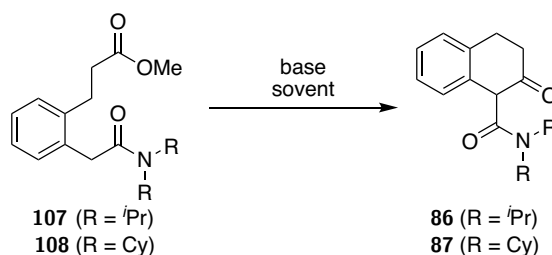


Scheme 2.4: Synthesis of the Dieckmann cyclisation precursor.

Amides **107** and **108** were subjected to various base/solvent systems to probe the feasibility of a Dieckmann cyclisation (Table 2.1). The use of sodium methoxide in toluene (entry 1) gave no reaction. Sodium hydride in THF (entry 2) resulted in ester hydrolysis and yielded no desired product. Similarly, potassium *tert*-butoxide in toluene (entry 3)

gave the hydrolysed ester as the only isolable product. Fortunately, use of KHMDS in anhydrous THF gave **86** in good yield, however, the reaction was unreliable, and when cyclohexyl substituted amide **108** was subjected to the same conditions, the yield was low (33%, entry 5). Water content was found to be extremely important for attaining good yields, as hydrolysis of the ester to the acid was always detected by mass spectrometry analysis. When anhydrous THF from a sodium still was used (approx. water content $\approx$ 45 ppm),^[67] the yield increased to 43% (entry 5). Use of THF stored under 4 Å MS for 72 h, in accordance with procedures suggested by Williams *et al.*^[67] (water content = 4.5 ppm as measured by Karl Fischer titration) yielded 60% of **87** and gave much more consistent results.

Table 2.1: Dieckmann condensation conditions.



Entry	R	Base	Solvent	Yield (%)
1	<i>i</i> Pr	NaOMe	toluene	0
2	<i>i</i> Pr	NaH	THF	0
3	<i>i</i> Pr	KO ^t Bu	toluene	0
4	<i>i</i> Pr	KHMDS	THF ^a	59
5	Cy	KHMDS	THF ^a	33
6	Cy	KHMDS	THF ^b	43
7	Cy	KHMDS	THF ^c	60

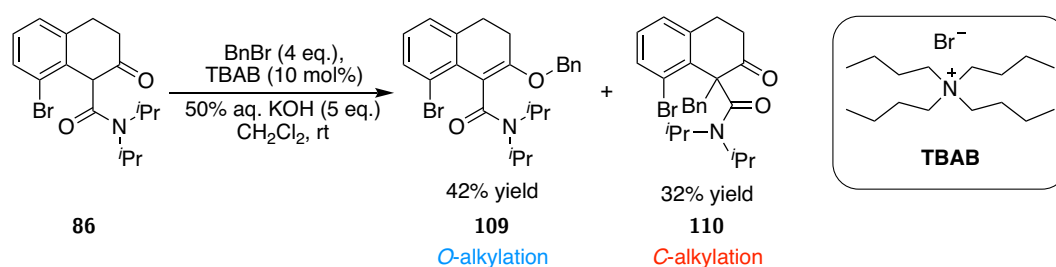
^a water content = 50–100 ppm.

^b water content $\approx$ 45 ppm.

^c water content = 4.5 ppm.

2.2 O-Alkylation to Racemic Product

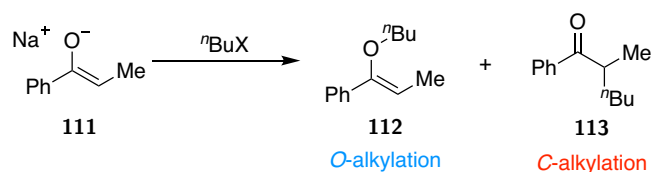
With the β -tetralones in hand, the desired *O*-alkylation was tested on **86** using an achiral catalyst, tetrabutylammonium bromide (TBAB) (Scheme 2.5). It immediately became apparent that two distinct products were forming during the reaction. After isolation and characterisation, these were determined to be desired product **109** and the undesired side product of *C*-alkylation, **110**.



Scheme 2.5: Phase-transfer catalysed reaction of β -tetralone **86** using achiral catalyst.

2.2.1 Ambidentate Reactivity of Ketones

The ambidentate reactivity of ketones is a known phenomenon and there are various ways to change the ratio of products observed.^[68] Wagner and co-workers investigated the important influence of solvent and electrophile leaving group on the *O*-alkylation of **111** (Table 2.2).^[69] Polar aprotic solvents increased the amount of *O*-alkylation; HMPA gives higher *O*-alkylation than DMSO and diethyl ether. This trend has been observed in many other enolate alkylations.^[70] Polar solvents increase the dissociation of the enolate and the cation leading to the general notion suggested by Le Noble and Morris that “*the freer the anion, the larger the O to C ratio.*”^[70] This suggests why protic solvents, such as MeOH, give less *O*-alkylation. The oxygen and the cation are completely separated but the oxygen atom is now surrounded by solvent molecules (i.e. less “free”), leading to less *O*-alkylation.^[71]

Table 2.2: Wagner’s investigations into *O* vs. *C*-alkylation showing yield of *O*-alkylated product **112**.

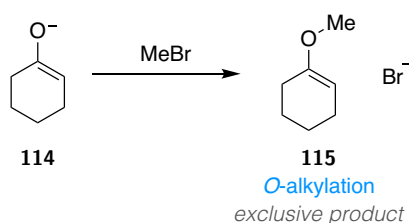
X	Solvent		
	HMPA	DMSO	Et ₂ O
I	15	10	1
Br	40	23	5
Cl	67	46	18
OTs	85	44	20
F	96	N/A	N/A

Herein lies the problem with regard to the desired *O*-alkylation of **86** under phase-transfer catalysis conditions. In general, enantioselective phase-transfer catalysis needs tight ion pairing to induce high stereoselectivity. This is evident in decreased selectivity when polar solvents are used.^[72–75] Furthermore, HMPA and DMF are miscible with water and it is unlikely the reaction would proceed with high enantioselectivity if the catalyst is not required for interaction of substrates with each other or with base. It appears likely that reaction conditions which will generate a higher amount of *O*-alkylation will give lower enantioselectivity.

Table 2.2 also demonstrates that the nature of the electrophile leaving group has a large impact on the ratio of *O*-alkylation to *C*-alkylation. In general, the trend observed is: $\text{F} > \text{OTs} > \text{Cl} > \text{Br} > \text{I}$.^[69,76,77] This effect was originally rationalised by hard and soft acids and bases theory,^[78] stating that the hard oxygen would prefer hard electrophiles.^[76,77] However, computational studies by Houk and co-workers show that *O*-alkylation with all electrophiles is kinetically favoured whilst *C*-alkylation is thermody-

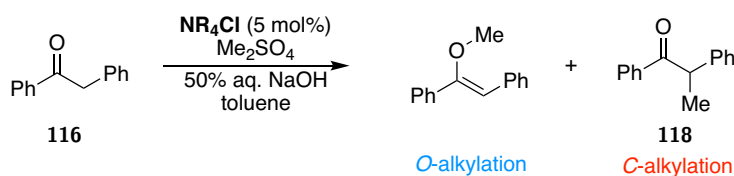
namically favoured.^[79] They predict that *C*- vs. *O*-alkylation is driven by “*the ability of the halide to influence the structures of metal enolate aggregates.*” It is likely that the extent of *O*-alkylation is determined by the transition state of the reaction and stronger electrophile–leaving group bonds lead to a more substrate-like transition state and will result in *C*-alkylation.

Gas-phase studies into the alkylation of cyclohexanone also indicate exclusive reaction on oxygen with methyl bromide (Scheme 2.6), a “soft” electrophile which showed strong tendencies towards *C*-alkylation in Table 2.2.^[80]



Scheme 2.6: Gas-phase study of alkylation of cyclohexanone.

Experiments carried out by Dehmlow and co-workers show the effect of the enolate counterion in phase-transfer catalysed reactions on *O*-alkylation of deoxybenzoin (Table 2.3).^[81] An increased amount of *O*-alkylation is observed with increased size and lipophilicity of the R group of the catalyst cation, until the counterion becomes too lipophilic (R = ⁿPen, entry 5), then the selectivity starts to shift towards *C*-alkylation.

Table 2.3: Effect of counterion on *O*-alkylation.

Entry	$^+\text{NR}_4$	<i>O</i> -alkylation (%) ^a
1	$^+\text{NMe}_4$	55
2	$^+\text{NEt}_4$	82
3	$^+\text{N}^n\text{Pr}_4$	93
4	$^+\text{N}^n\text{Bu}_4$	94
5	$^+\text{N}^n\text{Pen}_4$	93
6	$^+\text{N}^n\text{Hex}_4$	84

^a Conversion = 96–100%

The literature examples discussed above provide guidance on how to overcome the issue of enolate *C*-alkylation of **86** in this work. Despite the unclear reasons for the observed trend with differing electrophile leaving groups, this could be an effective way to increase *O*-selectivity for alkylation of **86**. The phase-transfer catalysed reaction was tested using a variety of leaving groups and analysed by ^1H NMR spectroscopy of the crude reaction mixture (Figure 2.3). The reaction always proceeded with 100% conversion to the two alkylation products.

The previously reported trend due to electrophile leaving groups is also observed for the alkylation of **86**. The “softest” leaving group, iodide, gave the least *O*-alkylation (34%) and tosylate, the “hardest” leaving group, gave the most (78%). Subjecting the reaction to a different catalyst cation, cinchona alkaloid **119**, led to a slight decrease in *O*-alkylation (50%) compared to use of TBAB (61%). Reaction with benzyl bromide at 0 °C was carried out to probe the kinetic preference for the *O*-alkylation product, but this yielded a similar

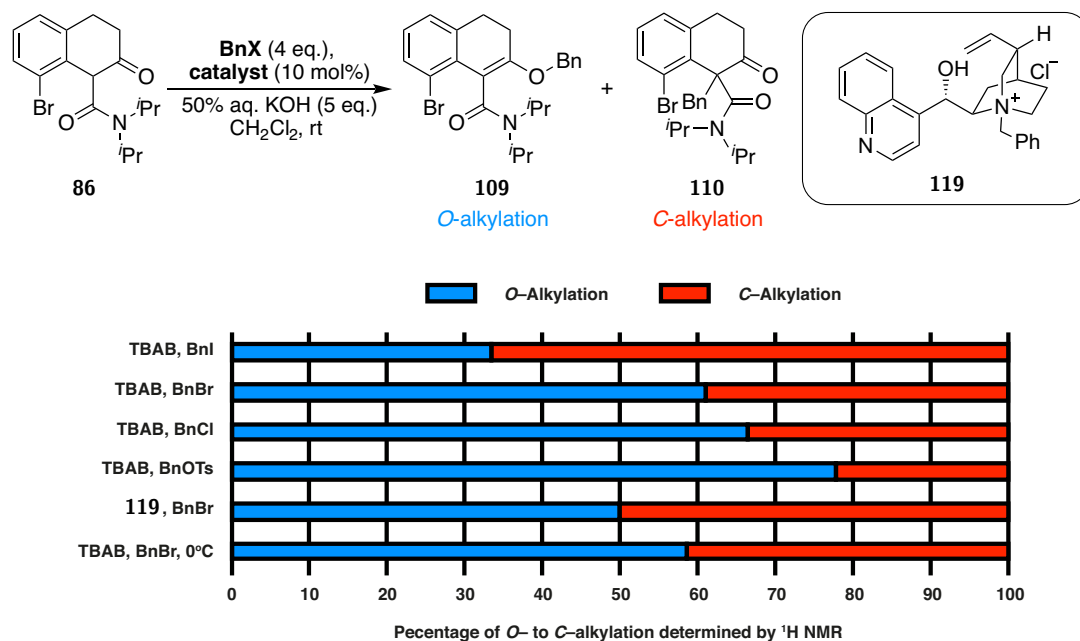


Figure 2.3: *O*- vs. *C*-alkylation varying electrophile and catalyst.

ratio of *O*-alkylation as the reaction at room temperature (59% and 61% respectively).

Whilst changing the electrophile did improve the ratio of the desired *O*-alkylated product, the yield was still limited by the presence of *C*-alkylation.

2.3 Barrier to Rotation of Enol Ethers

The presence of *C*-alkylation in the desired reaction presented an issue for this strategy to non-biaryl atropisomers. However, the barrier of rotation of enol ether **109** was still an unknown value that prompted exploration. The racemic compound was analysed by HPLC where it was discovered that the compound was racemising during the run of the sample leading to a “batman effect”. This is characterised by the presence of two peaks and a ledge between them where the trace does not reach the baseline as shown in Figure 2.4.^[82]

Trapp and co-workers developed a unified equation to calculate the rate of interconversion of two species based on the area between the two peaks on an HPLC trace.^[83] This was

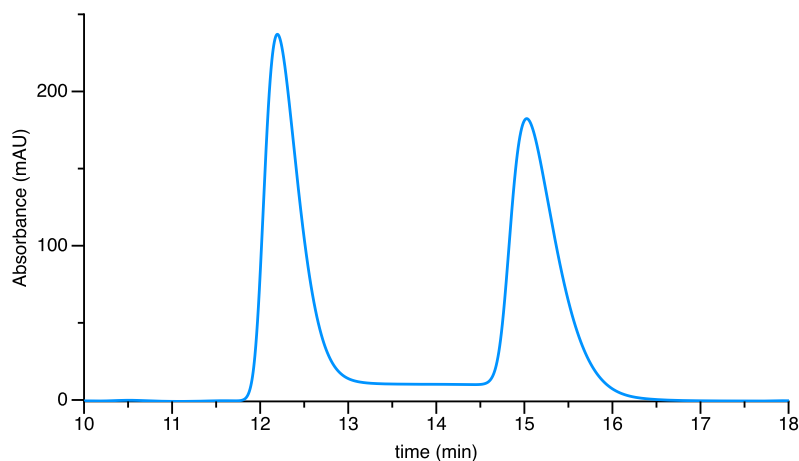


Figure 2.4: HPLC trace of **109** showing a “Batman effect”.

later developed into an easily accessible software, DCXplorer.^[84] This software generates the k_{ent} which can be used to calculate the k_{rac} and therefore $\Delta G^\ddagger$ using the equations shown in Chapter 1. Analysis of the HPLC trace of **109** using DCXplorer gives a barrier to rotation at 25 °C ($\Delta G_{298K}^\ddagger$) of 23.2 kcal mol⁻¹. This gives a $t_{\frac{1}{2}}(rac)$ of 96 min at this temperature. By Oki’s definition of atropisomerism, this compound is indeed atropisomeric. However, with such a low $t_{\frac{1}{2}}(rac)$, at the time of complete consumption of starting material (commonly 24–48 h), the product would be racemic, even if initial enantioselectivity was exceptionally high.

The low barrier of enol ether **109** was clearly a disadvantage of the current strategy for synthesising atropisomeric naphthamides, as was the *C*-alkylation issue. Nevertheless, perhaps modifying the structure of the substrate would not only improve the barrier to rotation of the enol ether, but would also increase the ratio of *O*-alkylation observed.

2.4 Changing Structure of β -Tetralone

Other potential 8-substituents that would restrict rotation of the amide are fused benzene (**120** and **121**, Figure 2.5) and trifluoromethyl (**122** and **123**).

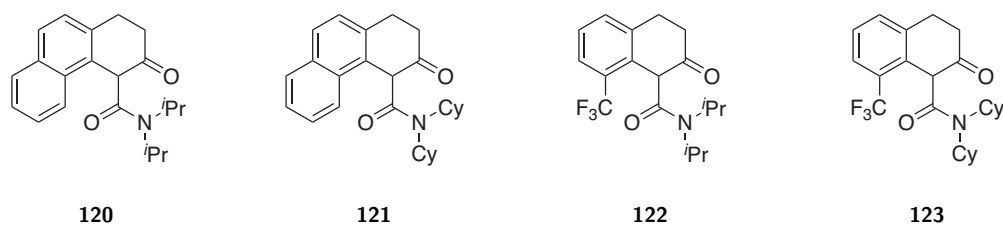
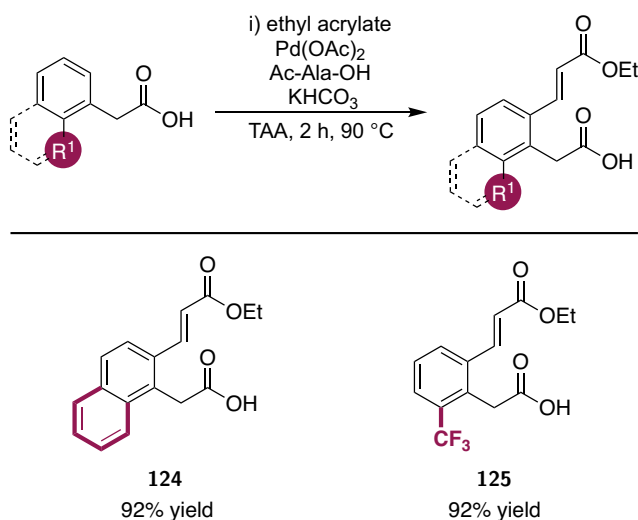


Figure 2.5: New target β -tetralone starting materials.

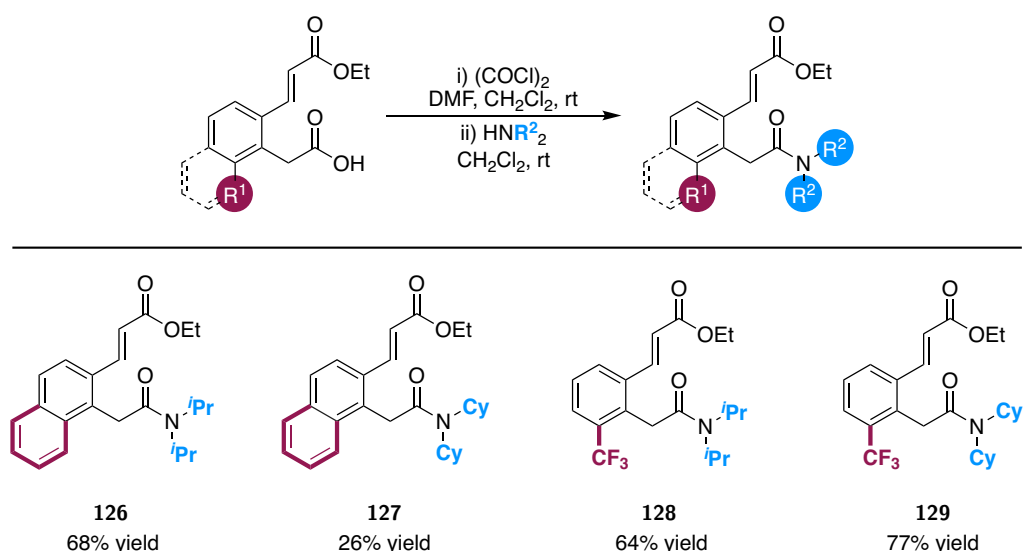
2.4.1 Synthesis of New β -Tetralones

These compounds could be synthesised similarly to the analogous bromide compounds in Scheme 2.4. However, the first step of this previous synthesis, an iodination, was only necessary to protect the C–Br bond from oxidative addition with the palladium catalyst. In the absence of an aromatic bromide, a C–H activation could be carried out on the relevant phenylacetic acid using chemistry developed by Yu (Scheme 2.7).^[85,86]



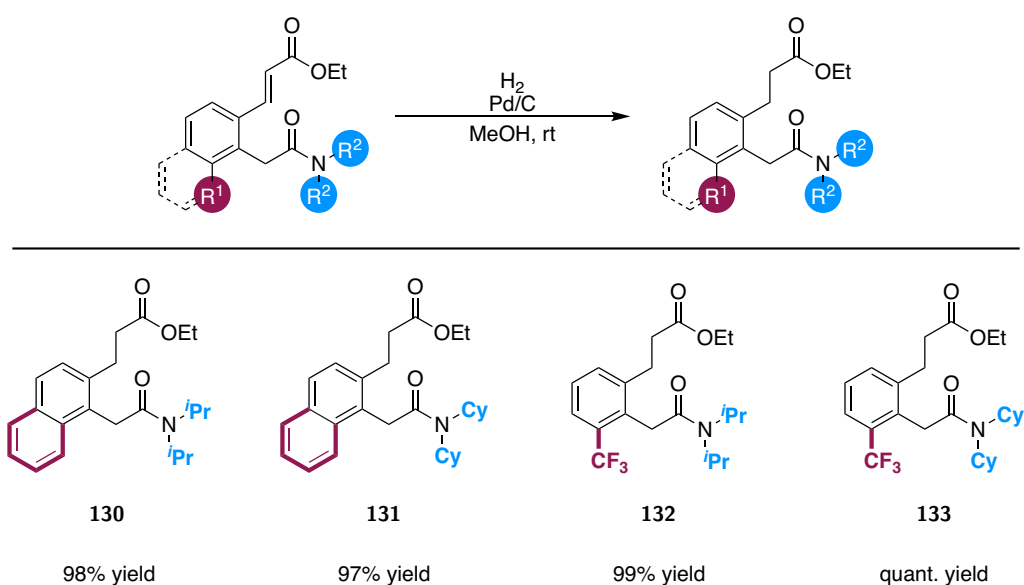
Scheme 2.7: C–H activation of phenylacetic acids.

Carboxylic acids **124** and **125** were synthesised in excellent yield (92%) from commercially available 1-naphthylacetic acid and 2-(trifluoromethyl)phenylacetic acid, respectively. Acids **124** and **125** were subjected to amide coupling with both diisopropylamine and dicyclohexylamine to give amides **126–129**. (Scheme 2.8).



Scheme 2.8: Amide coupling of acrylates.

Again, the absence of an aromatic bromide meant that a palladium catalyst could be used without the risk of C–Br reduction. Therefore palladium on carbon was used as the hydrogenation catalyst to yield four Dieckmann condensation precursors (Scheme 2.9).



Scheme 2.9: Amide coupling of acrylates.

The previously optimised conditions for the Dieckmann condensation (Table 2.1, entry 7) were employed for the cyclisation of **130–133**. This reaction proceeded in good yield to give four new β -tetralone structures.

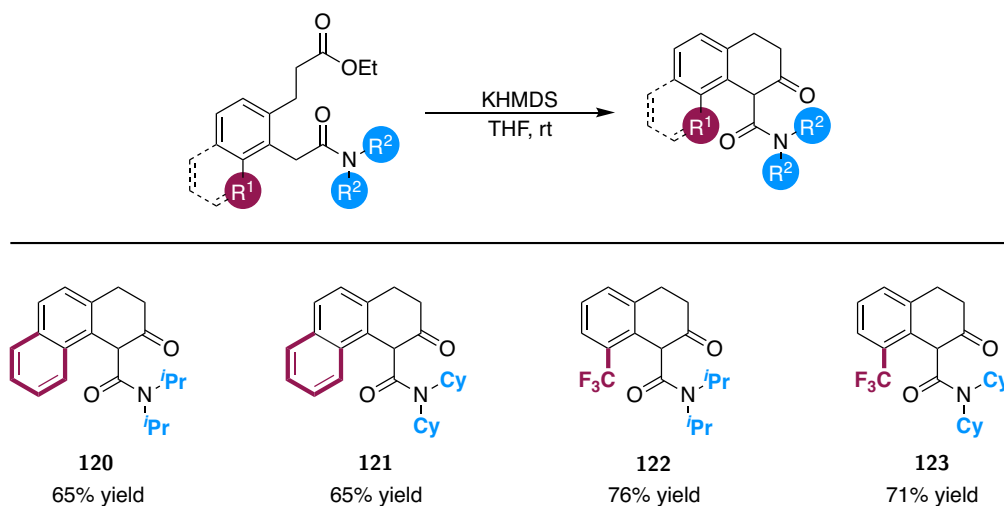


Figure 2.6: Dieckmann condensation to form β -tetralones.

2.4.2 Phase-Transfer Catalysed Alkylation of New β -tetralones

β -tetralones **120–123** and the cyclohexylamide derivative of 8-bromo tetralone (**87**), presented five opportunities to test and improve the phase-transfer catalysed alkylation. Results are shown in Table 2.4, arranged in order of increasing *O*-alkylation.

Unfortunately **121** gave very little *O*-alkylated product which could not be isolated (Table 2.4, entry 1). An unfavourable trend emerged from the remaining experiments. Alkylations that gave enol ethers with a high barrier to rotation, did so in low yields due to a high amount of *C*-alkylation (entries 2 and 3).

Tetralones **122** and **123** gave good yields and very little *C*-alkylation (< 10%), but the barriers to rotation were so low that product **137** gave a large batman effect (entry 5) and **138** was not observed to be chiral at room temperature by HPLC, indicating a very low barrier.

Table 2.4: Phase-transfer catalysed alkylation of new β -tetralone substrates.

Entry	Substrate (A)	Product (B)	Yield (%)	O-alkylation ^a (%)	$\Delta G_{298K}^{\ddagger}$ of B ^b (kcal mol ⁻¹)	$t_{\frac{1}{2}}$ (rac) (min)
1	 121	134	N/A	21	N/A	N/A
2	 87	135	20	33	23.7	218
3	 86	109	30	56	23.2 ^c	96
4	 120	136	43	69	23.0	69
5	 123	137	76	90	21.3 ^c	3
6	 122	138	74	95	N/A	N/A

^a Determined by crude ¹H NMR analysis.^b Measured in isopropanol/hexane.^c Calculated using software developed by Trapp.

This trend is opposite to what was previously seen in the development of the BINOL project (Figure 2.7).^[60] When R = H (**139**), alkylation proceeded principally on oxygen but with 12% *C*-alkylation. The product enol ether had a low barrier to rotation as shown by similar compound **82** (Figure 2.1). However, when R = OMe (**140**), *O*-alkylation product **83** was the lone isolated product and had a much higher barrier to rotation. When R¹ = OMe the nucleophilic carbon is too crowded for any *C*-alkylation to occur. However, the amides are less sterically shielded than these binaphthyl compounds. Here, it is likely the observed trend is linked to the degree of conjugation of the enolate. More resonance of the ketone leads to more *O*-alkylation.^[87] Conjugation of the enolate leads to a structure with high amounts of steric clashing and is therefore linked to the barrier to rotation.

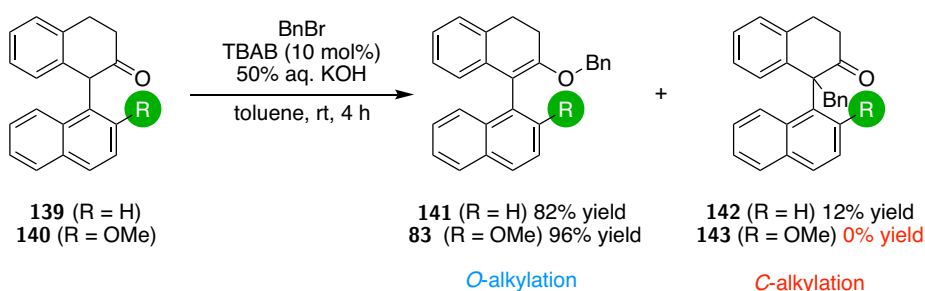
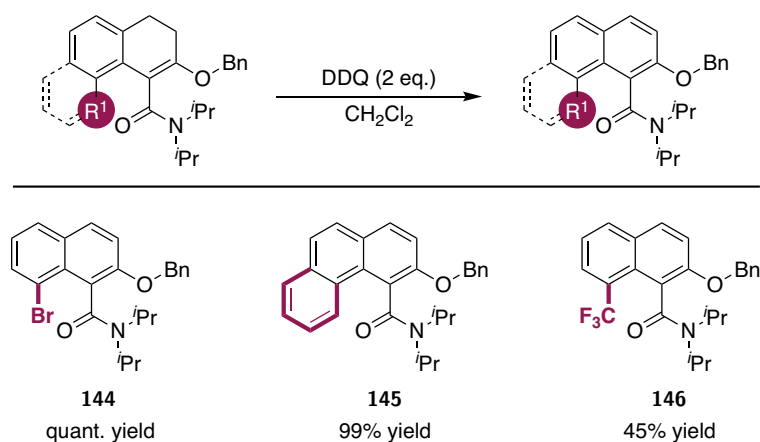


Figure 2.7: *O*- vs *C*-alkylation of naphthyl β-tetralones

It was becoming apparent that the current strategy would not succeed in producing the desired non-biaryl atropisomers; factors giving high barriers to rotation and factors giving high ratios of *O*-alkylated products, such as solvent or substrate structure, were mismatched. However, investigations of fully aromatic naphthamides of this kind would provide insight into novel atropisomeric compounds.

2.5 Barriers to rotation of Benzylated Naphthamides

The isopropyl amide enol ethers **109**, **136** and **138** were subsequently oxidised using DDQ (Scheme 2.10).^[58,88] Oxidation worked well when $R^1 = \text{Br}$ or was a fused benzene, giving naphthamides **144** and **145** in quantitative or nearly quantitative yield. However, when $R^1 = \text{CF}_3$, oxidation proceeded very slowly leading to decomposition of the starting material and as a result the yield of **146** was reduced.



Scheme 2.10: Oxidation of enol ethers using DDQ.

The barriers to these compounds should be sufficiently high to allow them to be conformationally stable at room temperature.^[21] As there was not yet an asymmetric method to synthesise these naphthamides, the enantiomers were separated by semi-preparative HPLC. Then, a single enantiomer was heated in *m*-xylene and the erosion of e.e. was measured over time by HPLC (Figure 2.8).

When e.e. was plotted against time, a clear exponential decay was seen (Figure 2.9a). As mentioned in Chapter 1 (Equation 1.2), a plot of $\ln\left(\frac{100}{\text{e.e.}}\right)$ against time will give k_{rac} as the gradient (Figure 2.9b). Then, using Equation 1.5, $\Delta G_{394K}^\ddagger$ can be determined.

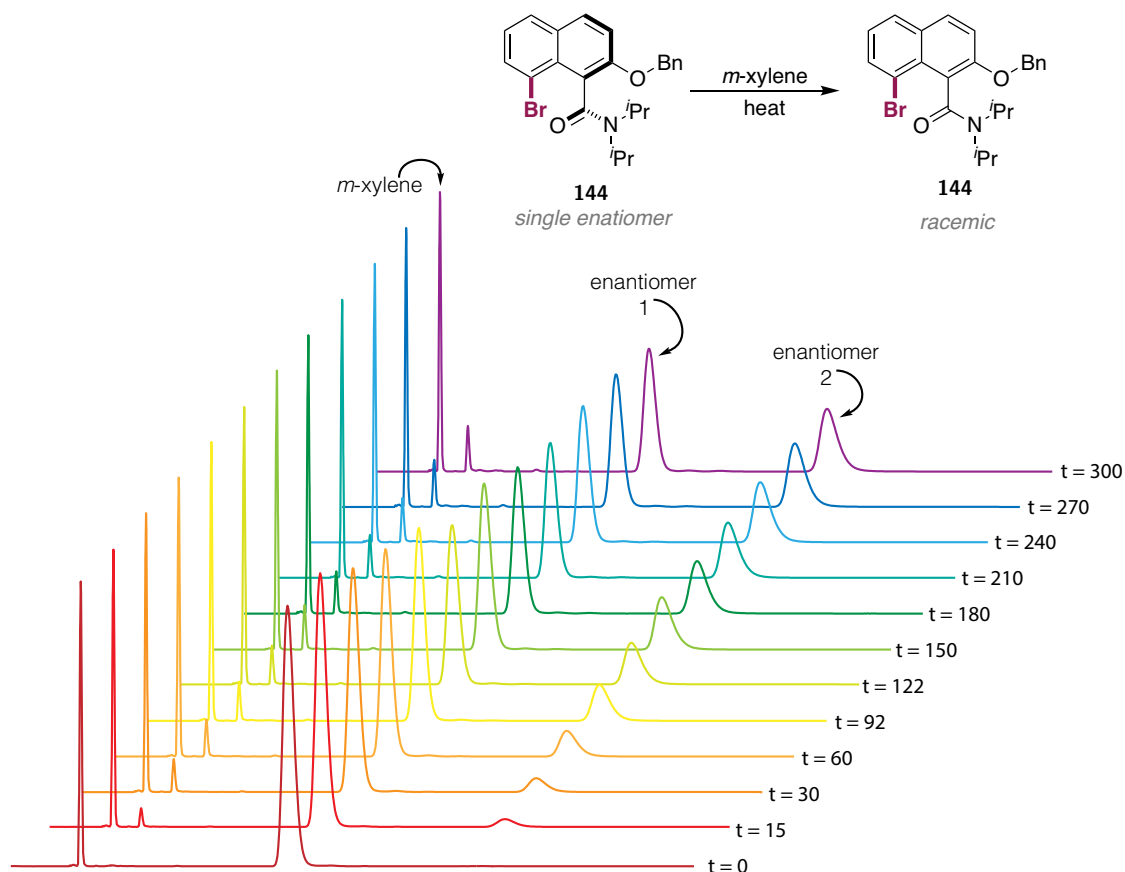


Figure 2.8: HPLC traces showing racemisation of **144**.

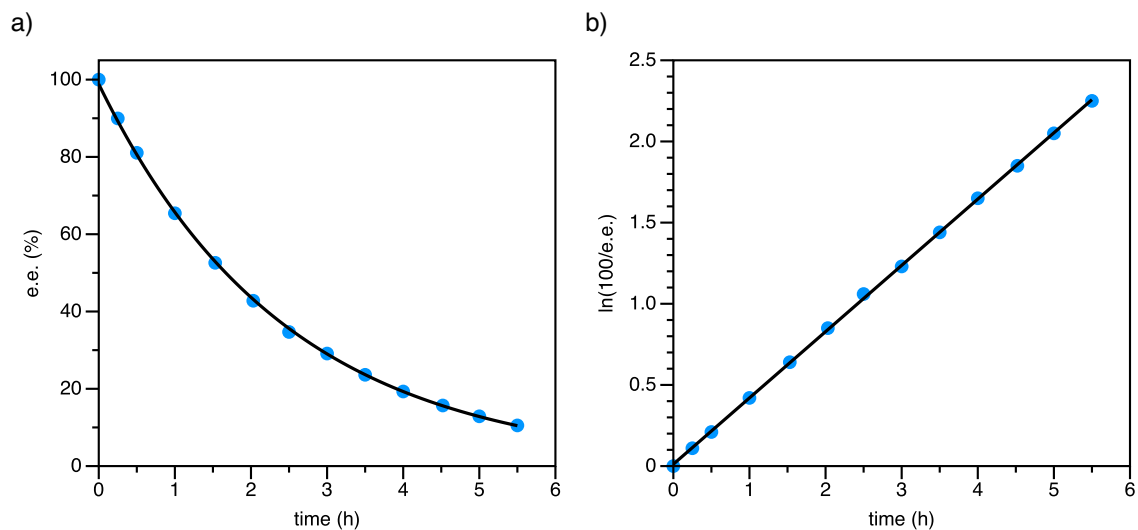


Figure 2.9: a) Erosion of e.e. of **144** over time. b) $\ln(100/\text{e.e.})$ over time.

$\Delta G_{394K}^\ddagger$ can be used to estimate the $t_{1/2}(\text{rac})$ at room temperature. This process was repeated for the other naphthamides, **145** and **146**, although the latter's barrier was measured at a lower temperature due to its lower barrier to rotation (Figure 2.10).

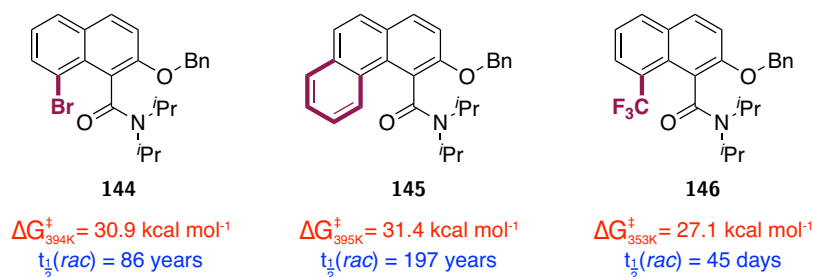


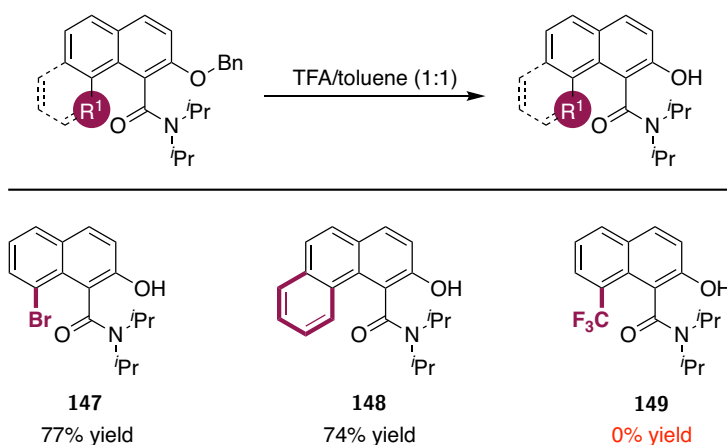
Figure 2.10: Barriers to rotation of benzylated naphthamides.

The oxidation to the more rigid aryl system led to a substantial increase in barrier to rotation, presumably by preventing partial rotation about the endocyclic Csp³–Csp³ σ-bond of the enol ethers. Trifluoromethyl-substituted enol ether **138** is not atropisomeric at room temperature, but once oxidised to **146**, has a $t_{\frac{1}{2}}(rac)$ of 45 days. In the fused benzene system, oxidation of **136** to **145** increased the barrier to rotation by 8.4 kcal mol^{–1}.

Having established the barriers of the benzylated naphthamides to be high, attention was turned to the barriers of the debenzylated compounds.

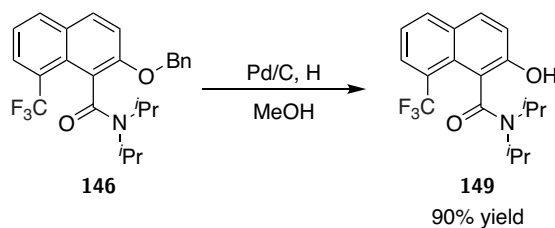
2.6 Barriers to Rotation of Naphthols

Deprotection of benzyl groups is primarily achieved by hydrogenation using palladium on carbon,^[89] but, as already discussed, **144** is incompatible with palladium catalysts due to proto-debromination. Therefore palladium catalysts were initially avoided. Fortunately, debenylation was possible using trifluoroacetic acid (TFA).^[90] This method requires a chelating group, present here as the amide carbonyl. Dissolving **144** and **145** in a mixture of toluene and TFA resulted in debenylation to give **147** and **148** in good yields (77% and 74%, Scheme 2.11). Unfortunately, subjecting electron poor trifluoromethyl-substituted **146** resulted in no formation of product **149** formation and only starting material was isolated.



Scheme 2.11: Debenzylation using TFA.

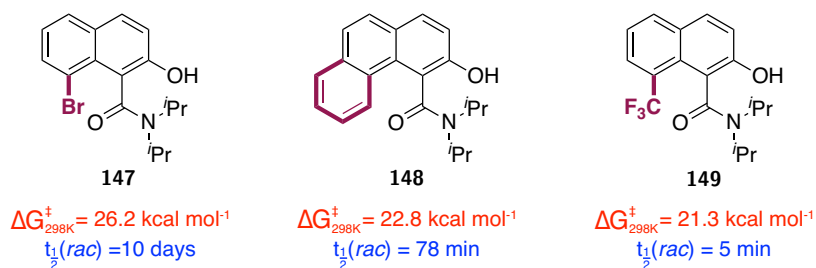
However, since no aromatic bromide was present, **146** could be debenzylated using hydrogenation with palladium on carbon. (Scheme 2.12).



Scheme 2.12: Debenzylation using Pd/C.

The barriers to rotation of the debenzylated compounds were examined. It became apparent that these compounds racemised readily at room temperature. Due to the speed of racemisation, for practical reasons, the barrier was measured in the eluent for enantiomer separation, a mixture of isopropanol and hexane (Scheme 2.13). At this point it was not anticipated that the solvent would affect the barrier to a large extent, but this will be discussed in more depth in Chapter 3.

Comparing these values to those in Figure 2.10, the removal of the benzyl group has a marked effect on the barrier to rotation of the amide. Bromo-substituted naphthol **147** has a barrier to rotation about 5 kcal mol⁻¹ lower than benzylated compound **144**, and



Scheme 2.13: Barriers to rotation of naphthols.

the barrier of fused benzene naphthamide **145** decreases by over 8 kcal mol⁻¹ once debenzylated to form **148**. The barrier to rotation of trifluoromethyl-substituted compound **149** was sufficiently low enough to racemise on the HPLC column, and a large batman effect was observed.

These remarkably decreased barriers to rotation was an interesting and dramatic effect that warranted further investigation.

3 Investigating Low Barrier to Rotation of Naphthols

The magnitude of the effect of debenzylation on the barrier to rotation of naphthols was greater than anticipated. Considering only steric effects, a benzyl group is not notably larger than a hydroxy group (Figure 3.1). The benzyl group is able to rotate to avoid any steric clash with the rotating amide (**150** to **151**). In this case, the steric bulk is somewhat comparable to the hydroxy group in **152**.

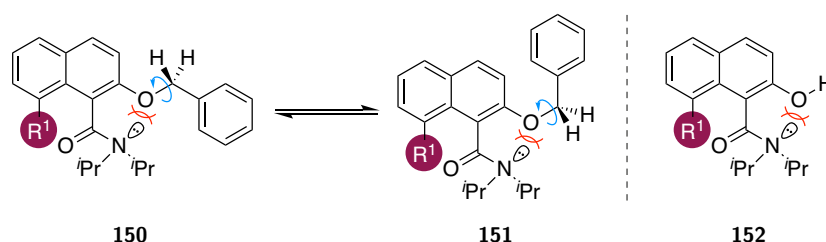
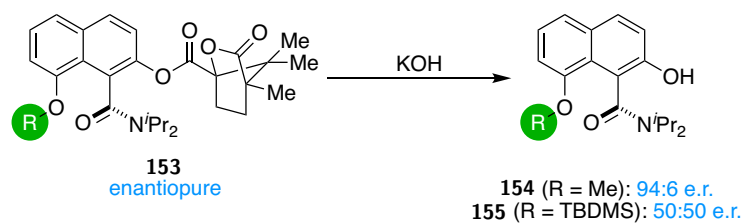


Figure 3.1: Transition states for rotation of benzylated naphthol and naphthol.

The low barriers to rotation of naphthols have been observed previously by Dai and co-workers who found that ester hydrolysis of enantiopure **153** (Scheme 3.1) led to slight racemisation of product **154** when $R = \text{Me}$.^[91] Compound **155**, ($R = \text{silyl group}$) was completely racemic after hydrolysis, and exhibited a batman effect when analysed by HPLC, indicating a very low barrier to rotation. They postulated that this was due to a low energy transition state caused by either a hydrogen bond or metal chelation during hydrolysis. As the barriers shown in Scheme 2.13 (Chapter 2) have been calculated in the absence of any metal, the idea of accelerated racemisation due to metal chelation can be eliminated. The possibility of a stabilising hydrogen bond remained.



Scheme 3.1: Hydrolysis of ester resulting in reduced enantiopurity of naphthol products.

The high barrier of benzylated compounds is due to the steric clash and electrostatic repulsion between the amide and the OBn group in transition state **156** (Figure 3.2). However, once the benzyl group is replaced by a proton, instead of a steric clash, a hydrogen bond becomes possible in transition state **157**. This would give a stable six membered ring^[92] and lower the energy of the transition state, enabling rotation at lower temperatures. Computational analysis of these naphthols would provide an initial indication of the validity of this hypothesis.

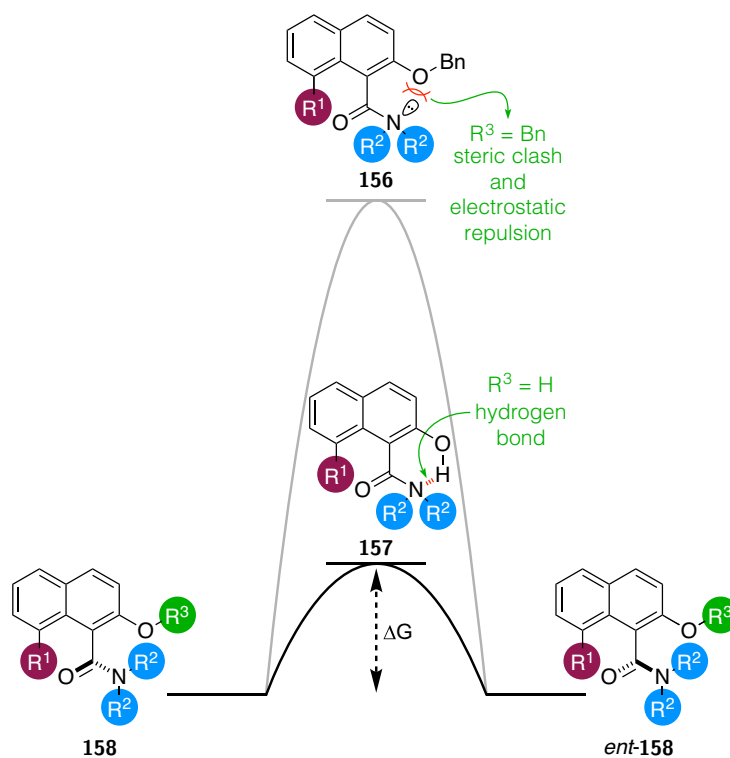


Figure 3.2: Energy level diagram for the rotation of benzylated naphthol and naphthol.

3.1 Computational Analysis

Computational studies of rotation about the Ar–CO bond of naphthamides were carried out by Jacqueline Tan. I am immensely grateful for her time and effort towards this work. Simplified structures, based on bromo-substituted naphthol **147** were used to examine the effect of alkylation of the hydroxy group on the barrier to rotation. The calculated ground state of methylated naphthol **159** (Figure 3.3a) shows the amide and the naphthyl ring are orthogonal to each other. Analysis of the transition state of rotation about the Ar–CO bond in compound **159** shows a conformation much like that predicted by Clayden and co-workers, discussed in Chapter 1; the amide is non-planar in order to move the lone pair of the nitrogen past the bulky methoxy substituent. When the methyl group is removed to give naphthol **160** (Figure 3.3b), the ground state possesses a hydrogen bond between the amide carbonyl and the OH as one would expect given the higher Lewis basicity of carbonyls in amides. In the transition state of enantiomerisation, the required non-planarity of the amide is stabilised by the hydrogen bond between the nitrogen of the amide and the OH, lowering the barrier to rotation.

These experiments calculated the difference in the barriers to rotation ($\Delta\Delta G^\ddagger$) between methylated **159** and naphthol **160** to be 10.2 kcal mol⁻¹. This is over double the experimentally determined difference in barriers to rotation (4.7 kcal mol⁻¹). Although the compounds used for *in silico* studies are structurally slightly different to those used experimentally, the magnitude of the difference should be more similar. However, the experimental value for the barrier to rotation of naphthol **147** was determined in a mixture of isopropanol and hexane. If the transition state is stabilised by an intramolecular hydrogen bond, as this work suggests, then solvent will have a large effect on barrier to rotation.

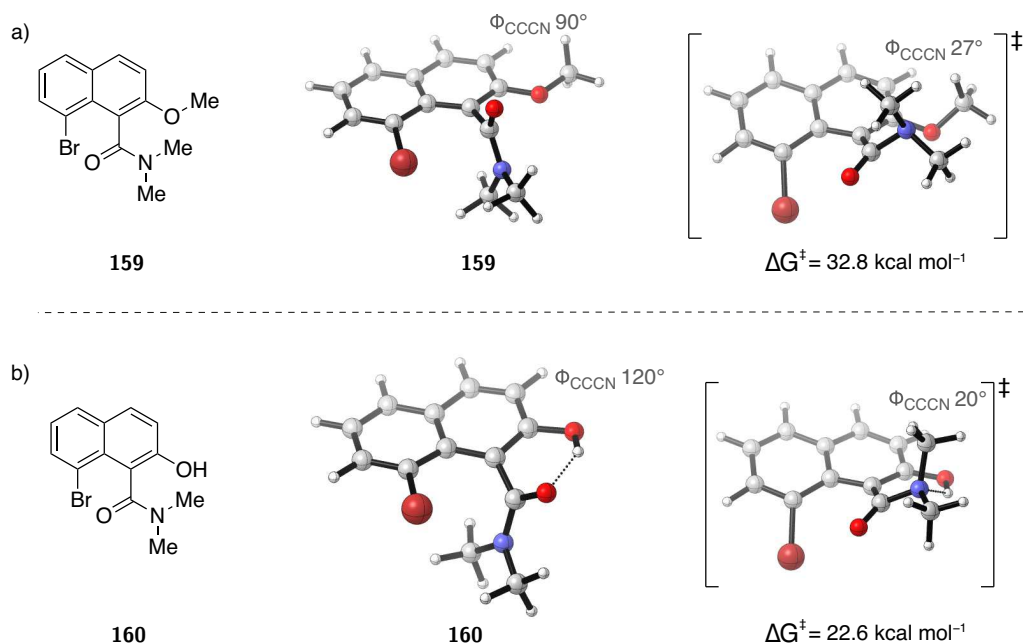


Figure 3.3: Computationally calculated ground and transition state structures for a) **159** and b) **160**.

3.2 Effect of Solvent

Substrate **147** was chosen as a model system as the $t_{\frac{1}{2}}(rac)$ was sufficiently long enough to allow separation and concentration of single enantiomers without prohibitive racemisation, but short enough to obtain meaningful results on a decent timescale. The enantiomers of **147** were separated by HPLC and concentrated under a steady stream of nitrogen at room temperature so as to avoid racemisation at elevated temperatures. A single enantiomer was dissolved in two separate solvents, a hydrogen-bonding solvent, isopropanol, and an anhydrous non-hydrogen bonding solvent, dichloromethane. The racemisation of **147** was then monitored in each solvent (Figure 3.4).

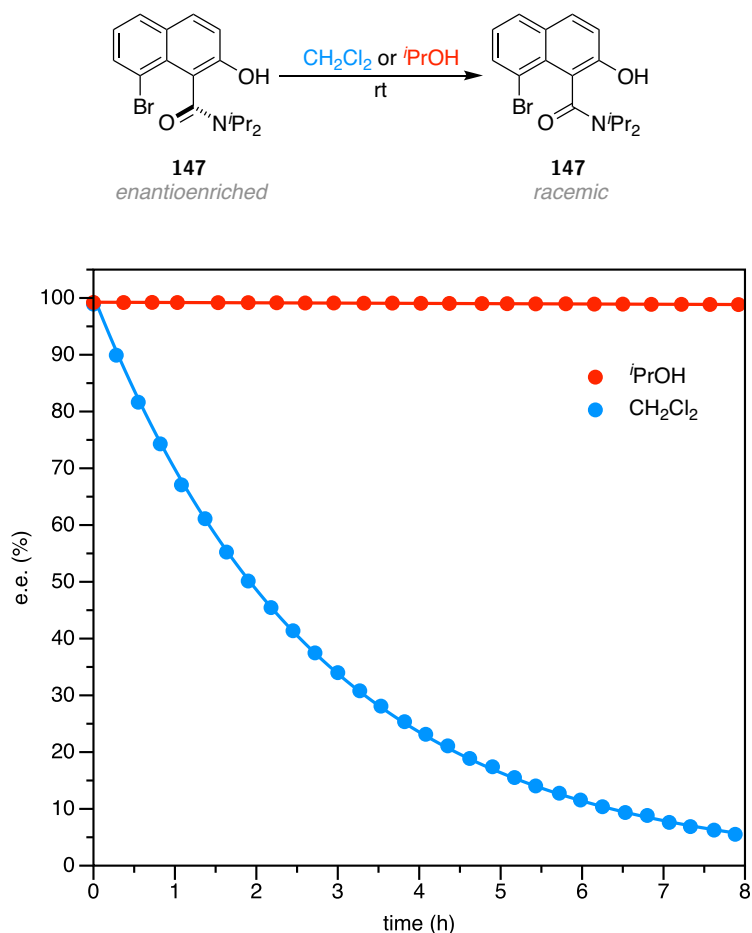


Figure 3.4: Effect of solvent on racemisation of **147**.

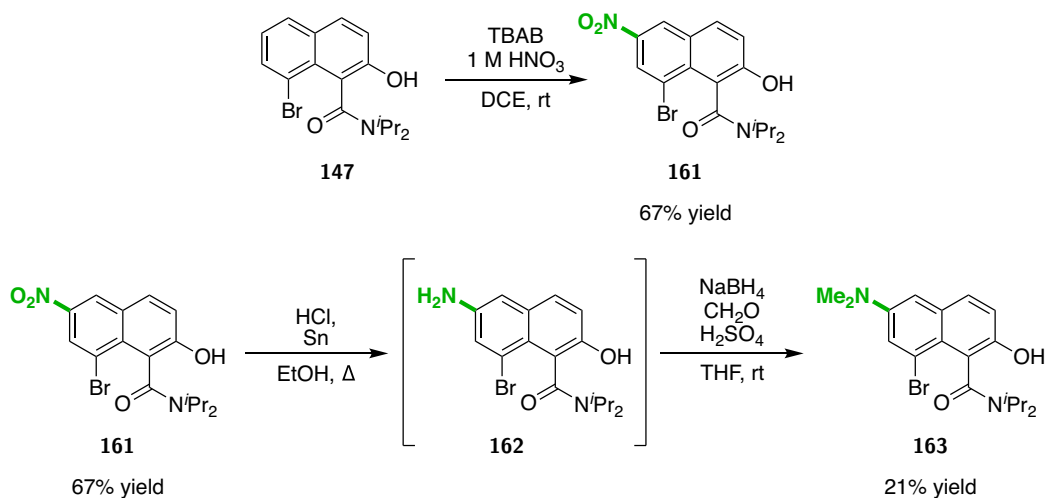
Figure 3.4 shows a clear difference in barrier to rotation in the two contrasting solvents. In dichloromethane, the $t_{\frac{1}{2}}(\text{rac})$ was 115 min and the compound was racemic within 8 hours (Table 3.1, entry 1). This corresponds to a barrier to rotation of $23.3 \text{ kcal mol}^{-1}$. In contrast, racemisation in isopropanol proceeds very slowly with a $t_{\frac{1}{2}}(\text{rac})$ of 53 days, corresponding to a barrier to rotation of $27.1 \text{ kcal mol}^{-1}$. In fact, after 8 hours of observation, the compound only racemised from 99.6:0.4 e.r. to 99.4:0.6 e.r.. This solvent effect is far greater than the $0.5\text{--}0.7 \text{ kcal mol}^{-1}$ increase Clayden initially discovered for 2-substituted naphthamides in polar solvents,^[21] and so goes beyond simple stabilisation of resonance effects. The $\Delta\Delta G^\ddagger$ for benzylated naphthol **144** and naphthol **147** calculated in dichloromethane is now $7.4 \text{ kcal mol}^{-1}$ much closer to the value calculated *in silico*.

Table 3.1: Barriers to rotation and half-life to racemisation of **147** in different solvents.

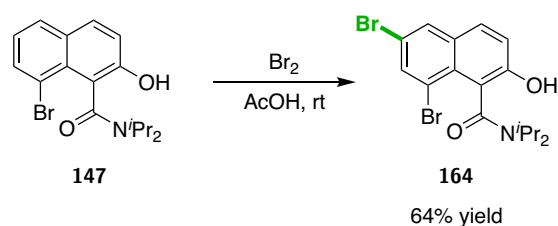
Entry	Solvent	$\Delta G_{298K}^\ddagger$ (kcalmol ⁻¹)	$t_{\frac{1}{2}}$ (rac)
1	dichloromethane	23.3	115 min
2	isopropanol	27.1	53 days

3.3 Effect of Substituents

In order to investigate the electronic effect of substituents on rate of racemisation, derivatives of **147** were synthesised. Reaction of **147** with nitric acid and TBAB led to nitration at the 6-position (**161**, Scheme 3.2). This is a convenient position for these investigations, as it is far from the site of rotation so steric factors will not contribute to the barrier to rotation. Reduction of **161** using tin and concentrated hydrochloric acid yielded aniline **162**. This was found to be unstable at room temperature and also insoluble in solvents compatible with HPLC studies. Therefore, **162** was reacted further with sodium borohydride and formaldehyde to give dimethylaniline **163**. This route enabled access to compounds containing an electron withdrawing group (NO₂, **161**) and an electron donating group (NMe₂, **163**) in addition to electron neutral group (H, **147**).

**Scheme 3.2:** Adding electron donating and withdrawing groups to **147**.

Another facile modification of naphthol **147** was bromination using bromine in acetic acid (Scheme 3.3). This provided di-brominated naphthol **164** in 64% yield.



Scheme 3.3: Bromination of **147**.

With four substituents with differing electronic properties in hand, the barriers to rotation of each was examined. Once again, enantiomers were separated by HPLC and concentrated under a steady stream of nitrogen, then redissolved in anhydrous dichloromethane and allowed to racemise at room temperature (Figure 3.5).

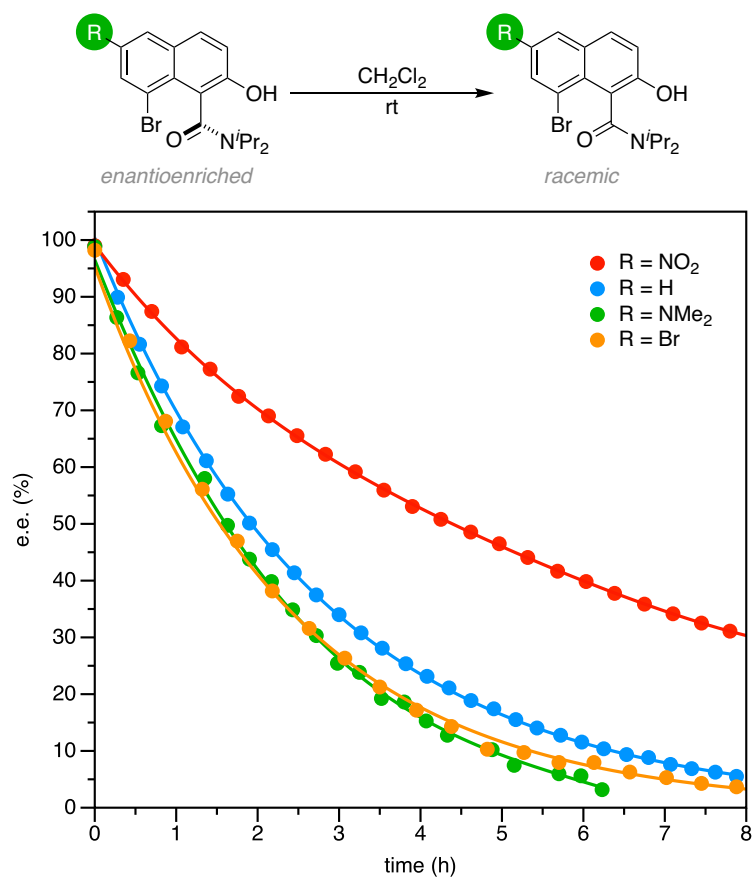


Figure 3.5: Effect of substituent R on racemisation of naphthol.

Whilst not as dramatic an effect as changing the solvent, the substituent at the 6-position of the naphthol had a tangible effect on the rate of racemisation. The barriers to rotation and half-life to racemisation were calculated for these compounds (Table 3.2).

Table 3.2: Barriers to rotation and half-life to racemisation when varying substituent

Entry	R	$\Delta G_{298K}^\ddagger$ (kcalmol ⁻¹)	$t_{\frac{1}{2}}(\text{rac})$ (min)
1	NO ₂	24.0	350
2	H	23.3	115
3	Br	23.2	97
4	NMe ₂	23.1	82

Electron withdrawing group NO₂ raised the barrier to rotation compared to H by only 0.7 kcal mol⁻¹ (Table 3.2, entries 1 and 2). However, as can be seen in Figure 3.5, this small increase leads to a large difference, on a practical timescale, in the time taken for compound to racemise, tripling the half-life to racemisation. When R = NMe₂, an electron donating group, the barrier decreases by 0.2 kcal mol⁻¹ (Table 3.2, entry 4), a very small but appreciable difference.

It is difficult to ascertain from these results if the difference is caused by transition state stabilisation by a stronger hydrogen bond, or due to ground state stabilisation. It is likely to be a complex mixture of both effects, as varying the substituent modifies the electronic properties of the hydrogen bond donor and acceptor. This is something to be examined further in future work.

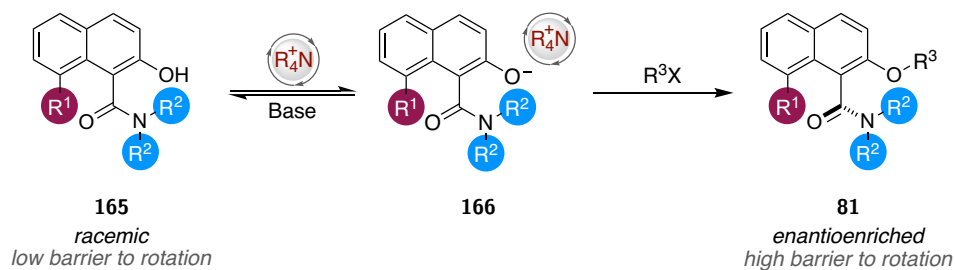
Although the low barriers to rotation of the naphthols was not anticipated or initially desired, the effect could be exploited to synthesise the originally targeted benzylated atropisomers *via* a dynamic kinetic resolution (DKR). This will be explored in the next chapter.

4 Dynamic Kinetic Resolution *via*

O-Alkylation

4.1 Project Aims

It was now known that the naphthol compounds possessed a low barrier to rotation, but once benzylated were stable to racemisation at room temperature. Therefore, a dynamic kinetic resolution of naphthols could be executed to generate benzylated naphthamides with high enantioenrichment (Scheme 4.1).

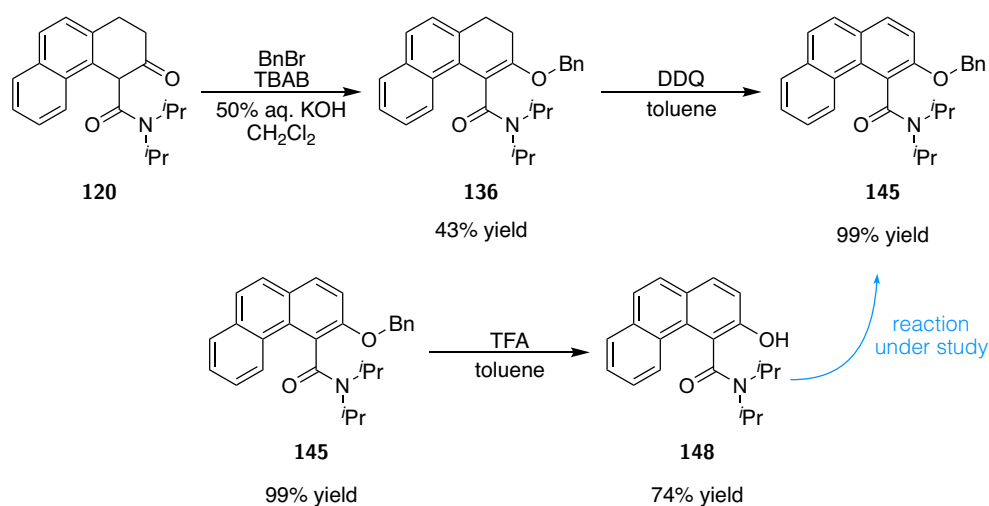


Scheme 4.1: Dynamic kinetic resolution of naphthols.

Following reversible deprotonation under phase-transfer conditions, **165** will form a diastereomeric ion pair (**166**) with the chiral catalyst anion. One diastereomer should react faster than the other and once alkylated, will no longer racemise at room temperature. The less reactive enantiomer will racemise, generating more of the reactive enantiomer throughout the reaction.

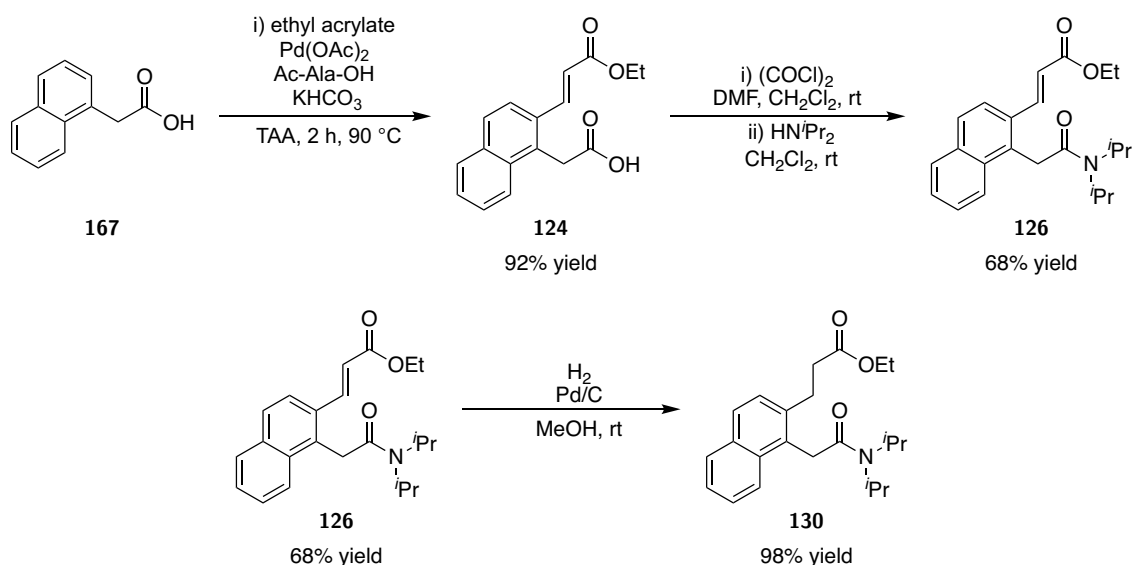
4.2 Substrate Synthesis

Naphthol **148** was chosen as a suitable starting material for probing this strategy as it does not possess any strongly electron withdrawing or donating groups. The original route to **148** had two major issues. First, was a low yielding step to **136** due to undesired *C*-alkylation of **120** (see Chapter 2). Secondly, this route proceeded *via* **145**, the product of the reaction now under development. Due to these inefficiencies, a new route was required.



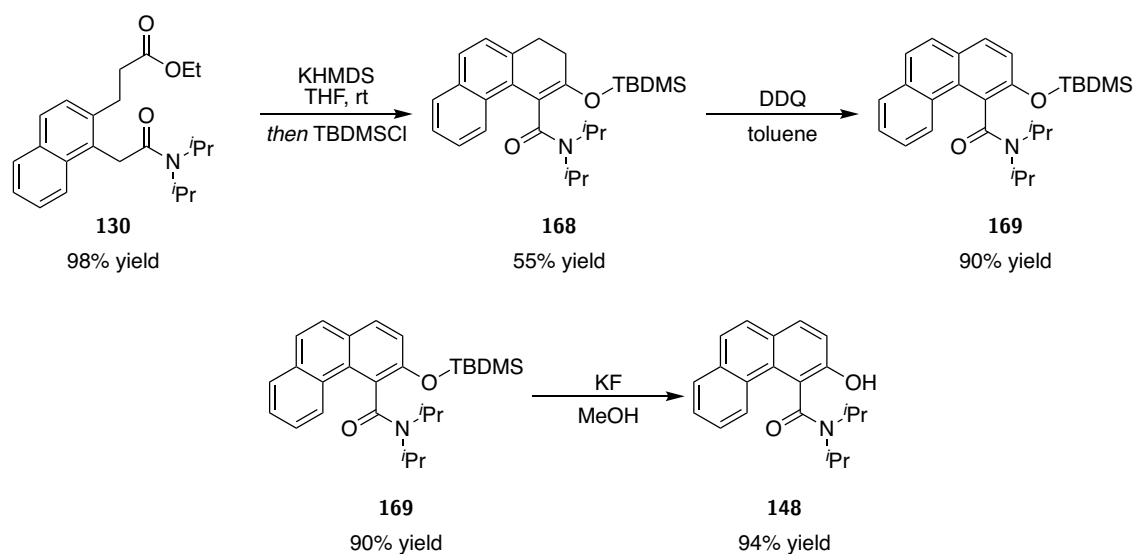
Scheme 4.2: Previous route to starting material **148** *via* desired product **145**.

Based on the old route, 1-naphthylacetic acid **167** was reacted with ethyl acrylate to give **124** (Scheme 4.3). Following an amide coupling with diisopropylamine to give **126**, hydrogenation gave the Dieckman cyclisation precursor **130**.



Scheme 4.3: Previous route to cyclisation precursor **130**.

Amide **130** was subjected to cyclisation conditions, as before, but instead of quenching the reaction with water to form the β -tetralone, a silylating agent was introduced to form silyl enol ether **168** in a one-pot procedure (Scheme 4.4). Oxidation of **168** using DDQ gave the protected naphthol **169**, which was deprotected in near quantitative yield to produce the desired naphthol starting material.

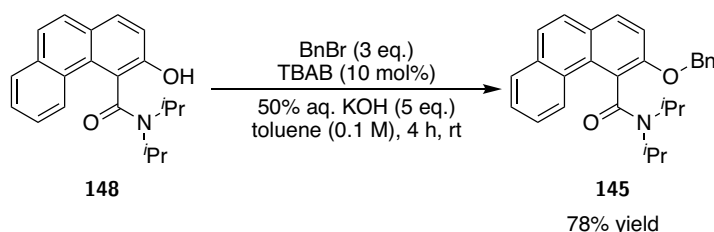


Scheme 4.4: Synthesis of naphthol **148**.

4.3 Enantioselective *O*-Alkylation

4.3.1 Racemic Reaction

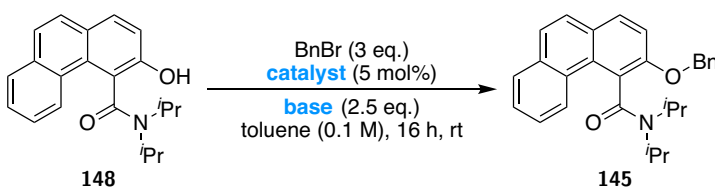
First, the desired *O*-alkylation was tested using achiral catalyst TBAB and potassium hydroxide (Scheme 4.5). Starting material was fully consumed within 4 hours, with an isolated yield of 78%.



Scheme 4.5: Unselective *O*-alkylation.

The enantioselective reaction was evaluated using simple cinchona alkaloid-based catalysts and aqueous potassium hydroxide (Table 4.1). Unfortunately, all reactions gave racemic product (entries 1–4) which was most likely due to background reactivity caused by the strong base. Reaction of **148** with aqueous potassium hydroxide in the absence of any catalyst did indeed lead to some product formation (entry 5). Repetition of this experiment using a weaker base, potassium carbonate, gave no reaction without a catalyst (entry 6) and use of chiral phase-transfer catalysts gave non-racemic results (entries 7–10). Pseudoenantiomeric catalysts **119** and **170**, derived from cinchonine and cinchonidine respectively, showed equal selectivity for opposite enantiomers, (entries 7 and 8). This was also true for quinine and quinidine derived **70** and **171** (entries 9 and 10). Cinchonine and cinchonidine derived catalysts gave better enantioselectivity than the methoxy-substituted catalysts and therefore cinchonine based **119** was chosen to continue the optimisation process.

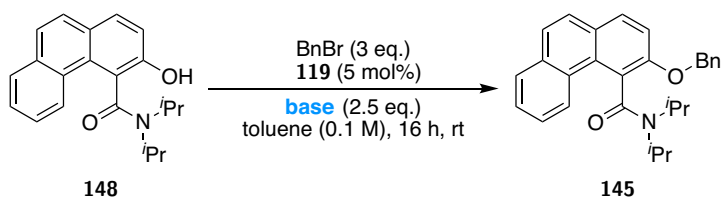
Table 4.1: Initial enantioselective reactions.

			
Entry	Catalyst	Base	e.r.
1	119	50% aq. KOH	50:50
2	170	50% aq. KOH	50:50
3	70	50% aq. KOH	50:50
4	171	50% aq. KOH	50:50
5	none	50% aq. KOH	50:50
6	none	50% aq. K ₂ CO ₃	N/A ^a
7	119	50% aq. K ₂ CO ₃	75:25
8	170	50% aq. K ₂ CO ₃	25:75
9	70	50% aq. K ₂ CO ₃	36:64
10	171	50% aq. K ₂ CO ₃	64:36

^a Poor conversion.

4.3.2 Optimisation of *O*-Alkylation

The first test reactions of the enantioselective *O*-alkylation gave promising results, but there were many parameters to further optimise, such as catalyst, base, temperature and electrophile. For a full optimisation table see Appendix 7.2. The process began with a small base screen (Table 4.2). Aqueous hydroxide bases, sodium hydroxide, caesium hydroxide, and rubidium hydroxide, gave racemic or near racemic product (entries 1–3). Weaker bases gave good enantioselectivity with phosphate giving less enantioenriched product than carbonate (entries 4 and 5). Aqueous caesium carbonate gave the best selectivity in this screen with 77:23 e.r. (entry 6).

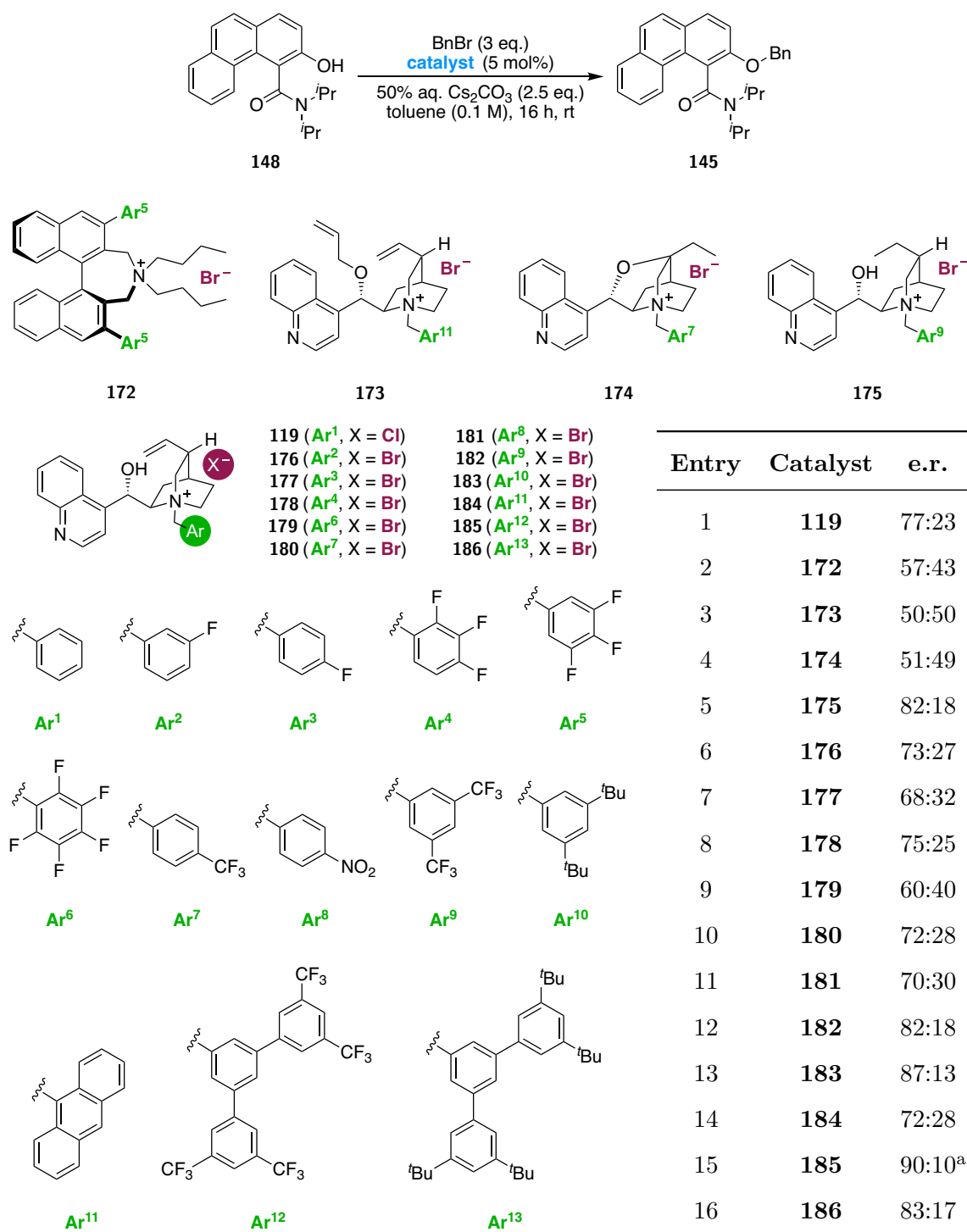
Table 4.2: Primary base screen.

Entry	Base	e.r.
1	25% aq. NaOH	50:50
2	25% aq. CsOH · H ₂ O	52:48
3	50% aq. RbOH · H ₂ O	54:46
4	50% aq. K ₂ CO ₃	74:26
5	50% aq. K ₃ PO ₄	70:30
6	50% aq. Cs ₂ CO ₃	77:23

Next, different catalysts were screened (Table 4.3). Binaphthyl based catalyst **172** gave very low selectivity (entry 2) so no further catalysts of this class were explored. Catalysts based on cinchonine generally yielded product with good enantioenrichment. Different *N*-benzyl substituents (Ar) were tested, varying the steric and electronic properties of this quaternising group and the influences of the hydroxy and vinyl groups were also explored.

Use of fluorinated catalysts **176**, **177** and **178** did not yield any improvement in enantioselectivity (entries 6–8), and pentafluoro-substituted **179** led to a large decrease in selectivity (entry 9). 4-Substituted benzyl derivatives **180** and **181**, also led to decreased selectivity (entry 9). Alkylation of the hydroxy group in catalysts **173** and **174** gave racemic product (entries 3 and 4), compared to good results when OH is present in catalysts **184** and **180** respectively (entries 14 and 10). Clearly the hydroxy group is vital for strong substrate catalyst interactions. Hydrogenation of the vinyl group of catalyst **182** to give catalyst **175** gave no change in enantioselectivity (entries 12 and 5).

Table 4.3: Catalyst screen.



^a Poor conversion.

Large groups in the 3- and 5- position of the benzyl group gave the best enantioselectivity. Bis-trifluomethyl-substituted catalyst **182** (entry 12) and di-*tert*-butyl catalyst **183** (entry 13) gave excellent enantioselectivity compared to unsubstituted benzene (**119**, entry 1). Further increasing the steric bulk in these positions in catalyst **185** gave high selectivity although the reaction was notably slower (entry 15). Catalyst **186** also generated highly enantioenriched product but was not as effective as the other bulky catalysts under these conditions (entry 16).

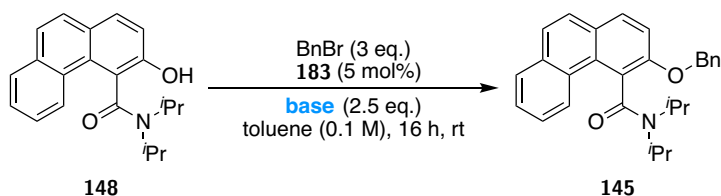
Comparison of *tert*-butyl-substituted catalysts and trifluoromethyl-substituted catalysts saw differing trends between di-substituted catalysts **182** and **183** and tetra-substituted catalysts **185** and **186**. *Tert*-butyl-substituted catalysts give higher selectivity than the trifluoromethylated catalysts when di-substituted, but lower selectivity when tetra-substituted. These results suggest the observed increase in enantioselectivity is not due to electronic factors, but due to the steric nature of the benzyl substituent.

Due to the higher conversion obtained whilst still maintaining high selectivities, **183** was carried forward as the catalyst for further optimisation.

A wider base screen was then carried out (Table 4.4). Changing the concentration of base from 50% to 25% did not substantially change the enantioselectivity (entries 1 and 2) and aqueous potassium carbonate also gave comparable selectivity. Solid caesium carbonate led to a marked decrease in enantioselectivity, giving almost racemic product (entry 4). In contrast, solid sodium carbonate and sodium phosphate (entries 6 and 8), gave better selectivity than their aqueous counterparts (entries 5 and 7), but conversion using solid sodium carbonate was very low. Solid lithium carbonate gave no conversion to product (entry 9), and silver carbonate gave a slight increase in enantioselectivity (entry 10). Potassium phosphate led to a drop in selectivity for both aqueous (entry 11) and solid base

(entry 12). Aqueous potassium fluoride generated the highest enantioselectivity (entry 13), whilst maintaining reasonable conversion. Therefore further optimisation continued with this base.

Table 4.4: Secondary base screen.



Entry	Base	e.r.
1	50% aq. Cs ₂ CO ₃	80:20
2	25% aq. Cs ₂ CO ₃	81:19
3	50% aq. K ₂ CO ₃	81:19
4	Cs ₂ CO ₃	54:46
5	2 M aq. Na ₂ CO ₃	84:16
6	Na ₂ CO ₃	94:6 ^a
7	15% aq. Na ₃ PO ₄	89:11
8	Na ₃ PO ₄	88:12
9	Li ₂ CO ₃	N/A ^b
10	Ag ₂ CO ₃	83:17
11	50% aq. K ₃ PO ₄	77:23
12	K ₃ PO ₄	73:27
13	25% aq. KF	92:8
14	KF	91:9

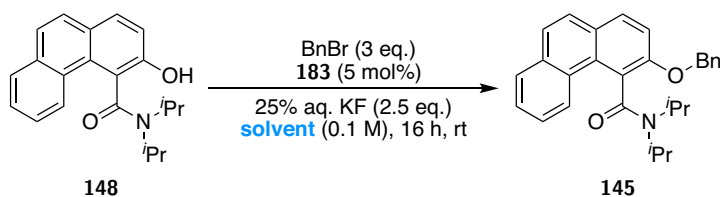
^a Poor conversion.

^b No conversion.

The effect of solvent on enantioselectivity was subsequently tested (Table 4.5). Aromatic solvents gave the best selectivity, with benzene generating the product in the highest enantioselectivity (entry 2), then toluene (entry 1) followed by the xylene isomers (entries 3–5). Chlorinated solvents gave slightly reduced selectivity compared to aromatic solvents.

More polar chlorinated solvents, such as dichloromethane (entry 8) gave lower selectivity than less polar solvent such as carbon tetrachloride (entry 6). Etheral solvents gave poorer enantioselectivity (entries 11–13). The substrate anion and catalyst cation must have a strong interaction to induce enantioselectivity; in polar solvents this ion pair will be less tightly bound and enantioselectivity will decrease, as is observed in Table 4.5.

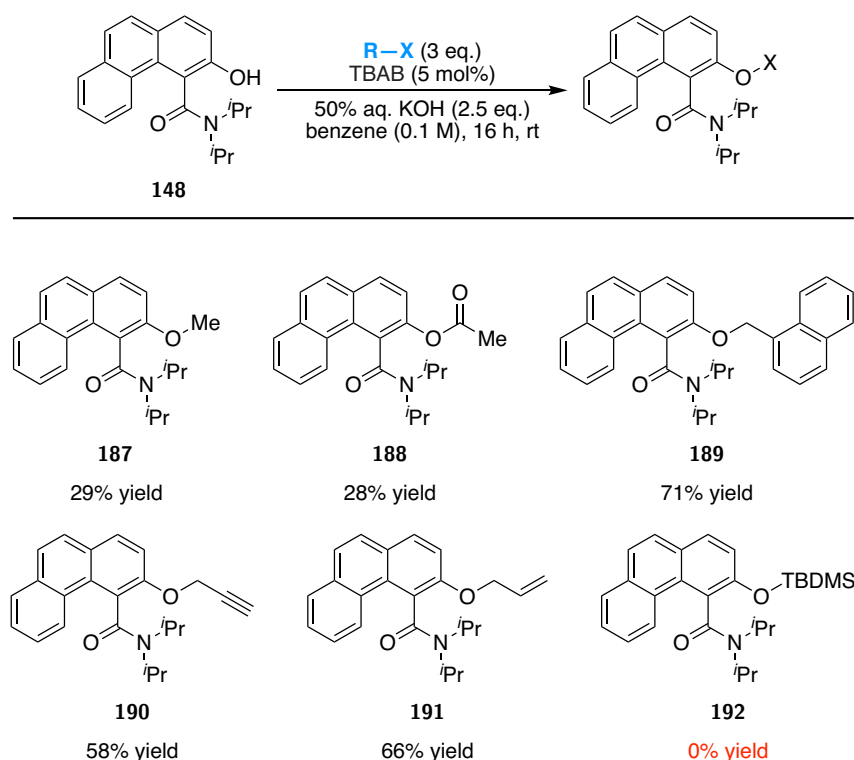
Table 4.5: Solvent screen.



Entry	Solvent	e.r.
1	toluene	93:7
2	benzene	94:6
3	<i>p</i> -xylene	88:12
4	<i>m</i> -xylene	90:10
5	<i>o</i> -xylene	91:9
6	CCl ₄	90:10
7	CHCl ₃	87:13
8	CH ₂ Cl ₂	86:14
9	1,2-dichloroethane	80:20
10	trichloroethane	92:8
11	Et ₂ O	79:21
12	<i>i</i> Pr ₂ O	60:40
13	MTBE	80:20

The effect of different electrophiles and leaving groups was investigated next. First, racemic samples were synthesised under phase-transfer conditions to test the viability of the reaction and to obtain references for HPLC analysis (Scheme 4.6). Naphthol **148** was reacted with methyl iodide to give product **187**, acetic anhydride to give **188** and

1-(bromomethyl)naphthalene to give product **189**. The reactions with propargyl bromide gave compound **190** and allyl bromide yielded product **191**. Unfortunately, reaction with TBDMSCl gave no product **192**, returning only starting material, presumably due to hydrolysis of the silylating agent.

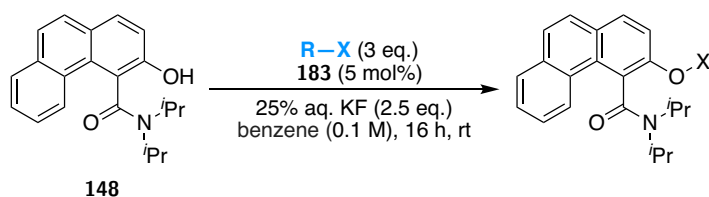


Scheme 4.6: Synthesis of racemic atropisomers with differing electrophiles.

With racemic samples in hand, naphthol **148** was subjected to asymmetric alkylating conditions using the previously optimised conditions (Table 4.6). Changing the leaving group had a small effect on enantioselectivity. Benzyl chloride and iodide gave increased selectivity (entry 1 and 3), whereas benzyl tosylate decreased selectivity significantly (entry 4). The opposite trend was seen in allylation, as a bromide leaving group gave slightly better results than iodide (entries 5 and 6), however both were less selective than the benzylations. Reaction with methyl iodide yielded poor selectivity (entry 7), as did reaction with propargyl bromide (entry 8) and acetylation yielded nearly racemic product.

The only electrophile that generated good selectivity approaching that of benzylation was 1-(bromomethyl)naphthalene (entry 10). This may be due to the fact that the current conditions were optimised for benzylation but this also suggests presence of an aromatic group on the electrophile is key for strong interactions with the aryl groups on the catalyst, leading to good selectivity. Therefore benzyl iodide was selected as the alkylating agent.

Table 4.6: Electrophile screen.



Entry	Electrophile	e.r.
1	BnCl	94:6
2	BnBr	93:7
3	BnI	95:5
4	BnOTs	85:15
5	allyl bromide	75:25
6	allyl iodide	73:27
7	MeI	73:27
8	propargyl bromide	64:36
9	Ac ₂ O	44:56
10	1-(bromomethyl)naphthalene	90:10

The effect of concentration and catalyst loading on enantioselectivity was examined next with the results shown in Table 4.7. A clear trend emerged showing that the more dilute the reaction, the better the enantioselectivity. This trend could be partially explained by the solubility of the starting material. Throughout the screening process it was noted that the starting material **148** was not entirely in solution at the start of the reaction. Over time, as the material reacted, the solution turned clear and the remaining starting

material dissolved. The amide will racemise more readily in solution than in the solid state, although this can occur when the barrier to rotation is low.^[12] Therefore, if the reaction is too concentrated, the compound will not be able to racemise at a high enough rate for good selectivity.

Table 4.7: Effect of catalyst loading and concentration.

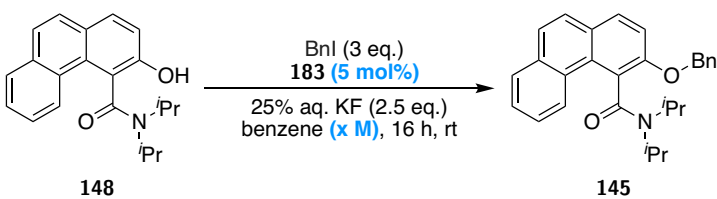
				
Catalyst Loading (%)	Concentration (M)			
	0.01	0.05	0.10	0.20
5	97:3	96:4	95:5	94:6
10	97:3	95:5	94:6	93:7
20	96:3	94:6	92:8	87:13

Table 4.7 also shows that higher catalyst loading led to decreased selectivity. Time, as well as solubility, is vital to allow the unwanted enantiomer to racemise, generating more of the reactive enantiomer. The rate of alkylation must be finely balanced with the rate of racemisation. Therefore factors that slow down reactivity, such as lower catalyst loading and higher dilution, allow racemisation to occur, and therefore increase the enantioenrichment of the product.

This led to an issue of conversion; a slow reaction is needed for high selectivity but a fast reaction is required for high yields, as over time the rate of reaction decreases due to catalyst decomposition.^[75,93,94] The currently optimised conditions led to low conversion, even using 10 mol% catalyst for 48 h (Table 4.8, entry 3). In general, concentrating the reaction led to higher conversion until a point where solubility becomes limiting (0.2 M,

entry 4). At 0.5 M, no product formation was observed as the starting material was too insoluble at this concentration to undergo alkylation (entry 5).

Table 4.8: Effect of concentration on conversion and enantioselectivity.

148 145

Entry	Concentration (M)	Conversion ^a (%)	e.r.
1	0.01	36	97:3
2	0.05	36	96:4
3	0.1	50	95:5
4	0.2	33	94:6
5	0.5	0%	N/A

^a calculated by crude ¹H NMR analysis after 48 h reaction time.

Conversion increased with addition of solubilising solvents dichloromethane (Table 4.9, entry 2) and chloroform (entry 3). However, conversion was still low, despite the long reaction times, and selectivity was also reduced.

Table 4.9: Effect of chlorinated solvent addition on conversion.

148 145

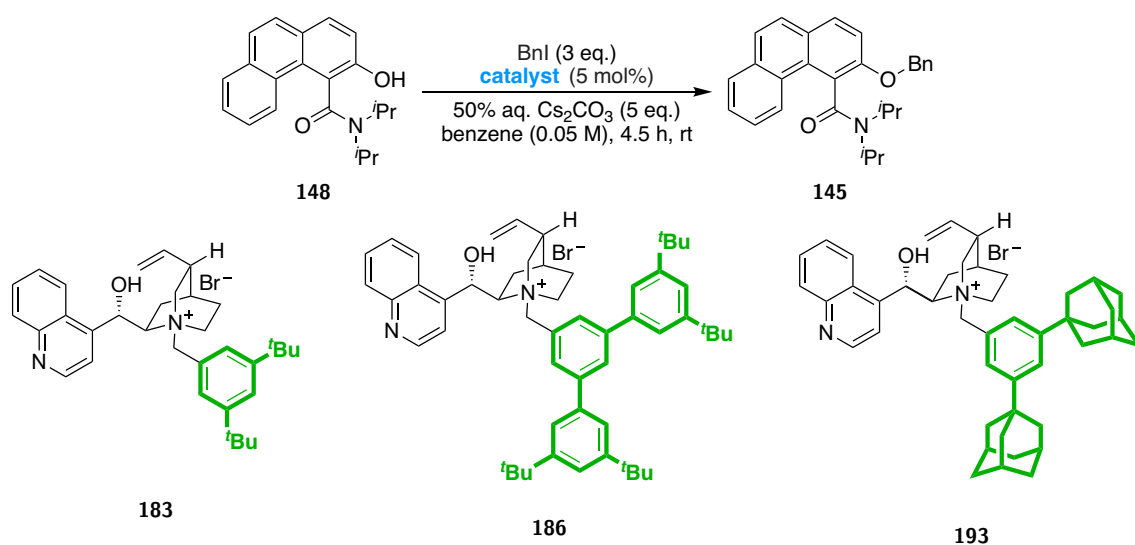
Entry	Solvent	Conversion ^a (%)	e.r.
1	benzene	38	96:4
2	10% dichloromethane in benzene	54	94:6
3	10% CHCl ₃ in benzene	45	94:6
4 ^b	benzene	100	86:14

^a calculated by crude ¹H NMR analysis after 48 h reaction time.

^b 50% aq. Cs₂CO₃ used as base.

Although potassium fluoride and catalyst **183** were producing very high selectivity, this combination was not giving complete conversion. Therefore the base was changed to caesium carbonate which resulted in 100% consumption of starting material within 48 h and also gave promising enantioselectivity (Table 4.9, entry 4). The catalyst structure was re-examined, focusing on lipophilic benzyl substituents as these gave better conversions (Table 4.10).

Table 4.10: Electron-rich catalyst screen.



Entry	Catalyst	Conversion ^a (%)	e.r.
1 ^b	183	68	93:7
2	186	73	95:5
3	193	65	96:4

^a calculated by crude ¹H NMR analysis after 4.5 h reaction time.

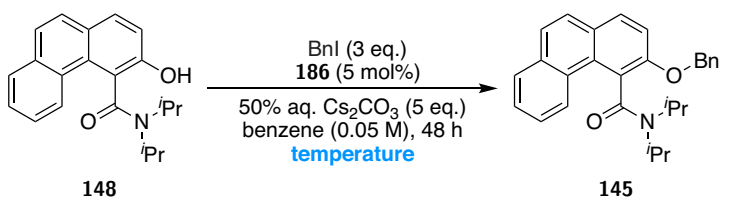
^b 10 mol% catalyst loading.

After only 4.5 h, conversion was promising and high enantioselectivity was displayed. Catalyst **183** was notably slower than the other two catalysts as 10 mol% loading was required to obtain comparative conversion to the other catalysts (entry 1). Tetra-*tert*-butyl catalyst **186** gave the best conversion at 73% and high selectivity (entry 2). The

most selective catalyst was found to be di-adamantyl **193** (entry 3), consistent with the trend discovered in Table 4.3 that bulky 3,5-substituents are necessary for high selectivity. However, **193** gave lower conversion than **186** and as a result **186** was chosen to continue optimisation.

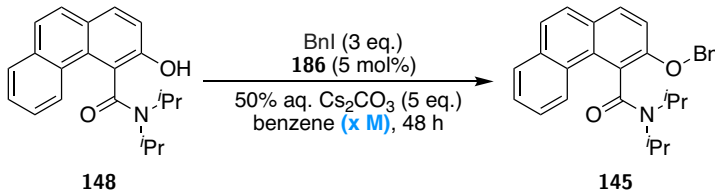
Investigations into the effect of temperature on conversion and selectivity yielded mixed results. (Table 4.11). Increasing the temperature increases the conversion but decreases the enantioselectivity as the rate of the background reaction is increased (entries 3 and 4). However, cooling the reaction to 10 °C also lowers the rate of racemisation of the starting material, and therefore the enantioenrichment of the product is reduced (entry 1). Room temperature gave the best enantioselectivity, so all further experiments were carried out at this temperature.

Table 4.11: Temperature screen.

			
Entry	Temperature (°C)	Conversion ^a (%)	e.r.
1	10	69	93:7
2	rt	73	95:5
3	30	79	94:6
4	40	96	92:8

^a calculated by crude ¹H NMR analysis after 4.5 h reaction time.

Finally, the conversion was tested at higher dilutions, which should give greater selectivity (Table 4.12). This was successful and even at the high dilution of 0.01 M, the reaction reached 96% conversion within 48 h and gave excellent selectivity (entry 2).

Table 4.12: Electron-rich catalyst screen.


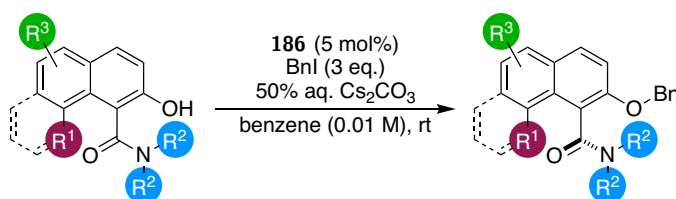
Entry	Concentration (M)	Conversion ^a (%)	e.r.
1	0.025	97	96:4
2	0.01	96	97:3

^a calculated by crude ¹H NMR analysis after 48 h reaction time.

After extensive optimisation, these results gave the best combination of both conversion and enantioselectivity and so were selected to investigate the substrate scope of the enantioselective *O*-alkylation.

4.4 Substrate Scope

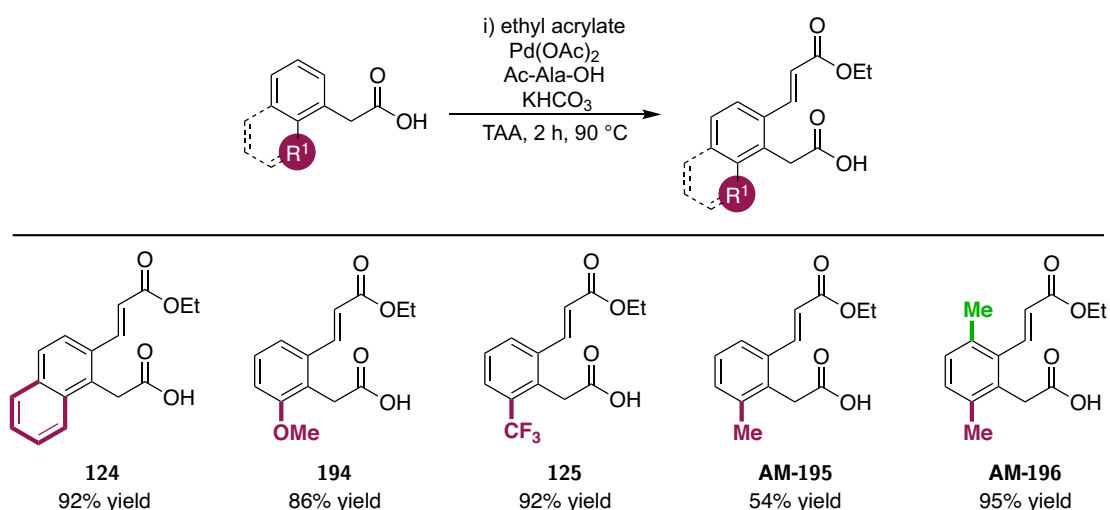
To investigate the breadth of the enantioselective *O*-alkylation, the synthesis of many substrates was required (Scheme 4.7). The main variables of interest were the 8-substituent of the naphthol (R^1) as well as the substituents of the tertiary amide (R^2). It would also be interesting to test the functional group tolerance of the reaction to substituents on the naphthol moiety (R^3) particularly adjacent to the hydroxy group.

**Scheme 4.7:** Sites of substitution for enantioselective reaction.

4.4.1 Substrate Synthesis

At this point two people joined the project to aid in substrate synthesis, Dr Aroonroj Mekareeya (whose compounds will be prefixed with **AM-**) and Dr Antti Lahdenperä (whose compounds will be prefixed with **ASL-**). I am extremely grateful to both for their contributions.

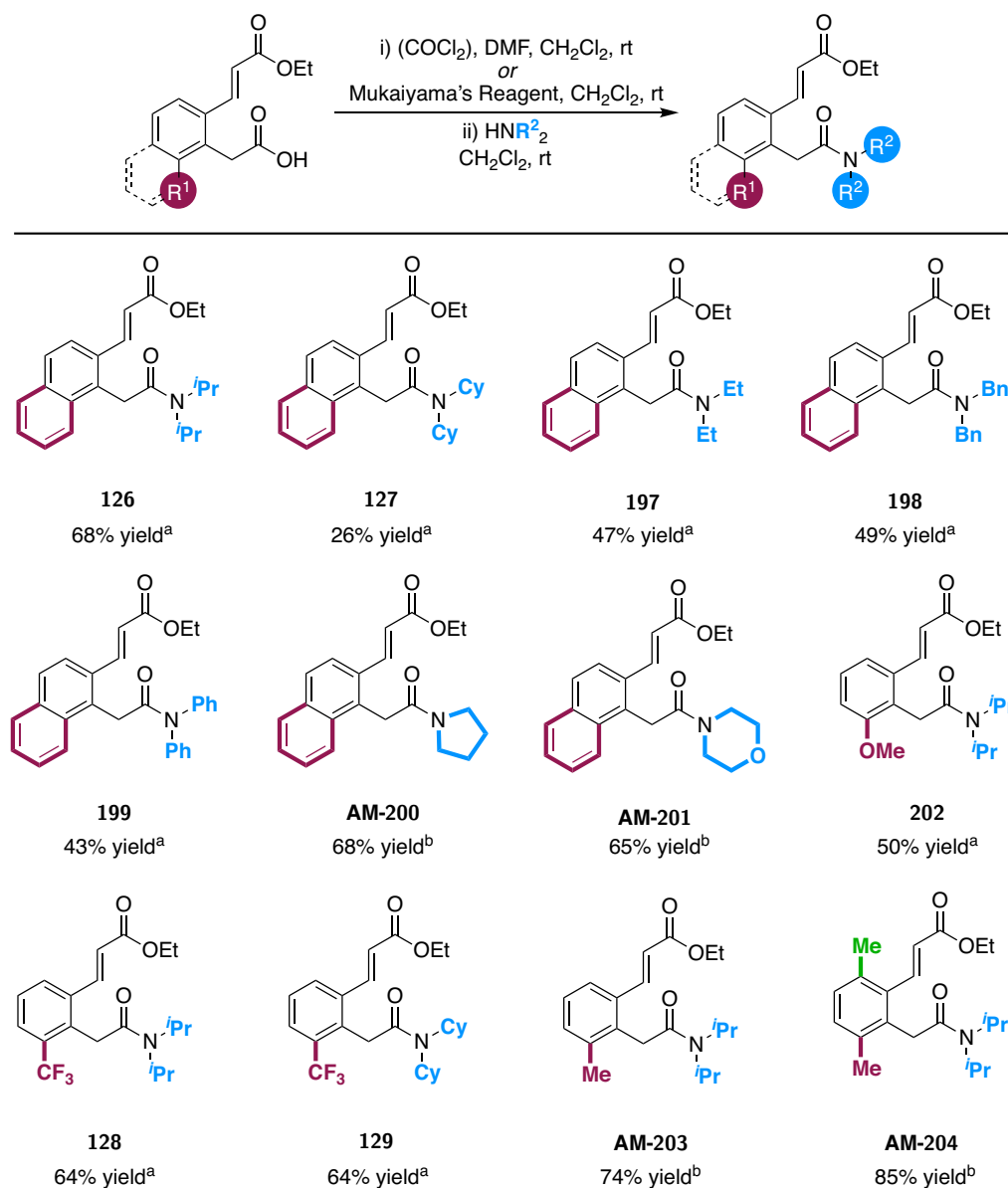
Several substrates were made following the same synthetic route as for **148**. The C–H activation of commercially available phenylacetic acids yielded five acrylates (**124**, **194**, **125**, **AM-195** and **AM-196**) with differing substituents that would eventually become the 8-substituent (Scheme 4.8).



Scheme 4.8: C–H activation of commercial phenylacetic acids.

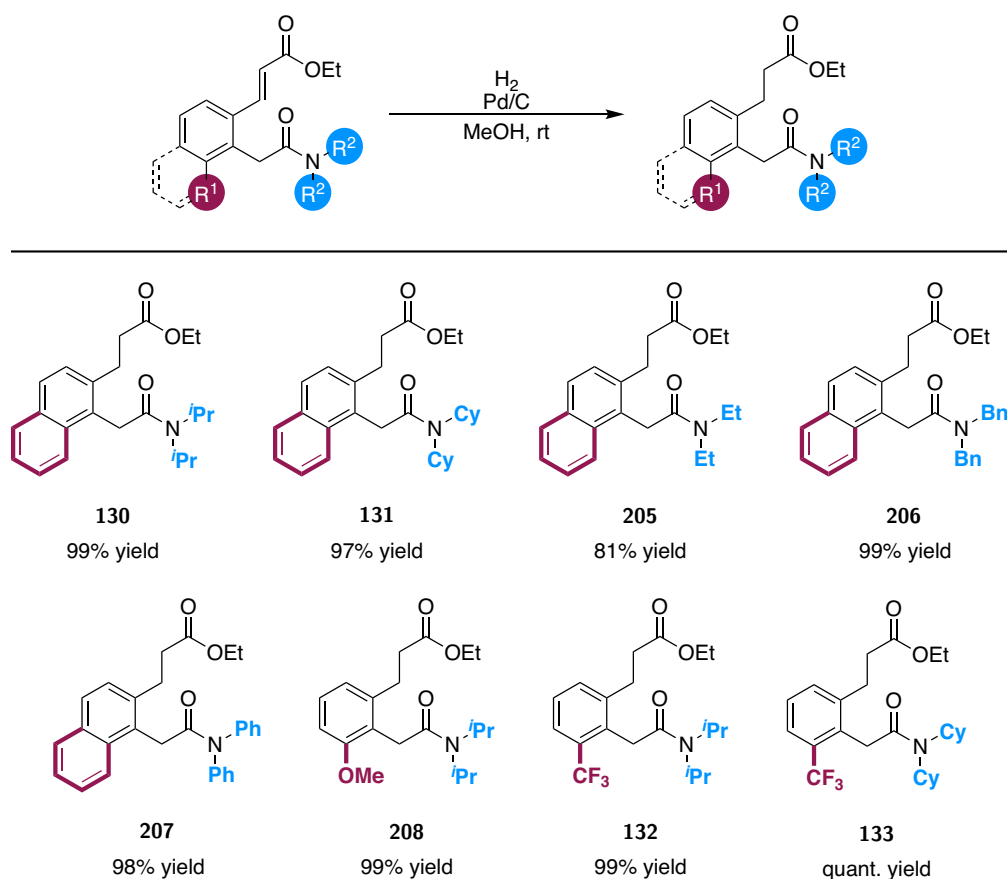
These acids were then coupled to diisopropylamine *via* the acid chloride to give amides **126**, **202**, **128**, **AM-203** and **AM-204** (Scheme 4.9). Acid **124** was coupled to other amines to give different amide substituted compounds. Reaction with dicyclohexylamine, diethylamine, dibenzylamine and diphenylamine provided amides **127**, **197**, **198** and **199** respectively. Coupling of **124** with cyclic amines pyrrolidine and morpholine produced

amides **AM-200** and **AM-201**. Trifluoromethyl-substituted acid **125** was also coupled with dicyclohexylamine to give **129**.



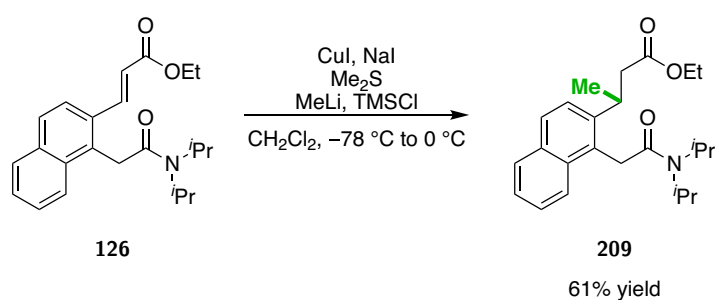
Scheme 4.9: Amide couplings. ^a (COCl_2) , DMF. ^bMukaiyama's reagent.

Following amidation, most of the amides in Scheme 4.9 above were hydrogenated using palladium on carbon under a hydrogen atmosphere to give the products in excellent yields (Scheme 4.10). The remaining acrylate amides (**AM-200**, **AM-201**, **AM-203** and **AM-204**) were utilised later in a different synthetic route.



Scheme 4.10: Hydrogenation of acrylates.

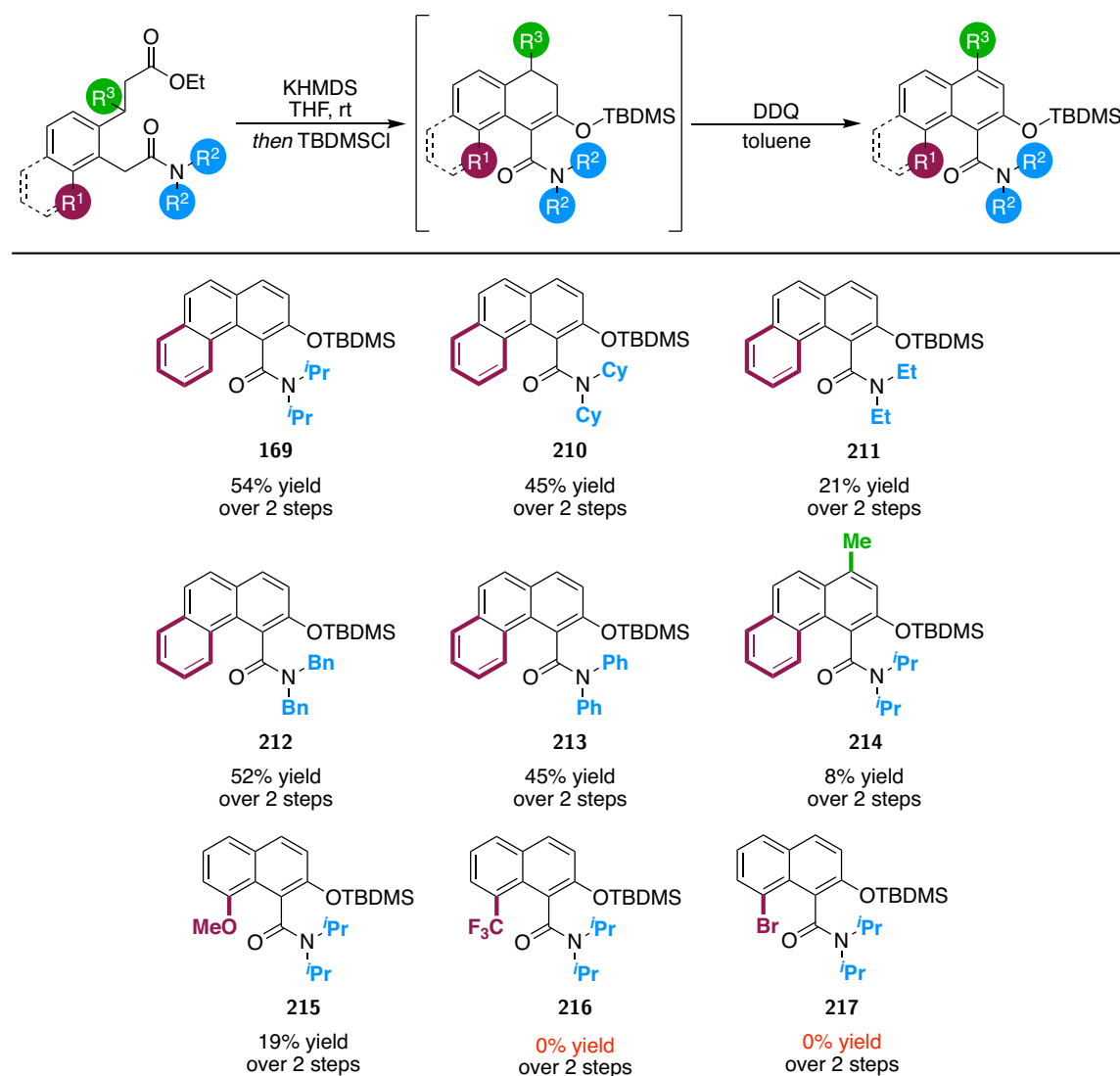
Acrylate amide **126** underwent a conjugate addition with methyl lithium to give methyl substituted compound **209** in 61% yield (Scheme 4.11). This would eventually generate a 1-methylphenanthren-3-ol substrate.



Scheme 4.11: Conjugate addition of methyl lithium and **126**.

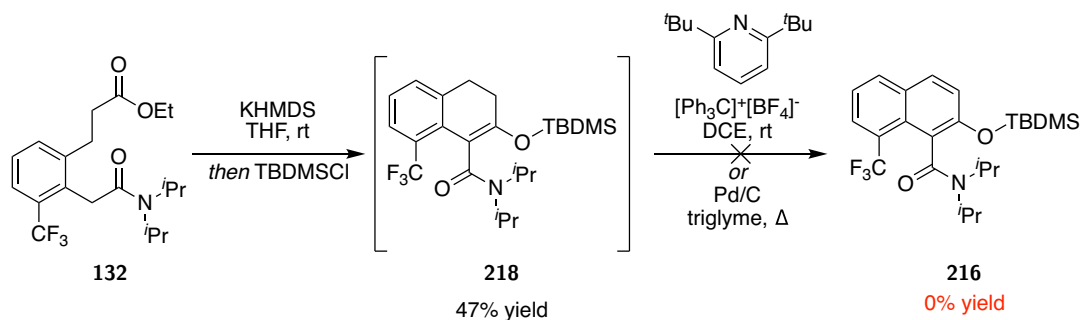
All of these compounds, as well as **107** (previously synthesised in Chapter 2, Scheme 2.4), were cyclised upon treatment with KHMDS, and the silyl enol ethers were all isolated (though not characterised due to rapid decomposition) (Scheme 4.12). The oxidation with DDQ proceeded well when R^1 was a fused benzene to give protected naphthols **169** and

210–215, but proved difficult for other compounds. Following silyl enol ether formation from **208**, the methoxy-substituted compound reacted with DDQ in very low yield. This was presumably due to rapid decomposition of the product or the silyl enol ether intermediate under the acidic reaction conditions caused by DDQ.^[95,96] When $R^1 = CF_3$ or Br, the reaction yielded no product (**216** or **217**) with complete consumption of starting material. Electron withdrawing groups slow the rate of oxidation so it is likely that decomposition of intermediate silyl enol ethers occurred before oxidation could occur. Silylated naphthol **214** was also isolated in low yield, principally due to a low yield of the silyl enol ether intermediate post cyclisation (23%).



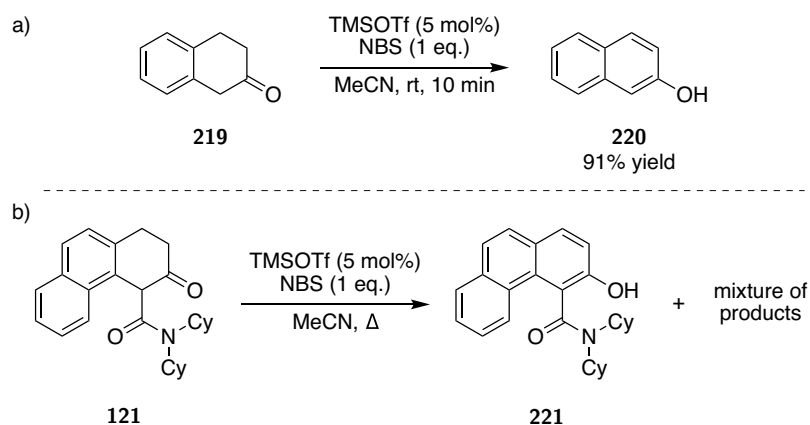
Scheme 4.12: Cyclisation and DDQ oxidation.

Oxidation of dihydronaphthyl compounds have been previously carried out in the literature using palladium on carbon^[97] or trityl tetrafluoroborate.^[98] Unfortunately, subjecting silyl enol ether **218** to these conditions yielded no product (Scheme 4.13).



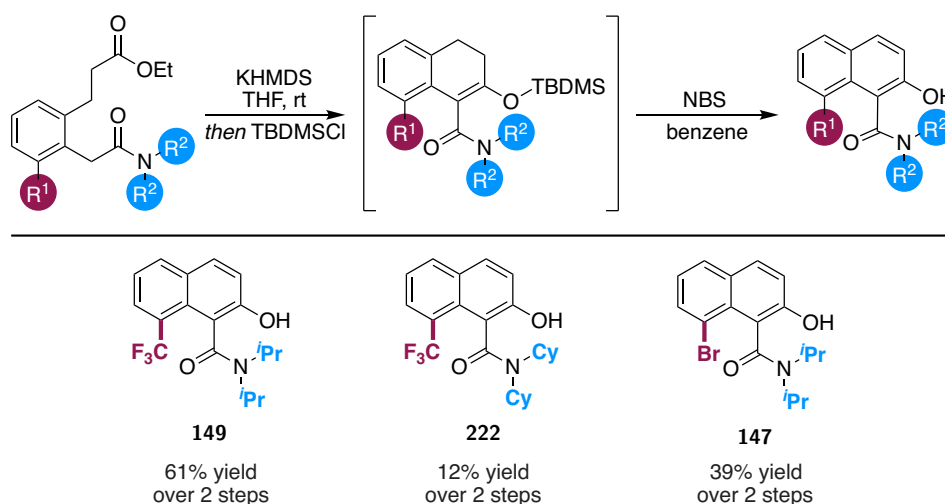
Scheme 4.13: Attempted oxidation of **218**.

Koo and co-workers found that subjecting β -tetralone **219** (Scheme 4.14a) to *N*-bromosuccinimide (NBS) with catalytic TBDMSOTf, gave rapid production of 2-naphthol **220** in 91% yield within 10 min.^[99] These conditions were tested on β -tetralone **121**, as this compound was already in hand. However, the reaction of **121** was a lot slower than the literature example and led to a complex mixture of products, although analysis by mass spectrometry confirmed product formation (Scheme 4.14b).



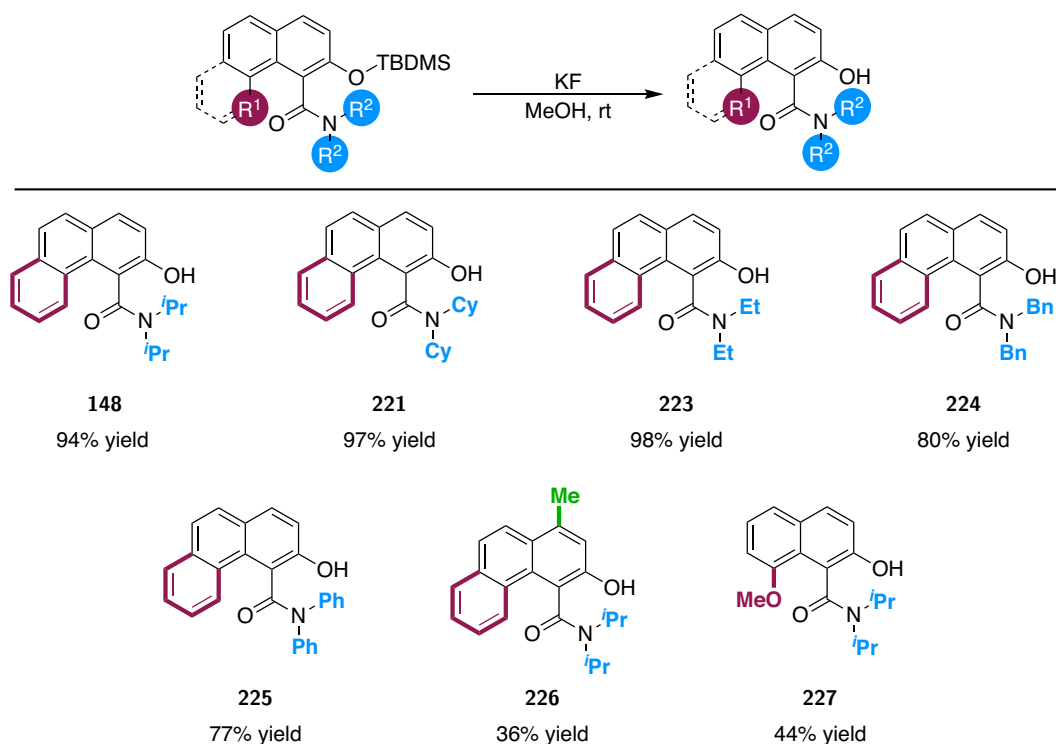
Scheme 4.14: Oxidation of β -tetralone to 2-naphthol.

As the reaction above most likely proceeds *via* the silyl enol ether, reaction of previously synthesised trifluoromethyl substituted silyl enol ether **218** with NBS in benzene was attempted. This would bypass the initial silylation step of the reaction above. Higher temperatures were required and the reaction was heated to reflux overnight to yield the alcohol in good yield (Scheme 4.15). These conditions were also applied to the other substrates that could not undergo oxidation with DDQ (**107** and **133**).



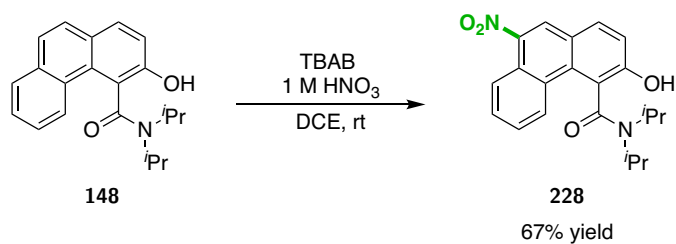
Scheme 4.15: Oxidation of silyl enol ethers to 2-naphthol substrates with NBS.

The silylated naphthols from Scheme 4.12 (**169**, **210** and, **211–215**) were efficiently deprotected using potassium fluoride in methanol (Scheme 4.16) to give the relevant naphthols **148**, **221–227**.



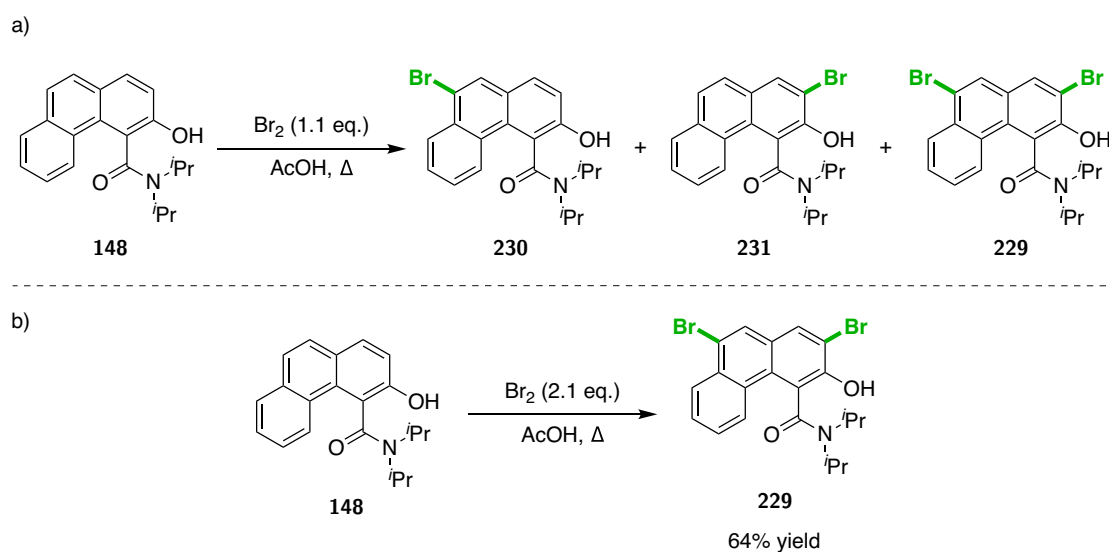
Scheme 4.16: Deprotection of naphthols.

Having synthesised several naphthol substrates, late stage diversification of the naphthols was explored, exploiting their reactivity towards electrophilic aromatic substitution. Phenanthren-3-ol **148** was subjected to nitration conditions under phase-transfer catalysis to install a nitro group in the 9-position of **228** (Scheme 4.17).



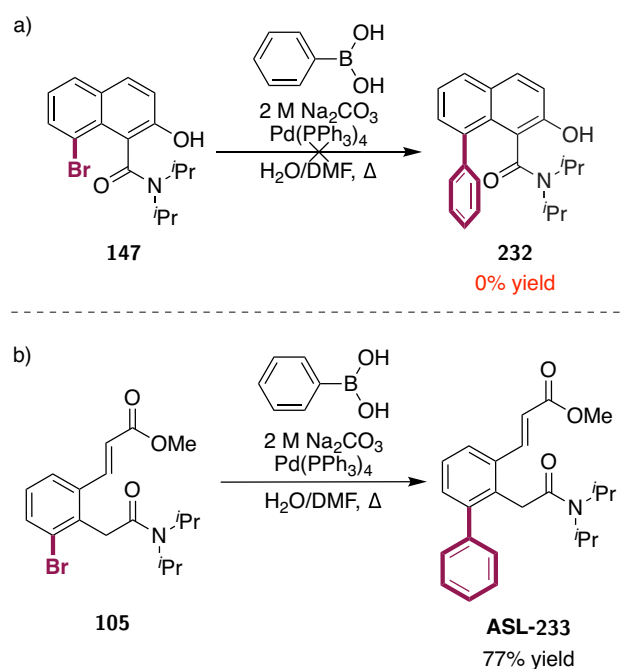
Scheme 4.17: Nucleophilic aromatic substitution of **148**.

Reaction of **148** with 1.1 equivalents of bromine resulted in unselective bromination and an inseparable mixture of starting material, 9-bromo (**230**), 2-bromo (**231**) and 2,9-dibromo (**229**) products were observed (Scheme 4.18a). Use of 2.1 equivalents of bromine enforced complete consumption of starting material and enabled isolation of 2,9-dibrominated naphthol **229** (Scheme 4.18b).



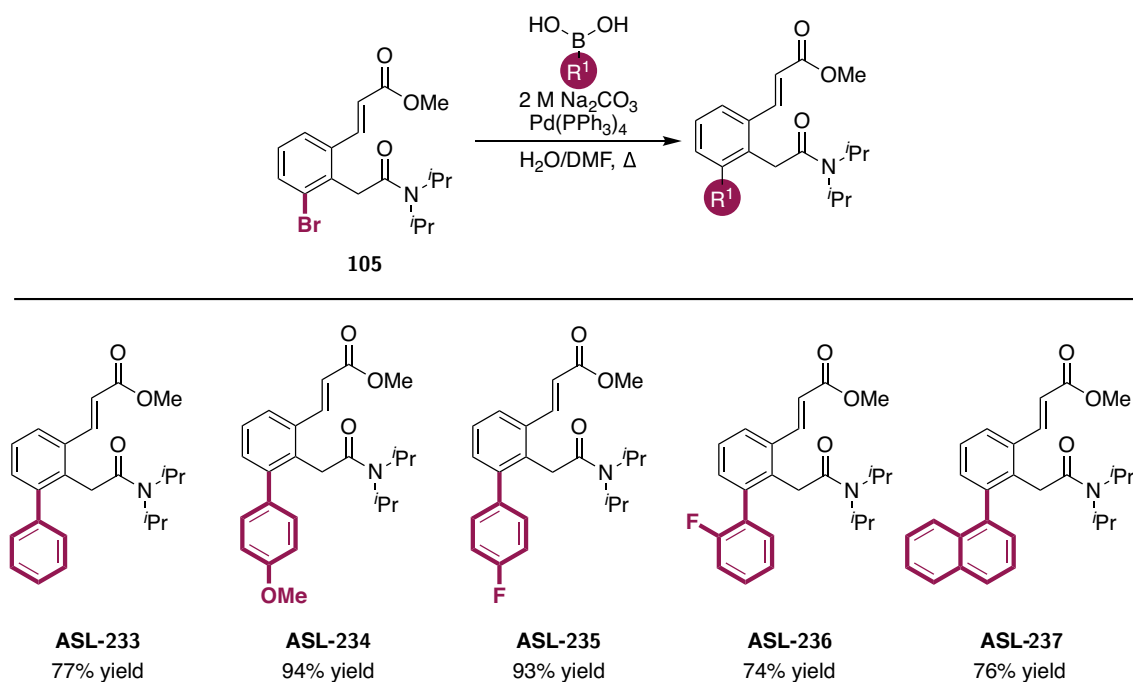
Scheme 4.18: Bromination of **148**.

Another strategy for late stage functionalisation utilised the aromatic bromide of **147** in a cross-coupling reaction. The reaction of **147** with phenylboronic acid under standard conditions was attempted, but no formation of product **232** was observed (Scheme 4.19a). This was attributed to the hindered nature of the aromatic bromide, making it notoriously difficult to couple successfully.^[100–102] Fortunately, a successful Suzuki coupling of phenylboronic acid and acrylate **105** was accomplished using palladium acetate, yielding compound **ASL-233** in 77% yield (Scheme 4.19b).



Scheme 4.19: Suzuki couplings of **147** and **105**

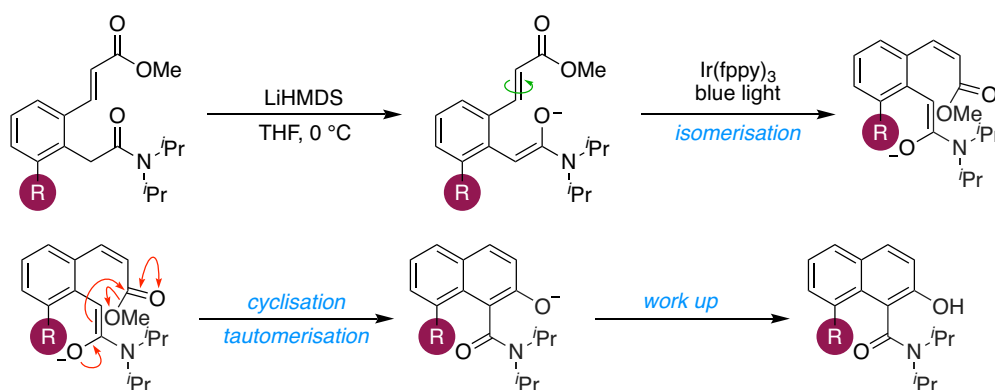
This cross-coupling was repeated with a varied selection of boronic acid partners to yield acrylates **ASL-233–ASL-237** in good to excellent yield (Scheme 4.20).



Scheme 4.20: Suzuki couplings of **105** with different boronic acids.

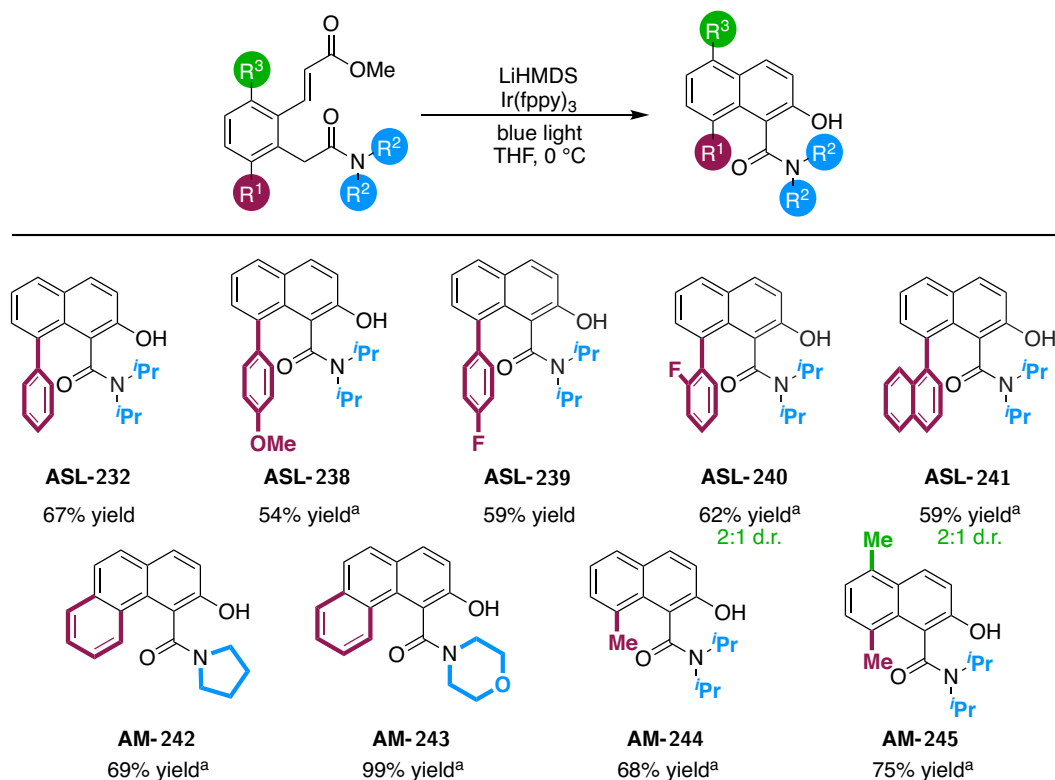
In order to streamline the synthesis of naphthols, Dr Antti Lahdenperä developed a novel cyclisation involving an energy-transfer mediated isomerisation of the acrylates, followed

by a Dieckmann cyclisation (Scheme 4.21). This would form the aromatic ring in one step, decreasing the number of reactions required for a new, redox neutral route.



Scheme 4.21: Photocyclisation of acrylates.

Amides **ASL-233–ASL-237** and remaining amides from Scheme 4.9 (**AM-200**, **AM-201**, **AM-203** and **AM-204**) were subjected to these conditions to yield nine new naphthol substrates in good yield (Scheme 4.22), resulting in a total of 21 diverse substrates on which to test the enantioselective *O*-alkylation.



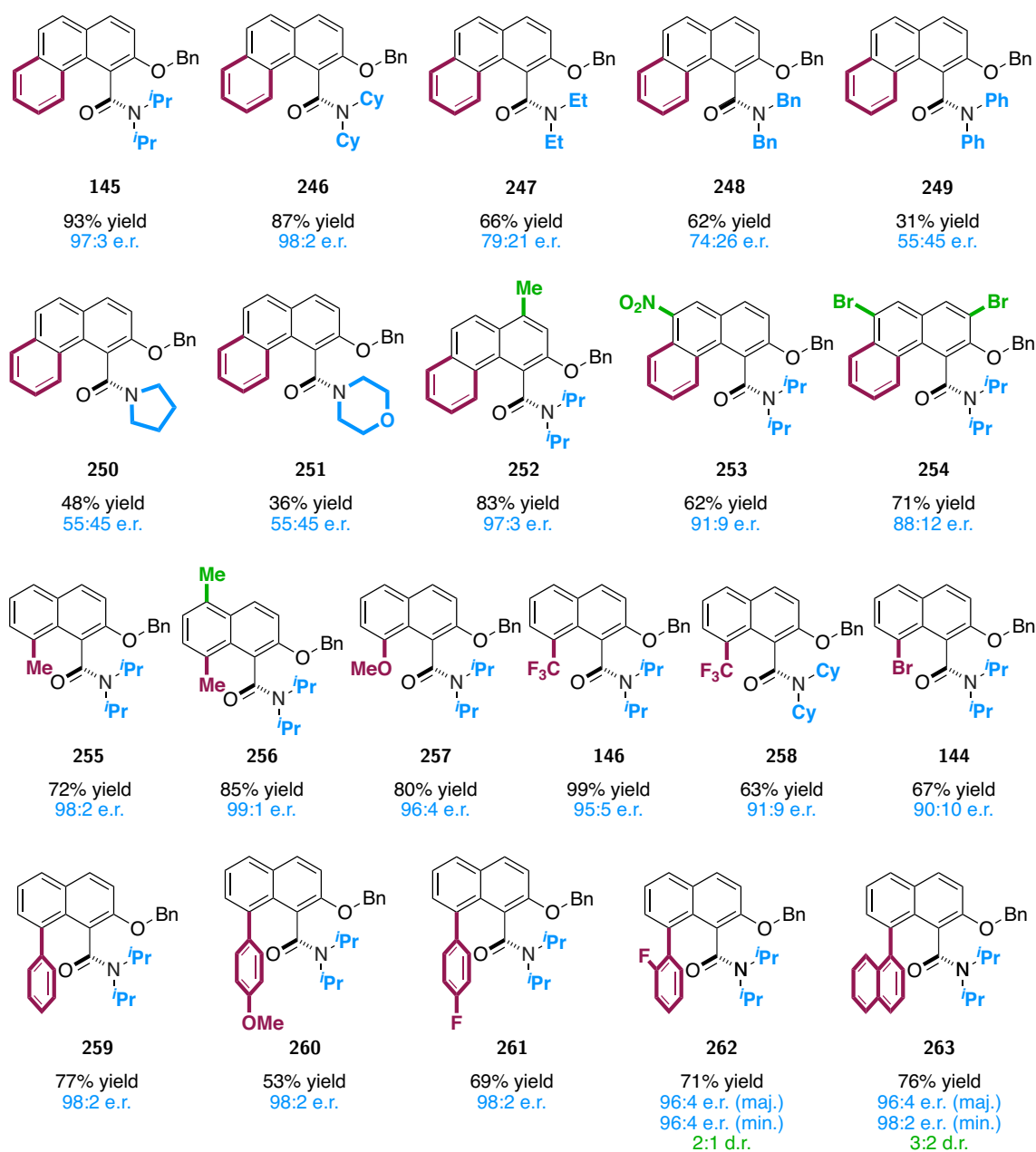
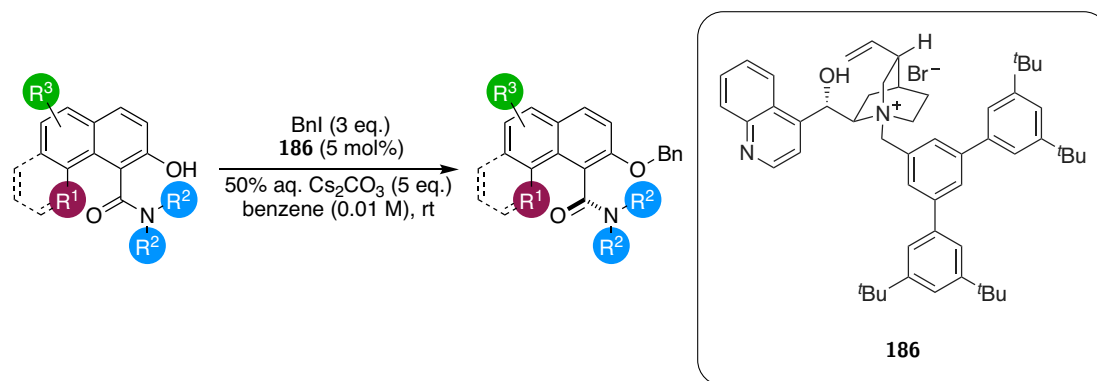
Scheme 4.22: Photocyclisation of acrylates. ^aWithout Iridium catalyst.

4.4.2 Enantioselective Alkylation of New Substrates

With a range of substrates now in hand, the enantioselective reaction was tested using the optimised conditions. These reactions were all carried out on a 0.1–0.2 mmol scale (Scheme 4.23).

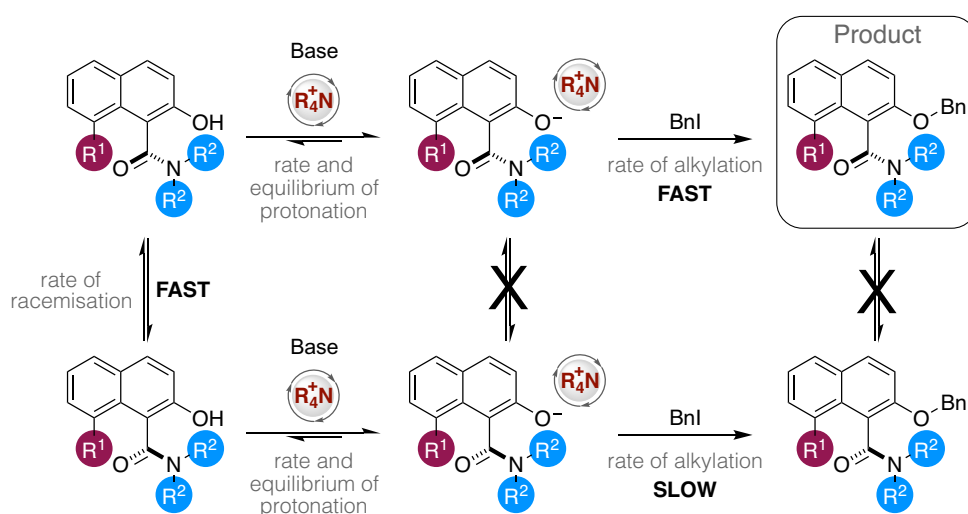
A variety of amide substituents were tested. Diisopropyl amide **148**, the substrate the reaction was optimised for, gave excellent yield and enantioenrichment of **145** (97%, 97:3 e.r.). Changing these groups to cyclohexyl increased selectivity to 98:2 e.r. (**246**). However less sterically demanding amide substituents such as ethyl or benzyl led to a drop in yield and enantioselectivity (79:21 e.r. for **247** and 74:26 e.r. for **248**). The selectivity dropped further for diphenyl, pyrrolidine and morpholine amides **249–251** (55:45 e.r.). These results suggest large amide substituents with steric bulk around the nitrogen are essential for high enantioselectivity. Methyl substitution on the aromatic ring was well tolerated, generating the same selectivity and comparable yield for **252**. Nitro substitution in **253** led to a drop in enantioselectivity (91:9 e.r.) and the presence of bromine ortho to the hydroxy group decreased the enantioselectivity of **254** further to 88:12 e.r..

A wide assortment of 8-substituents were well tolerated. Methyl, methoxy, trifluoromethyl and phenyl based substituents all gave excellent enantioselectivity. Adding a methyl group in the 5-position to give product **256** made a small difference to the enantioselectivity (99:1 e.r. compared to 98:2 e.r. of **255**). 8-Bromo substitution led to a slightly decreased enantioenrichment of **144** (90:10 e.r.). Phenyl-derived 8-substituents in **259–263** all gave excellent enantioselectivity (96:4–98:2 e.r.). Compounds **262** and **263** possess two axes of restricted rotation and therefore led to formation of two inseparable diastereomers, both of which were found to have high enantioenrichment.



Scheme 4.23: Enantioselective *O*-alkylation of naphthols.

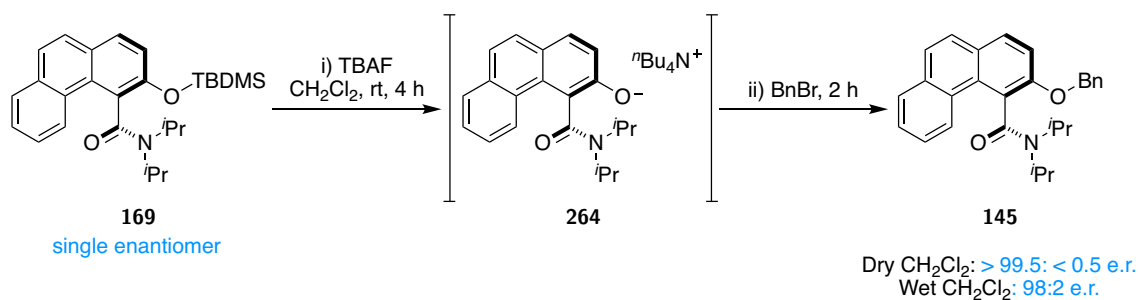
It is hard to predict the reasons behind the observed reaction outcomes as there are a lot of factors to consider, such as the solubility of the starting material, rate of racemisation, rate of deprotonation, equilibrium of deprotonation and rate of alkylation (Scheme 4.24). The rate of racemisation and deprotonation and equilibrium of deprotonation will affect the amount of time the starting material will spend in solution in the protonated form required for facile racemisation. If the rate of unwanted alkylation is too fast compared to these, then more of the unwanted enantiomer will form.



Scheme 4.24: Proposed mechanism.

It has already been shown that the barrier to rotation of the benzylated product is too high to racemise at room temperature, but it was unknown whether the naphtholate anion was able to racemise readily. To examine this, a single enantiomer of silylated phenanthrol **169** (separated by semi-preparative HPLC) was deprotected in anhydrous dichloromethane (< 5 ppm) and wet dichloromethane (210 ppm), giving naphtholate **264** (Scheme 4.25). This was stirred for 4 hours to allow time for possible racemisation to occur, after which the phenanthrolate was quenched with benzyl bromide. Under anhydrous conditions, there was very little loss of enantiopurity. Comparatively, under wet conditions, the benzylated phenanthrol **145** was isolated in slightly lower enantioenrichment. This

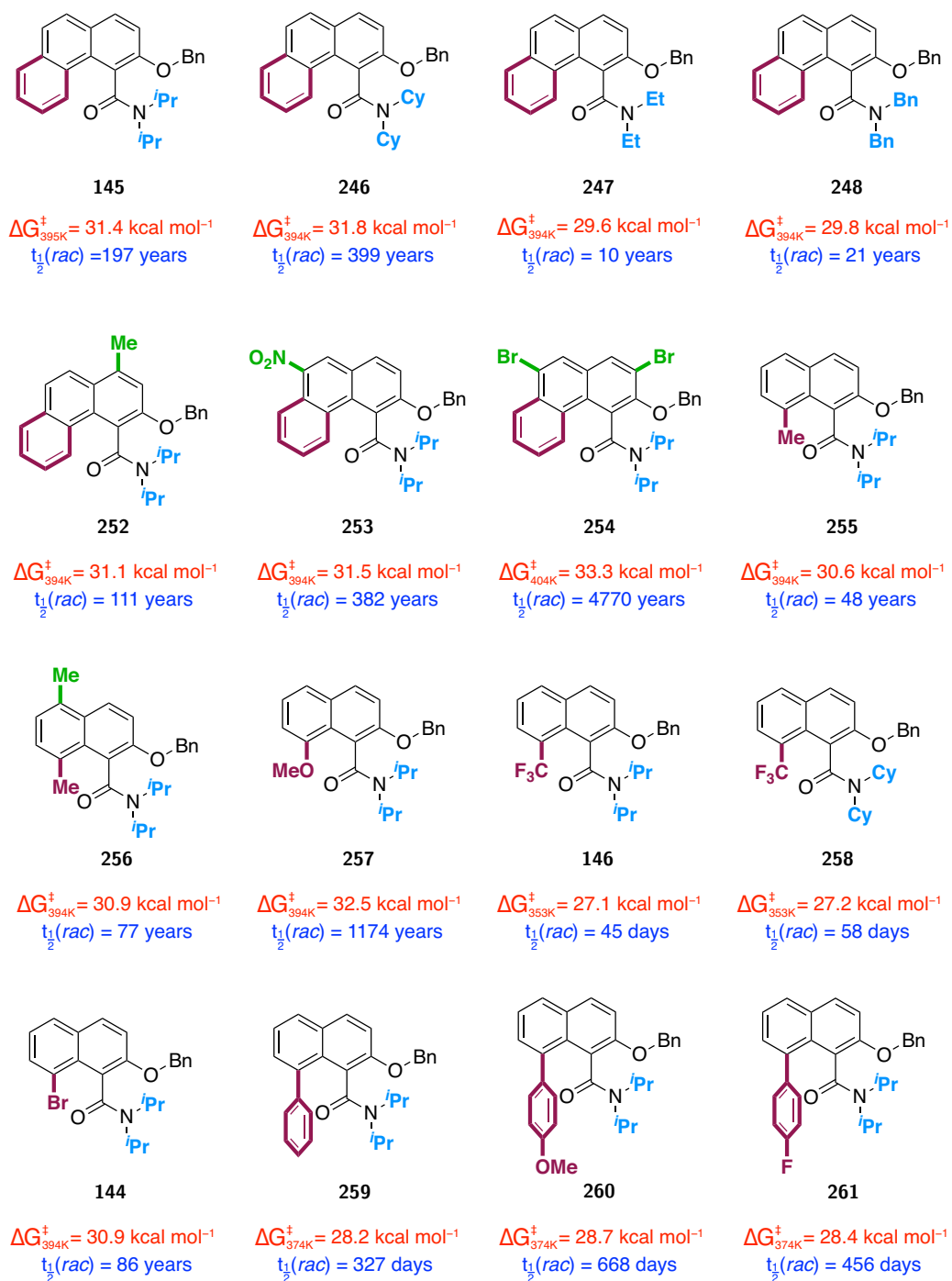
gives some evidence that under anhydrous conditions, where the naphtholate is forced to remain deprotonated until quenched with benzyl bromide, there is very little rotation of **264**. However, when a source of protons is present, the naphtholate can be protonated, after which rotation occurs due to the hydrogen bond stabilised transition state, then deprotonated and finally alkylated to give slightly racemised product.



Scheme 4.25: Investigating rotation of phenanthrolate.

4.5 Barriers to Rotation of Products

Since many novel atropisomeric compounds had been enantioselectively synthesised using the developed dynamic kinetic resolution, it would be interesting to determine their barriers to rotation (Scheme 4.26). This unfortunately was not possible for compounds with very low enantioenrichment, so the barriers were not calculated for **249**, **250** or **251**.



Scheme 4.26: Barriers to rotation of benzylated naphthamides.

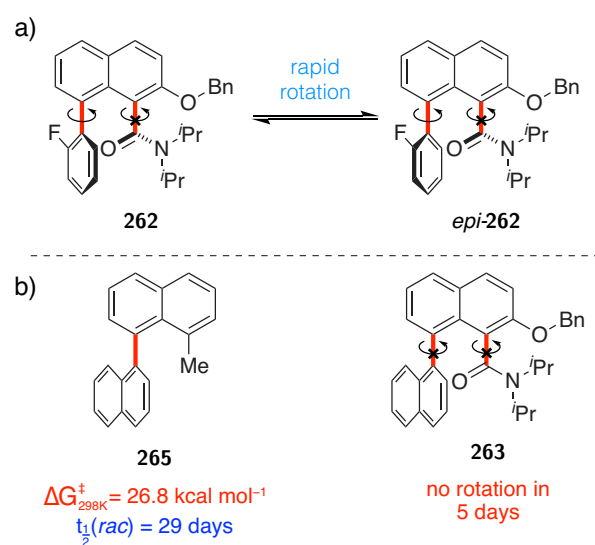
Changing the amide group of the phenanthryl product had a large effect on barrier to rotation. Cyclohexyl substituents in **246** gave the highest barrier followed by isopropyl (**145**), benzyl (**248**) then ethyl (**247**). This follows the trend in group size as shown by the A-values in Table 4.13. Addition of a methyl group in the 1-position (**252**) led to a small decrease in barrier to rotation and a nitro group at the 9-position (**253**) did not change the barrier to rotation extensively. Rotation of di-bromo substituted compound **254** is much more restricted with a barrier of 33.3 kcal mol⁻¹. This large increase in barrier to rotation is likely caused by “buttressing” by the bromine adjacent to the oxygen, which prevents the distortion of the C–OBn bond required for facile racemisation.^[19,103]

Varying the 8-substituent of the naphthamide had a considerable effect on the barrier to rotation. Trifluoromethyl-substituted compounds **146** and **258** had the lowest barriers to rotation of the benzylated compounds at 27.1 and 27.2 kcal mol⁻¹. Phenyl substituted naphthol compounds **259–261** gave the next lowest barrier at 28–29 kcal mol⁻¹. Substitution on this phenyl ring in compounds **260** and **261** gave very small increases in barrier to rotation. Bromo- and methyl- substituted naphthamides **144**, **255** and **256** had barriers to rotation of 30–31 kcal mol⁻¹ and phenanthryl compounds had barriers to rotation of 31–32 kcal mol⁻¹. 8-Methoxynaphthamide **257** had a very large barrier to rotation (32.5 kcal mol⁻¹). Therefore, the trend in 8-substituent is CF₃ < Ph < Me/Br < fused benzene < OMe. This trend does not follow that of size shown by A-values in Table 4.13, as can be exemplified by comparison of barriers for **146** and **257**. Trifluoromethyl is a much larger group than methoxy and yet gives a barrier 5 kcal mol⁻¹ lower. Instead, this data supports the findings of Clayden and co-workers, discussed in Chapter 1, that the electronic properties of substituents in this position are more important than steric effects.^[24] Functional groups which have a bonding interaction with the electrophilic amide carbonyl have a higher barrier to rotation than electron withdrawing groups (Figure 1.6a).

Table 4.13: A-values of substituents.

Substituent	A-value ^[104–107]
Cy	2.15
<i>i</i> Pr	2.15
Bn	1.81
Et	1.75
Ph	3.00
CF ₃	2.10
Me	1.70
OMe	0.75
Br	0.38

Barriers of **262** and **263** were not measured due to the complexity of rotation about two separate chiral axes. However, the barriers to rotation of the biaryl bond, were investigated. Single diastereomers were isolated by small scale semi-preparative HPLC and monitored at room temperature in a mixture of isopropanol and hexane (the HPLC eluent of separation). Compound **262**, bearing an *o*-fluoro group, was found to equilibrate rapidly to the thermodynamic mixture of diastereomers seen in the originally isolated product but no racemisation, suggesting rotation about one axis only (Scheme 4.27a). As previous studies show, the barrier to rotation of the Ar–CO bond is high enough to preclude racemisation at room temperature. Therefore, it can be assumed that the observed epimerisation is caused by rotation about the biaryl bond. Binaphthyl amide **263** should have a high barrier to rotation about the biaryl bond as similar compound binaphthyl **265** (Scheme 4.27b) has a barrier to rotation ($\Delta G_{298K}^\ddagger$) of 26.8 kcal mol^{−1}, corresponding to a half life to racemisation of 29 days.^[108] A single diastereomer of **263** at room temperature led to no racemisation or epimerisation within 5 days, suggesting the barrier to rotation is indeed high. Further studies are required for a more complete understanding of the interconversion of the diastereomers of these molecules.

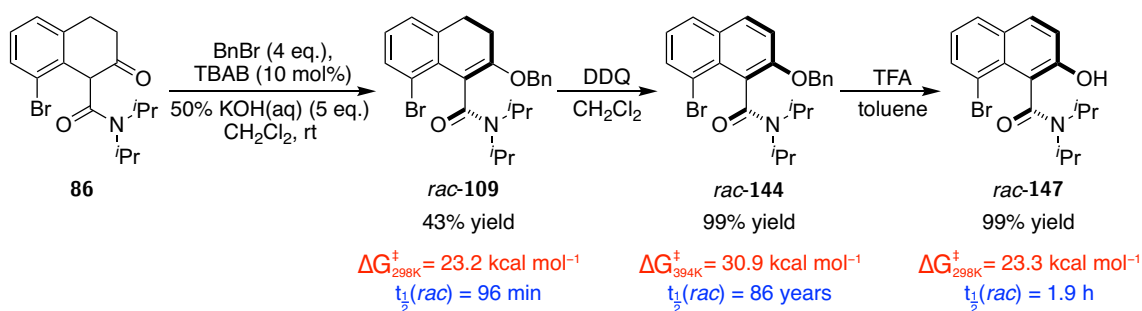


Scheme 4.27: a) Rapid rotation of biaryl bond in **262**. b) Barrier to rotation of **265** and hindered rotation of **263**.

5 Conclusion and Future Work

5.1 Conclusion

This thesis has focused on the development of novel methods to synthesise non-biaryl atropisomers. The first strategy, described in Chapter 2, concerned the *O*-alkylation of β -tetralones (Scheme 5.1). However, this approach was hindered by low yields due to unwanted *C*-alkylation, which could not be eliminated through change of reaction conditions. It was also discovered that the enol ethers had very low barriers to rotation, which would prohibit their enantioselective synthesis on the time scale of phase-transfer reactions (24–48 h). Unfortunately, substrates that led to products with a high barrier to rotation also led to a larger ratio of *C*-alkylation. For these reasons this approach was abandoned.

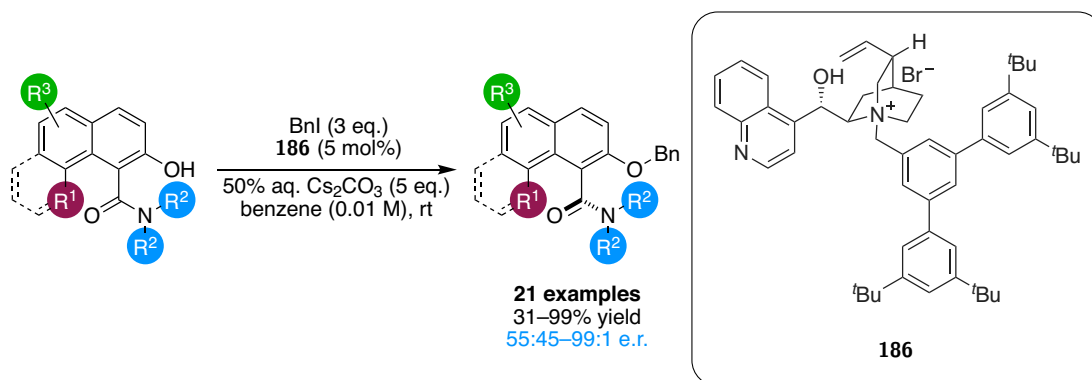


Scheme 5.1: Reaction of β -tetralone to enol ether and barriers to rotation of atropisomeric amides.

The barriers to rotation of the oxidised naphthamides were measured and found to be much higher than the enol ethers, and enantioenriched samples were stable at room tem-

perature. When the benzyl group was removed, the barrier decreased to the extent where rotation was facile at room temperature. This discrepancy was further investigated both computationally and experimentally. It was successfully shown that the transition state can be stabilised by an intramolecular hydrogen bond. Therefore, the rate of racemisation could be modified by solvent and variations of substituents on the aromatic ring.

In Chapter 4, the low barrier of these naphthols was exploited to carry out a dynamic kinetic resolution to generate the benzylated compound *via* *O*-alkylation under phase-transfer catalysis (Scheme 5.2). Extensive optimisation of both enantioselectivity and reactivity led to high yields and selectivity. The substrate scope was broad; variation of the 8-substitution of the naphthol with electron donating and electron withdrawing functional groups was well tolerated. The amide substituents could be adjusted to an extent, but gave better enantioselectivity when large.

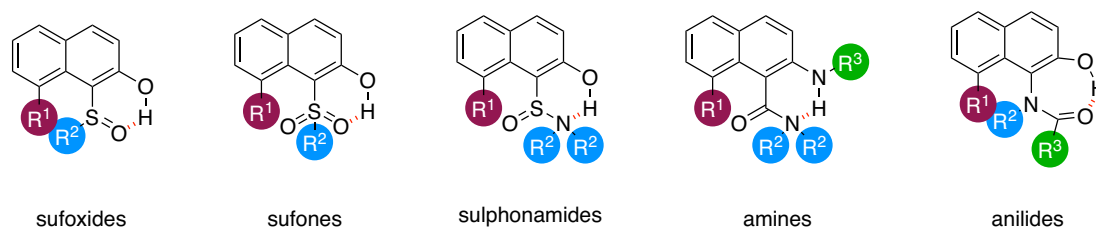


Scheme 5.2: Enantioselective *O*-alkylation of atropisomeric naphthamides.

Finally the barriers to rotation of the benzylated naphthamides were determined and it was found that the electronic properties of the 8-substituent had a large effect on the rate of racemisation.

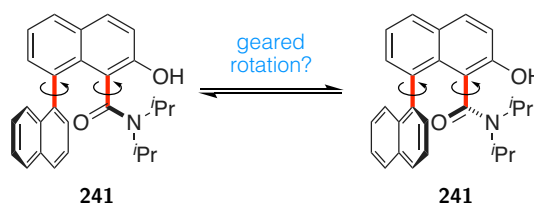
5.2 Future Work

This thesis has concentrated on the enantioselective synthesis of naphthamides, but the strategy above could be used to generate other, novel, non-biaryl atropisomeric structures (Scheme 5.3). Structures containing a hydrogen bond donor and hydrogen bond acceptor in the correct positions would have a low barrier to rotation.



Scheme 5.3: Potential starting materials for enantioselective *O*-alkylation.

As well as this, the nature of the hydrogen bond in the naphthol starting material could be explored further. NMR studies would reveal how solvent and substitution affect the strength of the hydrogen bond. Furthermore, it would be interesting to examine naphthol **ASL-241**, containing two axes of hindered rotation. Rotation about the Ar–CO bond should occur readily at room temperature. This may enable the biaryl bond to also rotate in a geared manner (Scheme 5.4). Once alkylated, the amide will no longer rotate, halting rotation about the biaryl bond.



Scheme 5.4: Potential geared rotation of naphthol **AM-241**.

6 Supplementary Information

6.1 General Information

6.1.1 Naming and Numbering

Compounds have been named according to IUPAC recommendations or according to commonly utilised names where appropriate. The atomic numbering system for compounds does not correspond to IUPAC names, but numbered arbitrarily to allow for simple assignment of spectra.

6.1.2 Reaction Conditions

Where specified, anhydrous conditions correspond to use of oven dried glassware and an inert nitrogen or argon atmosphere. Room temperature refers to 20–25 °C. Temperatures of 0 °C were obtained using an ice/water bath. Temperatures of –78 °C were obtained using a dry ice/acetone bath. Reflux and heating conditions were obtained using a Drysyn[®] heating block equipped with a contact thermometer. Temperatures of 10 °C were obtained using a Polar Bear Plus.

6.1.3 Solvents and Reagents

Anhydrous dichloromethane and tetrahydrofuran were obtained after purification according to Grubbs et al.^[109] Tetrahydrofuran was further dried by addition of 4Å molecular sieves for three days. All other solvents were used without further purification. “Petrol” refers to the fraction of petroleum ether boiling in the range 40–60 °C. Degassed solvents were prepared by freeze-pump thawing as described by Armarego and Perrin.^[110] Reagents were used directly as supplied by major chemical suppliers.

6.1.4 Chromatography

Thin layer chromatography was carried out on Merck Kieselgel 60, F₂₅₄ 0.25 mm precoated aluminium plates and visualisation was achieved by UV light ($\lambda_{\text{max}} = 254 \text{ nm}$) and/or by staining with potassium permanganate solution or bromocresol green solution. Column chromatography was performed using VWR silica gel 60 (40-63 μm particle size) of Aldrich silica gel 60 (40-63 μm particle size) using pressure by means of a nitrogen line.

6.1.5 NMR Spectroscopy

NMR spectra were recorded on a Bruker Avance in the deuterated solvent stated and are referenced to the residual non-deuterated solvent peak. Chemical shifts are quoted in ppm with signal splittings recorded as singlet (s), doublet (d), triplet (t), quartet (q), hept (heptet), and multiplet (m). The abbreviation br denotes broad. Coupling constants, J , are measured to the nearest 0.1 Hz and are presented as observed. All ^{19}F NMR spectra are proton decoupled. Spectra assignment was aided by the results of COSY, HSQC, HMBC.

6.1.6 Infra-Red

Infra-red spectra were recorded on a Bruker Tensor 27 FTIR spectrometer equipped with a diamond ATR module. Absorbance maxima ($\nu_{\max}$) are reported in wavenumbers (cm^{-1}).

6.1.7 Mass Spectrometry

Accurate masses (HRMS) were recorded on Bruker MicroTOF and Micromass GCT spectrometers under conditions of electrospray ionisation (ESI), chemical ionisation (CI) or atmospheric pressure chemical ionization (APCI).

6.1.8 Polarimetry

Optical Rotations were determined using Perkin-Elmer 241 polarimeter with a path length of 1 dm (using the sodium D line, 589 nm). Concentrations are reported in g/100 mL. Temperatures are reported in °C.

6.1.9 HPLC

Chiral HPLC was performed on a Dionex Ultimate 3000 system comprising of a Dionex LPG-3400A pump, WPS-3000SL autosampler, TCC-3000SD column compartment, DAD-3000 diode array detector fitted with the appropriate Daicel Chiralpak column (dimensions: 0.46 cm $\varnothing$ $\times$ 25 cm) and corresponding guard column (0.4 cm $\varnothing$ $\times$ 1 cm). Wavelengths (λ) are reported in nm, retention times (τ_R) are reported in minutes and solvent flow rates are reported in mL min⁻¹.

6.1.10 Melting Points

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

6.1.11 Catalyst Synthesis

Catalysts that were not commercially available were prepared following established literature procedures of *N*-alkylation of cinchona alkaloids.^[111–113]

6.2 General Procedures

General Procedure A: C–H Olefination of 2-Phenyl Acetic Acids

Following a modified literature procedure,^[86] *The appropriate 2-phenyl acetic acid* (1.0 eq.), potassium bicarbonate (2.0 eq.), (*S*)-*N*-acetylalanine (0.2 eq.), and palladium acetate (0.1 eq.) were added to a 500 mL round bottom flask in 50 mL *tert*-amyl alcohol. The flask was evacuated and back filled with oxygen three times, then ethyl acrylate (2.0 eq.) was added. The solution was heated to 90 °C for 2 h after which it was cooled to room temperature and filtered through celite. 3 M HCl was added until the solution was at pH 1. The organic layer was extracted with ethyl acetate three times, dried with anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude mixture was purified by column chromatography (see experimental methods for specific details) to yield the corresponding acid.

General Procedure B: Amidation of 2-Phenyl Acetic Acids: Method 1 (with Oxalyl Chloride)

The appropriate acid (1.0 eq.) was suspended in anhydrous dichloromethane. Oxalyl chloride (2.0 eq.) and a catalytic amount of DMF were added and the reaction was stirred at room temperature for around 1 h until no more gas was produced. The solution was concentrated *in vacuo* and redissolved in anhydrous dichloromethane with *the appropriate amine* (2.0 eq.) and stirred at room temperature for 2 h. The solution was diluted with dichloromethane and washed with water and brine. The organic phase was dried with anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude mixture was purified (see experimental methods for specific details) to yield the corresponding amide.

General Procedure C: Amidation of 2-Phenyl Acetic Acids: Method 2 (with Mukaiyama's Reagent)

The appropriate acid (1.0 eq.) was dissolved in anhydrous dichloromethane and Mukaiyama's reagent (2-chloro-1-methylpyridinium iodide) (1.5 eq.) was added. The reaction mixture was stirred under a nitrogen atmosphere for 30 min. Then, *the appropriate amine* (3.0 eq.) was added to the mixture dropwise *via* syringe, and stirred for 1 h at room temperature. The reaction was quenched with 1 M HCl (5 mL) and extracted with ethyl acetate three times. The combined organic layers were washed with brine, dried with anhydrous magnesium sulfate, and concentrated *in vacuo*. The crude mixture was purified by column chromatography (see experimental methods for specific details) to yield the corresponding amide.

General Procedure D: Hydrogenation of 3-Phenyl Acrylates

The appropriate acrylate (1.0 eq.) was dissolved in methanol, with Pd/C (10% w/w). The flask was sealed and evacuated and back filled with hydrogen three times. The reaction was stirred under a hydrogen atmosphere overnight. The solution was filtered through celite and concentrated *in vacuo*. The crude was purified, as required, by column chromatography (see experimental methods for specific details) to yield the corresponding ester.

General Procedure E: Cyclisation of Esters to β -Tetralones

The appropriate ester (1.0 eq.) was dissolved in anhydrous THF and cooled to 0 °C under an argon atmosphere. KHMDS (0.5 M, 2.0 eq.) was added dropwise *via* syringe pump.

The solution was warmed to room temperature and stirred for 4 h. Ammonium chloride was added and the organic layer was extracted with diethyl ether. The organic layer was dried with anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude mixture was purified by column chromatography (see experimental methods for specific details) to yield the appropriate β -tetralone.

General Procedure F: Racemic *O*-alkylation of β -Tetralones

The appropriate β -tetralone (1.0 eq.) was dissolved in degassed dichloromethane in a vial under argon. Benzyl bromide (4.0 eq.) and TBAB (0.1 eq.) were added. The reaction was stirred vigorously before 50% aqueous potassium hydroxide (5.0 eq.) was added. After 4 h the reaction was quenched with saturated aqueous ammonium chloride and extracted with ethyl acetate. The organic layer was dried with sodium sulfate, filtered, and concentrated *in vacuo*. The crude mixture was purified by column chromatography (see experimental methods for details) to yield the corresponding enol ether.

General Procedure G: Cyclisation of Esters to Silyl Enol Ethers

The appropriate ester (1.0 eq.) was dissolved in anhydrous THF and cooled to 0 °C under an argon atmosphere. KHMDS (0.5 M, 2.0 eq.) was added dropwise *via* syringe pump. The solution was warmed to room temperature and stirred for 4 h. TBDMSCl (2.0 eq.) was added and the solution stirred for 1 h. Saturated aqueous ammonium chloride was added and the organic layer extracted with diethyl ether. The organic layer was dried with anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude mixture was purified by column chromatography (see experimental methods for specific details) to yield the appropriate silyl enol ether.

General Procedure H: Oxidation of Silyl Enol Ethers: Method 1 (with DDQ)

The appropriate silyl enol ether (1.0 eq.) was dissolved in toluene with DDQ (1.3 eq.) and heated at reflux for 10–40 min. The solution was cooled to room temperature, filtered through celite (washing with diethyl ether) and concentrated *in vacuo*. The crude mixture was purified by column chromatography (see experimental methods for specific details) to yield the appropriate silylated naphthol.

General Procedure I: Oxidation of Silyl Enol Ethers: Method 2 (with NBS)

The appropriate silyl enol ether (1.0 eq.) was dissolved in benzene. NBS (1.2 eq.) was added and the solution was heated at reflux overnight. The reaction was cooled to room temperature and the solution concentrated *in vacuo*. The crude was purified by column chromatography (see experimental methods for specific details). If necessary, the resultant solid was triturated with hexane and a small amount of dichloromethane and filtered to yield the corresponding naphthol.

General Procedure J: Deprotection of Silylated Naphthols

The appropriate silylated naphthol (1.0 eq.) was dissolved in methanol. Potassium fluoride (2.0 eq.) was added and the reaction was stirred at room temperature for 30 min. Saturated aqueous ammonium chloride was added to the solution and the organic layer was extracted with ethyl acetate, dried with anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude was purified, as required, by column chromatography or trituration with ethyl acetate (see experimental method for details) to yield the corresponding naphthol.

General Procedure K: Suzuki Reaction

The appropriate aryl bromide (1.0 eq.), was suspended in water in a glass vial with *the appropriate boronic acid* (1.1 eq.), palladium acetate (0.05 eq.), TBAB (1.0 eq.), and sodium carbonate (3.0 eq.) under nitrogen. The reaction mixture was stirred and heated to reflux until the aryl bromide was fully consumed (15–25 min). The reaction was cooled to room temperature and the organic layer was extracted with ethyl acetate three times. The combined organic layers were then dried with anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The resulting crude material was purified by column chromatography (see experimental methods for specific details) to yield the corresponding biaryl.

General Procedure L: Photocyclisation of Acrylates

The appropriate amide was dissolved in anhydrous THF in a flame-dried vial under a nitrogen atmosphere. The solution was cooled to 0 °C and LiHMDS in THF was added. The reaction mixture was allowed to stir while irradiating with a 12 W blue lamp ($\lambda = 450$ nm). After 1 h, the reaction was quenched with saturated aqueous ammonium chloride, then extracted with ethyl acetate three times. The combined organic phases were dried over anhydrous magnesium sulfate and concentrated *in vacuo*. The crude mixture was purified by column chromatography (see experimental methods for specific details) to yield the corresponding naphthol.

General Procedure M: Racemic *O*-Alkylation of Naphthols

The appropriate naphthol was suspended in toluene and benzyl bromide (3.0 eq.) and TBAB (0.1 eq.) were added. The mixture was vigorously stirred before 50% aqueous

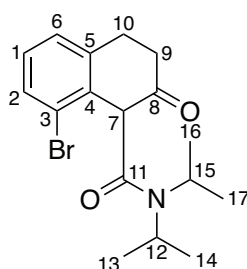
potassium hydroxide (5.0 eq.) or 50% caesium carbonate (5.0 eq.) was added. After 16 h the reaction was quenched with saturated aqueous ammonium chloride. The organic phase was extracted with ethyl acetate, dried with anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude mixture was purified by column chromatography or small scale TLC depending on scale (see experimental methods for details) to yield the corresponding benzylated naphthol.

General Procedure N: Asymmetric *O*-Alkylation of Naphthols

The appropriate naphthol was suspended in benzene (0.01 M) and benzyl iodide (3.0 eq.) and **186** (0.05 eq.) were added. The mixture was vigorously stirred before 50% aqueous caesium carbonate (5.0 eq.) was added. After 48 h the reaction was quenched with saturated aqueous ammonium chloride and extracted with ethyl acetate. The organic phase was dried with anhydrous sodium sulfate, filtered and concentrated *in vacuo* at room temperature. The crude mixture was purified by column chromatography (see experimental methods for details) to yield the corresponding benzylated naphthol.

6.3 Experimental Procedures for Individual Compounds

8-Bromo-*N,N*-diisopropyl-2-oxo-1,2,3,4-tetrahydronaphthalene-1-carboxamide
(86)



Prepared according to **General Procedure E** with **107** (383 mg, 0.997 mmol), KHMDS (5.0 mL, 0.5 M, 2.49 mmol) in anhydrous THF (5 mL). Purification by column chromatography eluting with 10% ethyl acetate in petrol yielded title compound **86** as a white solid (207 mg, 59%).

m.p. 108–112 °C

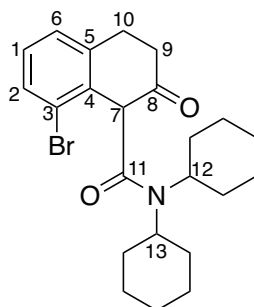
¹H NMR (500 MHz, CDCl₃) δ_H : 7.45 (d, J = 8.0 Hz, 1H, H2), 7.19 (d, J = 7.5 Hz, 1H, H6), 7.11 (t, J = 7.7 Hz, 1H, H1), 5.15 (s, 1H, H7), 4.78 (hept, J = 6.6 Hz, 1H, H12), 3.51–3.38 (m, 2H, H10a and H15), 3.04–2.93 (m, 1H, H10b), 2.93–2.87 (m, 1H, H9a), 2.48 (m, 1H, H9b), 1.37 (d, J = 6.8 Hz, 3H, H16), 1.35 (d, J = 6.7 Hz, 3H, H17), 1.32 (d, J = 6.7 Hz, 3H, H14), 1.30 (d, J = 6.5 Hz, 3H, H13).

¹³C{¹H} NMR (126 MHz, CDCl₃) δ_C: 206.1 (C8), 164.3 (C11), 140.4 (C5), 134.9 (C4), 131.0 (C2), 128.8 (C1), 127.6 (C6), 124.6 (C3), 60.0 (C7), 50.5 (C12), 47.0 (C15), 38.0 (C9), 29.4 (C10), 20.7 (C13), 20.7 (C14), 20.4 (C17), 20.3 (C16).

FTIR (neat) ν/cm^{-1} = 2966, 2928, 1717, 1642, 1442, 1370, 1319, 1156, 1132, 1040.

HRMS (m/z , ESI⁺): calculated for C₁₇H₂₃BrNO₂ ([M+H]⁺) = 352.0907, found = 352.0909.

8-Bromo-*N,N*-dicyclohexyl-2-oxo-1,2,3,4-tetrahydronaphthalene-1-carboxamide
(87)



Prepared according to **General Procedure E** with amide **108** (175 mg, 0.377 mmol) and KHMDS (1.1 mL, 0.5 M, 0.565 mmol) in anhydrous THF (3.0 mL). Purification by filtration through silica, washing through with ethyl acetate yielded title compound **87** as a white solid (97 mg, 60%).

m.p. 120–122 °C

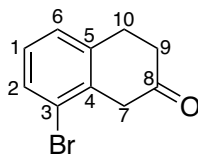
¹H NMR (500 MHz, CDCl₃) δ_H : 7.44 (d, J = 7.6 Hz, 1H, H2), 7.18 (d, J = 7.8 Hz, 1H, H6), 7.10 (t, J = 7.7 Hz, 1H, H1), 5.17 (s, 1H, H7), 4.35–4.23 (m, 1H, H13), 3.44 (ddd, J = 13.8, 9.3, 5.2 Hz, 1H, H10a), 3.00–2.92 (m, 2H, 9a and H12), 2.92–2.84 (m, 1H, H10b), 2.53–2.29 (m, 3H, H9b and H*Cy*), 2.01–1.79 (m, 4H, H*Cy*), 1.77–1.65 (m, 3H, H*Cy*), 1.58–1.36 (m, 7H, H*Cy*), 1.24–1.01 (m, 4H, H*Cy*).

¹³C{¹H} NMR (126 MHz, CDCl₃) δ_C : 205.9 (C8), 164.6 (C11), 140.5 (C5), 134.9 (C4), 131.0 (C2), 128.8 (C1), 127.6 (C6), 124.6 (C3), 60.2 (C7), 59.2 (C13), 57.3 (C12), 37.9 (C9), 31.1 (2 × C*Cy*), 29.6 (C*Cy*), 29.4 (C*Cy*), 29.4 (C10), 26.7 (C*Cy*), 26.6 (C*Cy*), 26.1 (C*Cy*), 25.9 (C*Cy*), 25.6 (C*Cy*), 25.5 (C*Cy*).

FTIR (neat) ν/cm^{-1} = 2928, 2853, 1716, 1641, 1447, 1302, 1126.

HRMS (m/z , ESI⁺): calculated for C₂₃H₃₁BrNO₂ ([M+H]⁺) = 432.1533, found = 432.1529.

8-Bromo-3,4-dihydronaphthalen-2(1H)-one (88)



2-Bromophenylacetic acid (5.0 g, 23.3 mmol) was added to an oven dried flask and dissolved in anhydrous dichloromethane (20 mL). Thionyl chloride (2.2 mL, 30.2 mmol) was added dropwise at room temperature and the mixture was stirred at reflux overnight. Once cooled to room temperature, a solution of aluminium trichloride (3.56 g, 26.7 mmol) in anhydrous dichloromethane (20 mL) at 0 °C was added and stirred for 15 min. Ethylene gas was bubbled thorough the solution at 10–18 °C for 100 min, then the solution was stirred for 90 min at 0 °C. Ice was added to the solution slowly, and the organic layer was extracted with dichloromethane, washed with water, then saturated aqueous sodium bicarbonate, dried with anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude was recrystallised in hot ethyl acetate/hexane and filtered to yield title compound **88** as a orange solid (3.02 g, 58%).

m.p. 70 °C

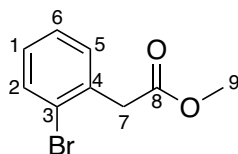
¹H NMR (400 MHz, CDCl₃) δ_H : 7.47 (dd, J = 8.0, 1.2 Hz, 1H, H2), 7.17 (dd, J = 7.5, 1.1 Hz, 1H, H6), 7.08 (t, J = 7.7 Hz, 1H, H1), 3.65 (s, 2H, H7), 3.19–2.97 (m, 2H, H10), 2.68–2.46 (m, 2H, H9).

$^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ_{C} : 209.1 (C8), 138.7 (C5), 133.2 (C4), 131.0 (C2), 128.1 (C1), 127.1 (C6), 124.3 (C3), 44.6 (C7), 38.5 (C9), 29.3 (C10).

FTIR (neat) ν/cm^{-1} = 2981, 2890, 1715, 1562, 1446, 1384, 1384, 1344, 1237, 1167, 778.

HRMS (m/z , APCI^+): calculated for $\text{C}_{10}\text{H}_{10}\text{BrO}$ ($[\text{M}+\text{H}]^+$) = 228.9859, found = 228.9862.

Methyl 2-(2-bromophenyl)acetate (**97**)



According to literature procedure,^[114] 2-bromophenyl acetic acid (7.0 g, 32.6 mmol) was dissolved in methanol (25 mL) with conc. hydrochloric acid (0.5 mL) and heated to reflux for 3 h. Once the solution was cooled to room temperature the solvent was removed *in vacuo* and redissolved in diethyl ether and washed with saturated aqueous sodium bicarbonate then brine. The organic layer was separated, dried with anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to yield title compound **97** as a colourless oil (6.93 g, 93%).

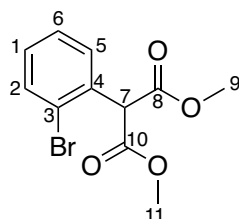
^1H NMR (400 MHz, CDCl_3) δ_{H} : 7.57 (d, J = 7.9 Hz, 1H, H2), 7.33–7.27 (m, 2H, H5 and H6), 7.20–7.10 (m, 1H, H1), 3.80 (s, 2H, H7), 3.72 (s, 3H, H9).

$^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ_{C} : 171.1 (C8), 134.3 (C4), 133.0 (C2), 131.6 (C5), 129.0 (C1), 127.7 (C6), 125.1 (C3), 52.3 (C9), 41.6 (C7).

FTIR (neat) ν/cm^{-1} = 2952, 1737, 1472, 1436, 1436, 1342, 1220, 1163, 1027, 735, 662.

HRMS (m/z , ESI⁺): calculated for C₉H₁₀BrO₂ ([M+H]⁺) = 228.9859, found = 228.9862.

Dimethyl 2-(2-bromophenyl)malonate (**98**)



According to a modified literature procedure,^[115] hexamethylenediamine (15 mL, 72.0 mmol) was dissolved in anhydrous THF (15 mL) and cooled to $-40\text{ }^{\circ}\text{C}$. *n*BuLi (26 mL, 2.5 M, 65.5 mmol) was added dropwise and the solution was stirred for 15 min. Ester **97** was dissolved in anhydrous THF (5 mL) and cooled to $0\text{ }^{\circ}\text{C}$. The LiHMDS solution was added dropwise and the solution was warmed to room temperature and stirred for 45 min. Dimethyl carbonate (5.5 mL, 65.5 mmol) was added dropwise and the solution was stirred for 16 h, after which the reaction was quenched with saturated aqueous ammonium chloride. The organic layer was extracted with ethyl acetate three times and washed with brine, then dried with anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude was purified by column chromatography eluting with dichloromethane to yield title compound **98** as a white solid (5.76 g, 92%).

m.p. $57\text{ }^{\circ}\text{C}$

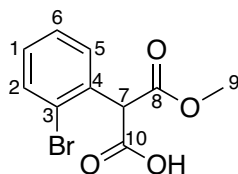
¹H NMR (400 MHz, CDCl₃) δ_H : 7.44 (dd, $J = 8.0, 1.4\text{ Hz}$, 1H, H2), 7.34 (dd, $J = 7.9, 1.7\text{ Hz}$, 1H, H5), 7.19 (td, $J = 7.6, 1.4\text{ Hz}$, 1H, H6), 7.05 (td, $J = 7.7, 1.7\text{ Hz}$, 1H, H1), 5.14 (s, 1H, H7), 3.63 (s, 6H, H9 and H11).

$^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ_{C} : 168.1 (C8 and C10), 132.9 (C2), 132.7 (C4), 130.4 (C5), 129.8 (C1), 127.8 (C6), 125.0 (C3), 56.8 (C7), 53.0 (C9 and C11).

FTIR (neat) ν/cm^{-1} = 2954, 1735, 1434, 1123, 1148, 1020, 745, 695, 659.

HRMS (m/z , ESI^+): calculated for $\text{C}_{11}\text{H}_{12}\text{BrO}_4$ ($[\text{M}+\text{H}]^+$) = 286.9914, found = 286.9914.

2-(2-Bromophenyl)-3-methoxy-3-oxopropanoic acid (**99**)



Malonate **98** (1.50 g, 5.23 mmol) was dissolved in THF (8.0 mL) and water (80 mL), and the solution was cooled to 0 °C. 1 M Sodium hydroxide (8.0 mL, 8.00 mmol) was added dropwise and the solution stirred for 4 h, after which 1 M hydrochloric acid was added until the solution was around pH 1–2. The organic layer was extracted with ethyl acetate, washed with brine, dried with anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to give the crude. This was purified by column chromatography, eluting with 1% acetic acid, 50% ethyl acetate in petrol, to yield title compound **99** as a white solid (1.03 g, 72%).

m.p. 150–152 °C

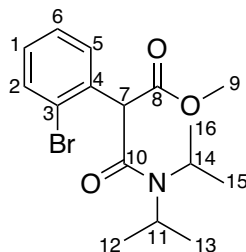
^1H NMR (400 MHz, CDCl_3) δ_{H} : 7.61 (dd, J = 8.0, 1.3 Hz, 1H, H2), 7.48 (dd, J = 7.8, 1.7 Hz, 1H, H5), 7.35 (td, J = 7.6, 1.3 Hz, 1H, H6), 7.22 (ddd, J = 8.0, 7.4, 1.7 Hz, 1H, H1), 5.25 (s, 1H, H7), 3.80 (s, 3H, H9).

$^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ_{C} : 171.7 (C10), 168.7 (C9), 133.2 (C2), 132.4 (C4), 130.7 (C5), 130.2 (C1), 128.0 (C6), 125.1 (C3), 56.6 (C7), 53.5 (C9).

FTIR (neat) ν/cm^{-1} = 1737, 1473, 1437, 1272, 1161, 1020, 746.

HRMS (m/z , ESI^+): calculated for $\text{C}_{10}\text{H}_9\text{BrNaO}_4$ ($[\text{M}+\text{Na}]^+$) = 294.9576, found = 294.9578.

Methyl 2-(2-bromophenyl)-3-(diisopropylamino)-3-oxopropanoate (**100**)



Prepared according to **General Procedure B** with **99** (764 mg, 2.81 mmol), oxalyl chloride (450 μL , 5.62 mmol) DMF (0.1 mL) in anhydrous dichloromethane (10 mL), then diisopropylamine (1.2 mL, 8.43 mmol) in anhydrous dichloromethane (10 mL). Purification by column chromatography, eluting with 10–30% ethyl acetate in petrol, yielded title compound **100** as a white solid (661 mg, 66%).

m.p. 109 $^{\circ}\text{C}$

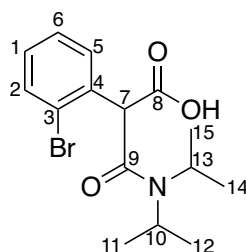
^1H NMR (400 MHz, CDCl_3) δ_{H} : 7.58 (dd, J = 8.0, 1.3 Hz, 1H, H2), 7.49 (dd, J = 7.8, 1.7 Hz, 1H, H5), 7.34 (td, J = 7.6, 1.3 Hz, 1H, H6), 7.18 (ddd, J = 8.0, 7.3, 1.7 Hz, 1H, H1), 5.25 (s, 1H, H7), 3.77 (s, 3H, H9), 3.65 (hept, J = 6.6 Hz, 1H, H12), 3.35 (hept, J = 6.4 Hz, 1H, H15), 1.46 (d, J = 6.8 Hz, 3H, H16), 1.39 (d, J = 6.8 Hz, 3H, H17), 1.20 (d, J = 6.6 Hz, 3H, H13), 0.67 (d, J = 6.6 Hz, 3H, H14).

$^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ_{C} : 168.8 (C8), 166.5 (C10), 133.9 (C4), 132.7 (C2), 130.7 (C5), 129.5 (C1), 127.8 (C6), 124.5 (C3), 57.6 (C7), 52.8 (C9), 49.7 (C12), 46.4 (C15), 20.8 (C13), 20.6 (C16), 19.8 (C17), 19.5 (C14).

FTIR (neat) ν/cm^{-1} = 1754, 1643, 1437, 1437, 1329, 1199, 1171, 1021, 745.

HRMS (m/z , ESI^+): calculated for $\text{C}_{16}\text{H}_{23}\text{BrNO}_3$ ($[\text{M}+\text{H}]^+$) = 356.0856, found = 356.0856.

2-(2-Bromophenyl)-3-(diisopropylamino)-3-oxopropanoic acid (**101**)



Ester **100** (642 mg, 1.81 mmol) was dissolved in methanol (20 mL) with 1 M aqueous sodium hydroxide (5.0 mL, 5.00 mmol) and heated to 40 °C for 24 h. The solvent was removed *in vacuo* and 1 M aqueous hydrochloric acid was added. The organic layer was extracted with ethyl acetate three times. This was washed with saturated aqueous sodium carbonate and then the aqueous was acidified with 1 M aqueous hydrochloric acid and extracted with ethyl acetate three times. This was dried with anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to yield title compound **101** as a white solid (536 mg, 87%).

m.p. 70 °C

^1H NMR (400 MHz, CDCl_3) δ_{H} : 7.66 (dd, J = 8.1, 1.3 Hz, 1H, H2), 7.36 (dd, J = 7.8,

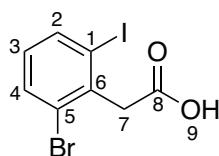
1.8 Hz, 1H, H5), 7.31 (td, $J = 7.5, 1.3$ Hz, 1H, H6), 7.18 (ddd, $J = 8.0, 7.2, 1.8$ Hz, 1H, H1), 5.11 (s, 1H, H7), 3.86 (hept, $J = 6.6$ Hz, 1H, H10), 3.40 (hept, $J = 6.8$ Hz, 1H, H13), 1.46 (d, $J = 6.8$ Hz, 3H, H14), 1.36 (d, $J = 6.8$ Hz, 3H, H15), 1.23 (d, $J = 6.6$ Hz, 3H, H11), 0.53 (d, $J = 6.6$ Hz, 3H, H12).

$^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ_{C} : 170.3 (C9), 170.2 (C8), 134.3 (C4), 133.7 (C2), 129.8 (C1), 128.6 (C5), 128.4 (C6), 125.0 (C3), 52.5 (C7), 49.5 (C10), 47.2 (C13), 20.5 (C11), 20.4 (C14), 19.4 (C15), 19.1 (C12).

FTIR (neat) $\nu/\text{cm}^{-1} = 2967, 1636, 1472, 1442, 1371, 1338, 1133, 1042, 1025, 728$.

HRMS (m/z , ESI^+): calculated for $\text{C}_{15}\text{H}_{21}\text{BrNO}_3$ ($[\text{M}+\text{H}]^+$) = 342.0701, found = 342.0699.

2-(2-Bromo-6-iodophenyl)acetic acid (102)



According to modified literature procedure,^[66,116] 2-bromoacetic acid (2.15 g, 10.0 mmol) was dissolved in anhydrous DMF (40 mL) with palladium acetate (225 mg, 1.00 mmol), PIDA (2.41 g, 7.5 mmol) and iodine (1.9 g, 7.50 mmol). The flask was covered in aluminium foil and heated to 60 °C. After 24 h, the mixture was cooled to room temperature and additional PIDA (2.41 g, 7.50 mmol) and iodine (1.9 g, 7.5 mmol) were added. The reaction was covered in foil and heated to 60 °C. After a further 24 h, additional palladium acetate (225 mg, 1.00 mmol), PIDA (2.41 g, 7.50 mmol) and iodine (1.9 g, 7.50 mmol) were added. The reaction was covered in foil and heated to 60 °C. After a further 24 h,

additional PIDA (2.41 g, 7.50 mmol) and iodine (1.90 g, 7.50 mmol) were added. The reaction was covered in foil and heated to 60 °C for 24 h. The mixture was cooled to room temperature and diluted with ethyl acetate and washed with saturated aqueous sodium sulfite, dried with sodium sulfate, filtered, and concentrated *in vacuo* to give a crude mixture. This was purified by column chromatography, eluting with 10–50% ethyl acetate in petrol, to yield title compound **102** as a white solid (2.83 g, 85%).

m.p. 145–148 °C

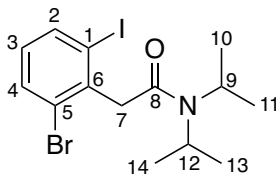
^1H NMR (500 MHz, CDCl_3) δ_{H} : 7.82 (dd, $J = 7.9, 1.2$ Hz, 1H, H2), 7.58 (dd, $J = 8.0, 1.2$ Hz, 1H, H4), 6.82 (t, $J = 8.0$ Hz, 1H, H3), 4.22 (s, 2H, H7).

$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ_{C} : 175.1 (C8), 139.0 (C2), 136.7 (C6), 133.2 (C4), 130.6 (C3), 124.9 (C5), 101.9 (C1), 47.3 (C7).

FTIR (neat) $\nu/\text{cm}^{-1} = 2981, 1698, 1550, 1428, 1410, 1244, 926, 775, 699$.

HRMS (m/z , CI^+): calculated for $\text{C}_8\text{H}_{10}\text{BrINO}_2$ ($[\text{M}+\text{NH}_4]^+$) = 357.8934, found = 357.8939.

2-(2-Bromo-6-iodophenyl)-*N,N*-diisopropylacetamide (**103**)



Acid **102** (2.00 g, 5.87 mmol) was dissolved in anhydrous dichloromethane. Oxalyl chloride (960 μL , 11.7 mmol) and DMF (0.1 mL) were added and the reaction was stirred at room temperature for 1 h until no more bubbles were produced. The solution was concentrated

in vacuo and redissolved in anhydrous dichloromethane with diisopropylamine (2.47 mL, 17.6 mmol) and stirred at room temperature for 2 h. The solution was diluted with dichloromethane and washed with water and brine. The organic phase was dried with anhydrous sodium sulfate, filtered and concentrated *in vacuo* to give the crude mixture, which was purified by column chromatography, eluting with 5–10% ethyl acetate in petrol, to yield title compound **103** as a white solid (2.07 g, 83%).

m.p. 114–116 °C

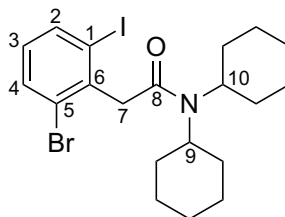
^1H NMR (500 MHz, CDCl_3) δ_{H} : 7.78 (dd, $J = 7.9, 1.2$ Hz, 1H, H2), 7.54 (dd, $J = 8.0, 1.2$ Hz, 1H, H4), 6.76 (t, $J = 7.9$ Hz, 1H, H3), 4.12 (s, 2H, H7), 4.12 (hept, $J = 6.5$ Hz, 1H, H12), 3.48 (hept, $J = 6.8$ Hz, 1H, H9), 1.41 (d, $J = 6.8$ Hz, 6H, H10 and H11), 1.32 (d, $J = 6.6$ Hz, 6H, H13 and H14).

$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ_{C} : 166.3 (C8), 139.4 (C6), 138.7 (C2), 132.9 (C4), 129.7 (C3), 125.0 (C5), 102.6 (C1), 48.9 (C12), 48.4 (C7), 46.3 (C9), 21.2 (C13 and C14), 20.9 (C10 and C11).

FTIR (neat) $\nu/\text{cm}^{-1} = 2962, 1639, 1572, 1549, 1432, 1374, 1336, 1283, 1134, 1045, 785, 700$.

HRMS (m/z , ESI^+) calculated for $\text{C}_{14}\text{H}_{20}\text{BrINO}$ ($[\text{M}+\text{H}]^+$) = 423.9768, found = 423.9761.

2-(2-Bromo-6-iodophenyl)-*N,N*-dicyclohexylacetamide (104)



Prepared according to **General Procedure B** with acid **102** (1.00 g, 2.93 mmol), oxalyl chloride (479 μ L, 5.87 mmol) and DMF (50 μ L) in anhydrous dichloromethane (20 mL) followed by dicyclohexylamine (1.80 mL, 8.80 mmol) in anhydrous dichloromethane (20 mL). Purification by column chromatography, eluting with 10% ethyl acetate in petrol, yielded title compound **104** as a white solid (859 mg, 58%).

m.p. 122–125 °C

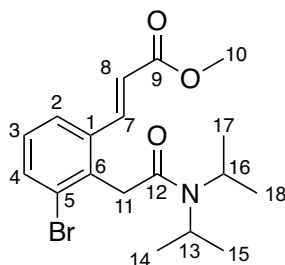
^1H NMR (500 MHz, CDCl_3) δ_{H} : 7.76 (dd, J = 7.9, 1.2 Hz, 1H, H2), 7.52 (dd, J = 8.0, 1.2 Hz, 1H, H4), 6.74 (t, J = 7.9 Hz, 1H, H3), 4.11 (s, 2H, H7), 3.66–3.50 (m, 1H, H9), 3.08–2.89 (m, 1H, H10), 2.60–2.33 (m, 2H, H Cy), 1.96–1.81 (m, 4H, H Cy), 1.81–1.66 (m, 3H, H Cy), 1.66–1.44 (m, 5H, H Cy), 1.44–1.28 (m, 2H, H Cy), 1.28–1.07 (m, 4H, H Cy).

$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ_{C} : 166.6 (C8), 139.5 (C6), 138.6 (C2), 132.8 (C4), 129.6 (C5), 124.9 (C5), 102.5 (C1), 58.2 (C9), 56.5 (C10), 48.5 (C7), 31.4 (2 $\times$ C Cy), 30.1 (2 $\times$ C Cy), 26.8 (2 $\times$ C Cy), 26.2 (2 $\times$ C Cy), 25.4 (C Cy), 25.4 (C Cy).

FTIR (neat) ν/cm^{-1} = 2962, 1638, 1548, 1431, 1371, 1282, 1133, 1044, 926, 784, 699.

HRMS (m/z , ESI^+): calculated for $\text{C}_{20}\text{H}_{28}\text{BrINO}$ ($[\text{M}+\text{H}]^+$) = 504.0394, found = 504.0390.

Methyl (*E*)-3-(3-bromo-2-(2-(diisopropylamino)-2-oxoethyl)phenyl)acrylate
(105)



Amide **103** (817 mg, 1.93 mmol) was dissolved in anhydrous DMF (2.0 mL) in a sealed vial with Pd₂(dba)₃ (88 mg, 0.0930 mmol), methyl acrylate (0.217 mL, 2.41 mmol) and potassium carbonate (532 mg, 3.85 mmol). The solution was heated to 110 °C for 16 h then diluted with ethyl acetate and washed with water. The organic phase was dried with anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to give the crude mixture which was purified by column chromatography, eluting with 5–10% ethyl acetate in petrol, to yield title compound **105** as a white solid (650 mg, 88%).

m.p. 126–128 °C

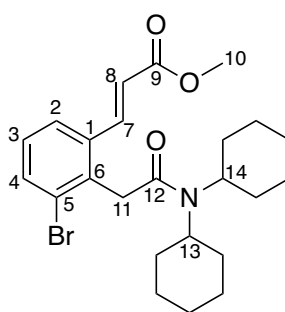
¹H NMR (500 MHz, CDCl₃) δ_H : 7.83 (d, *J* = 15.8 Hz, 1H, H7), 7.59 (dd, *J* = 8.0, 1.3 Hz, 1H, H4), 7.48 (dd, *J* = 7.7, 1.1 Hz, 1H, H2), 7.13 (t, *J* = 7.9 Hz, 1H, H3), 6.31 (d, *J* = 15.7 Hz, 1H, H8), 4.15 (hept, *J* = 6.7 Hz, 1H, H13), 3.96 (s, 2H, H11), 3.79 (s, 3H, H10), 3.55–3.39 (m, 1H, H16), 1.39 (d, *J* = 6.8 Hz, 6H, H17 and H18), 1.32 (d, *J* = 6.6 Hz, 6H, H14 and H15).

¹³C{¹H} NMR (126 MHz, CDCl₃) δ_C : 167.3 (C12), 167.1 (C9), 142.9 (C7), 136.9 (C1), 135.9 (C6), 134.1 (C4), 128.4 (C3), 127.1 (C5), 126.2 (C2), 121.4 (C8), 51.9 (C10), 49.1 (C13), 46.4 (C16), 39.4 (C11), 21.1 (C14 and C15), 20.7 (C17 and C18).

FTIR (neat) ν/cm^{-1} = 2981, 1719, 1639, 1556, 1443, 1372, 1334, 1315, 1276, 1196, 1169, 1042, 978, 909.

HRMS (m/z , ESI⁺): calculated for C₁₈H₂₅BrNO₃ ([M+H]⁺) = 382.1012, found = 382.1014.

Methyl (*E*)-3-(3-bromo-2-(2-(dicyclohexylamino)-2-oxoethyl)phenyl)acrylate
(106)



Amide **104** (1.25 g, 2.48 mmol) was dissolved in anhydrous DMF (2.0 mL) in a sealed vial with Pd₂(dba)₃ (114 mg, 0.123 mmol), methyl acrylate (0.300 mL, 6.20 mmol) and potassium carbonate (686 mg, 4.96 mmol). The solution was heated to 110 °C for 16 h then diluted with ethyl acetate and washed with water. The organic phase was dried with anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to give the crude mixture which was purified by column chromatography, eluting with 10–20% ethyl acetate in petrol to yield title compound **106** as a white solid (946 mg, 82%).

m.p. 122 °C

¹H NMR (400 MHz, CDCl₃) δ_H : 7.84 (d, J = 15.8 Hz, 1H, H7), 7.57 (dd, J = 8.0, 1.2 Hz, 1H, H4), 7.47 (dd, J = 7.8, 1.2 Hz, 1H, H2), 7.11 (t, J = 7.9 Hz, 1H, H3), 6.30 (d, J = 15.7 Hz, 1H, H8), 3.96 (s, 2H, H11), 3.78 (s, 3H, H10), 3.67–3.50 (m, 1H, H14), 3.10–2.82

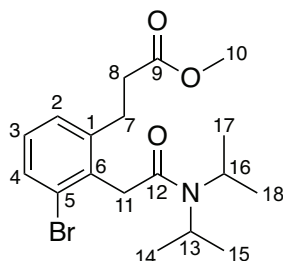
(s, 1H, H13), 2.57–2.26 (m, 2H, H Cy), 1.92–1.77 (m, 4H, H Cy), 1.80–1.65 (m, 3H, H Cy), 1.64–1.43 (m, 5H, H Cy), 1.43–1.27 (m, 2H, H Cy), 1.27–1.05 (m, 4H, H Cy).

$^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ_{C} : 167.6 (C12), 167.0 (C9), 142.8 (C7), 136.9 (C1), 135.9 (C6), 134.0 (C4), 128.3 (C3), 127.0 (C5), 126.2 (C2), 121.3 (C8), 58.3 (C14), 56.5 (C13), 51.8 (C10), 39.8 (C11), 31.4 ($2 \times \text{CCy}$), 30.0 ($2 \times \text{CCy}$), 26.8 ($2 \times \text{CCy}$), 26.2 ($2 \times \text{CCy}$), 25.5 (CCy), 25.4 (CCy).

FTIR (neat) ν/cm^{-1} = 2929, 2853, 1720, 1638, 1438, 1313, 1275, 1168, 731.

HRMS (m/z , ESI^+): calculated for $\text{C}_{24}\text{H}_{33}\text{BrNO}_3$ ($[\text{M}+\text{H}]^+$) = 462.1638, found = 462.1637.

Methyl 3-(3-bromo-2-(2-(diisopropylamino)-2-oxoethyl)phenyl)propanoate
(107)



Amide **105** (1.45 g, 3.79 mmol) was dissolved in MeOH (30 mL) with PtO_2 (14.5 mg, 1% w/w) and stirred for 24 h under a hydrogen atmosphere. The solution was filtered through silica, eluting with 50% ethyl acetate in petrol, and the solvent was evaporated *in vacuo* to yield title compound **107** as a white solid (1.45 g, 99%).

m.p. 77–80 °C

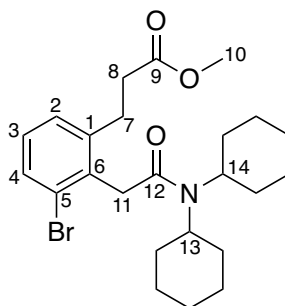
^1H NMR (500 MHz, CDCl_3) δ_{H} : 7.43 (dd, $J = 7.9, 1.2$ Hz, 1H, H4), 7.12 (dd, $J = 7.7, 1.4$ Hz, 1H, H2), 7.03 (t, $J = 7.8$ Hz, 1H, H3), 4.17 (m, 1H, H13), 3.89 (s, 2H, H11), 3.66 (s, 3H, H10), 3.52–3.40 (m, 1H, H16), 2.98–2.91 (m, 2H, H7), 2.64–2.55 (m, 2H, H8), 1.38 (d, $J = 6.8$ Hz, 6H, H17 and H18), 1.30 (d, $J = 6.7$ Hz, 6H, H14 and H15).

$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ_{C} : 173.5 (C9), 167.7 (C12), 141.8 (C1), 134.8 (C6), 131.0 (C4), 128.3 (C3), 128.1 (C2), 126.9 (C5), 51.8 (C10), 49.0 (C13), 46.2 (C6), 39.0 (C11), 34.9 (C8), 29.4 (C7), 21.1 (C14 and C15), 20.7 (C17 and C18).

FTIR (neat) $\nu/\text{cm}^{-1} = 2966, 1735, 1641, 1439, 1370, 1334, 1278, 1204, 1155, 1042, 781$.

HRMS (m/z , ESI^+): calculated for $\text{C}_{18}\text{H}_{27}\text{BrNO}_3$ ($[\text{M}+\text{H}]^+$) = 384.1169, found = 384.1171.

Methyl 3-(3-bromo-2-(2-(dicyclohexylamino)-2-oxoethyl)phenyl)propanoate
(108)



Amide **106** (3.00 g, 7.89 mmol) was dissolved in MeOH (20 mL) with PtO_2 (30 mg, 1% w/w) and stirred for 24 h under a hydrogen atmosphere. The solution was filtered through silica, eluting with 50% ethyl acetate in petrol, and the solvent was evaporated *in vacuo* to yield title compound **108** as a white solid (3.01 g, quant.).

m.p. 97–100 °C

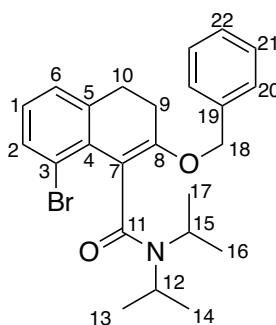
^1H NMR (500 MHz, CDCl_3) δ_{H} : 7.43 (dd, J = 8.0, 1.3 Hz, 1H, H4), 7.11 (dd, J = 7.7, 1.3 Hz, 1H, H2), 7.03 (t, J = 7.8 Hz, 1H, H3), 3.89 (s, 2H, H11), 3.67 (s, 3H, H10), 3.68–3.60 (m, 1H, H13), 2.98–2.82 (m, 3H, H7 and H14), 2.64–2.58 (m, 2H, H8), 2.54–2.34 (m, 2H, H Cy), 1.91–1.80 (m, 4H, H Cy), 1.77–1.67 (m, 3H H Cy), 1.57–1.44 (m, 5H, H Cy) 1.45–1.29 (m, 2H, H Cy), 1.23–1.09 (m, 4H, H Cy).

$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ_{C} : 173.5 (C9), 168.1 (C12), 141.8 (C1), 135.0 (C6), 131.1 (C4), 128.3 (C3), 128.1 (C2), 126.9 (C5), 58.2 (C13), 56.0 (C14), 51.8 (C10), 39.4 (C11), 34.9 (C8), 31.5 $2 \times$ (C Cy), 30.1 ($2 \times$ C Cy), 29.4 (C7), 26.8 ($2 \times$ C Cy), 26.2 ($2 \times$ C Cy), 25.5 (C Cy), 25.5 (C Cy).

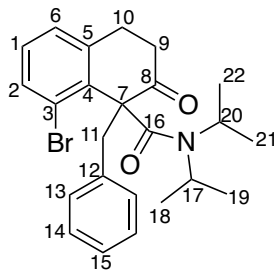
FTIR (neat) ν/cm^{-1} = 3064, 1699, 1669, 1626, 1593, 1490, 1346, 1299, 1262, 1178, 822, 757, 693.

HRMS (m/z , ESI^+): calculated for $\text{C}_{24}\text{H}_{35}\text{BrNO}_3$ ($[\text{M}+\text{H}]^+$) = 464.1795, found = 464.1796.

2-(Benzyloxy)-8-bromo-*N,N*-diisopropyl-3,4-dihydronaphthalene-1-carboxamide
(109)



and **1-Benzyl-8-bromo-*N,N*-diisopropyl-2-oxo-1,2,3,4-tetrahydronaphthalene-1-carboxamide (110)**



Prepared according to **General Procedure F** with **88** (30 mg, 0.0851 mmol), TBAB (3 mg, 0.00851 mmol), 50% w/w aqueous potassium hydroxide (16 μ L, 0.427 mmol) and benzyl bromide (40 μ L, 0.340 mmol) in degassed dichloromethane (851 μ L). Purification by column chromatography, eluting with 10–20% ethyl acetate in petrol, yielded title compounds **109** as a white solid (16 mg, 42%) and **110** as a white solid (12 mg, 32%).

O-Alkylation (**109**):

m.p. 161–164 °C

^1H NMR (400 MHz, CDCl_3) δ_{H} : 7.44–7.40 (m, 2H, H20), 7.39 (d, J = 8.0 Hz, 1H, H2), 7.37–7.31 (m, 2H, H21), 7.32–7.28 (m, 1H, H22), 7.04 (d, J = 7.3 Hz, 1H, H6), 6.86 (t, J = 7.7 Hz, 1H, H1), 4.95 (s, 2H, H18), 3.92 (hept, J = 6.6 Hz, 1H, H15), 3.42 (hept, J = 6.8 Hz, 1H, H12), 2.82 (t, J = 7.7 Hz, 2H, H10), 2.61–2.33 (m, 2H, H9), 1.55 (d, J = 6.8 Hz, 3H, H13), 1.43 (d, J = 6.8 Hz, 3H, H14), 1.09 (d, J = 6.5 Hz, 3H, H17), 1.07 (d, J = 6.3 Hz, 3H, H16).

$^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ_{C} : 166.9 (C11), 157.5 (C8), 137.0 (C19), 136.6 (C5), 133.3 (C2), 133.3 (C4), 128.4 (C21), 127.9 (C22), 127.6 (C20), 126.6 (C1), 126.4 (C6),

119.8 (C3), 117.8 (C7), 70.5 (C18), 50.6 (C15), 45.8 (C12), 30.3 (C10), 23.5 (C9), 21.2 (C16), 20.7 (C14), 19.8 (C17), 19.5 (C13).

FTIR (neat) ν/cm^{-1} = 2970, 2360, 2162, 1653, 1367, 1439, 1335.

HRMS (m/z , ESI⁺): calculated for C₂₄H₂₉BrNO₂ ([M+H]⁺) = 442.1376, found = 442.1378.

C-Alkylation (110):

m.p. 152–156 °C

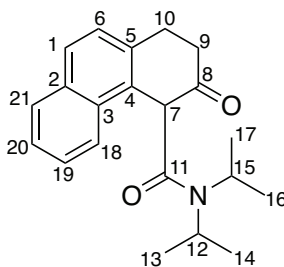
¹H NMR (400 MHz, CDCl₃) δ_H : 7.59 (d, J = 7.9 Hz, 1H, H2), 7.12 (d, J = 7.4 Hz, 1H, H15), 7.07 (t, J = 7.7 Hz, 1H, H1), 7.02 (t, J = 7.7 Hz, 2H, H14), 6.93 (d, J = 7.7 Hz, 1H, H6), 6.58 (d, J = 6.8 Hz, 2H, H13), 3.90 (d, J = 13.5 Hz, 1H, H11a), 3.76 (d, J = 13.4 Hz, 1H, H11b), 3.54 (hept, J = 6.5 Hz, 1H, H17), 3.25 (hept, J = 6.7 Hz, 1H, H20), 2.53–2.36 (m, 2H, H9a and H10a), 2.33–2.20 (m, 1H, H9b), 1.53 (d, J = 6.8 Hz, 3H, H22), 1.47 (d, J = 6.7 Hz, 3H, H21), 1.45–1.35 (m, 1H, H10b), 0.88 (d, J = 6.7 Hz, 3H, H19), 0.60 (d, J = 6.4 Hz, 3H, H18).

¹³C{¹H} NMR (101 MHz, CDCl₃) δ_C : 208.4 (C8), 167.3 (C16), 138.0 (C5), 136.8 (C12), 136.3 (C4), 134.0 (C2), 130.8 (C13), 128.8 (C1), 128.3 (C6), 128.1 (C14), 126.9 (C15), 123.3 (C3), 66.8 (C7), 48.0 (C17), 47.4 (C20), 44.7 (C11), 37.0 (C9), 27.3 (C10), 20.3 (C21), 20.3 (C22), 19.3 (C19), 19.0 (C18).

FTIR (neat) ν/cm^{-1} = 2967, 2928, 1708, 1648, 1433, 1370, 1311, 1215, 1138, 1036, 703.

HRMS (m/z , ESI⁺): calculated for C₂₄H₂₉BrNO₂ ([M+H]⁺) = 442.1376, found 442.1375.

***N,N*-Diisopropyl-3-oxo-1,2,3,4-tetrahydrophenanthrene-4-carboxamide (120)**



Prepared according to **General Procedure E** with amide **130** (525 mg, 1.42 mmol) and KHMDS (4.30 mL, 0.5 M, 0.213 mmol) in anhydrous THF (14 mL). Purification by filtration through silica with ethyl acetate yielded title compound **120** as a white solid (297 mg, 65%).

m.p. 109–113 °C

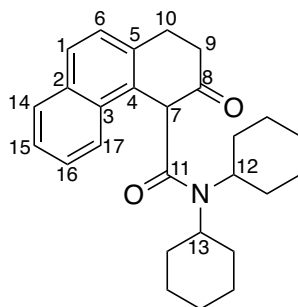
^1H NMR (400 MHz, CDCl_3) δ_{H} : 7.84 (dd, $J = 7.8, 1.6$ Hz, 1H, H21), 7.78–7.68 (m, 2H, H1 and H18), 7.53–7.37 (m, 2H, H20 and H19), 7.32 (d, $J = 8.3$ Hz, 1H, H6), 5.39 (s, 1H, H7), 4.76 (hept, $J = 6.6$ Hz, 1H, H12), 3.51 (dt, $J = 16.3, 7.0$ Hz, 1H, H9a), 3.43 (hept, $J = 6.7$ Hz, 1H, H15), 3.22 (ddd, $J = 16.3, 7.5, 6.2$ Hz, 1H, H9b), 3.09 (ddd, $J = 14.0, 7.5, 6.6$ Hz, 1H, H10a), 2.62 (ddd, $J = 13.9, 7.4, 6.2$ Hz, 1H, H10b), 1.37 (d, $J = 6.7$ Hz, 3H, H13), 1.36 (d, $J = 6.8$ Hz, 3H, H17), 1.31 (d, $J = 6.8$ Hz, 3H, H16), 1.20 (d, $J = 6.5$ Hz, 3H, H14).

$^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ_{C} : 206.9 (C8), 166.0 (C11), 134.8 (C5), 132.8 (C2), 131.8 (C3), 129.9 (C4), 129.1 (C21), 128.1 (C1), 127.0 (C6), 126.5 (C19), 125.4 (C20), 122.1 (C18), 57.4 (C7), 50.0 (C12), 47.0 (C15), 37.7 (C9), 30.4 (C10), 20.8 (C^iPr), 20.6 (C^iPr), 20.5 (C^iPr), 20.4 (C^iPr).

FTIR (neat) $\nu/\text{cm}^{-1} = 2970, 1714, 1637, 1437, 1371, 1317, 1240, 1135, 1039, 814, 735$.

HRMS (m/z , ESI⁺): calculated for C₂₁H₂₅NNaO₂ ([M+Na]⁺) = 346.1778, found = 346.1780.

***N,N*-Dicyclohexyl-3-oxo-1,2,3,4-tetrahydrophenanthrene-4-carboxamide (121)**



Prepared according to **General Procedure E** with amide **131** (1.13 g, 2.51 mmol) and KHMDS (10 mL, 0.5 M, 5.00 mmol) in anhydrous THF (25 mL). Purification by column chromatography, eluting with 20% ethyl acetate in petrol, yielded title compound **121** as a white solid (656 mg, 65%).

m.p. 91–92 °C

¹H NMR (500 MHz, CDCl₃) δ_H : 7.83 (d, J = 7.9 Hz, 1H, H14), 7.81 (d, J = 7.7 Hz, 1H, H17), 7.74 (d, J = 8.3 Hz, 1H, H1), 7.48 (dd, J = 8.4, 6.8 Hz, 1H, H16), 7.44 (dd, J = 8.0, 6.8 Hz, 1H, H15), 7.32 (d, J = 8.4 Hz, 1H, H6), 5.38 (s, 1H, H7), 4.16–4.05 (m, 1H, H13), 3.50 (ddd, J = 16.4, 8.2, 6.6 Hz, 1H, H10a), 3.22 (dt, J = 16.4, 6.5 Hz, 1H, H10b), 3.06 (dt, J = 14.3, 6.6 Hz, 1H, H9a), 2.90 (tt, J = 11.9, 3.7 Hz, 1H, H12), 2.68–2.56 (m, 1H, H9b), 2.45 (qd, J = 12.5, 3.7 Hz, 1H, H Cy), 2.34 (qd, J = 12.6, 3.8 Hz, 1H, H Cy), 1.88–1.58 (m, 6H, H Cy), 1.56–1.42 (m, 4H, H Cy), 1.42–1.33 (m, 2H, H Cy), 1.30–0.99 (m, 6H, H Cy).

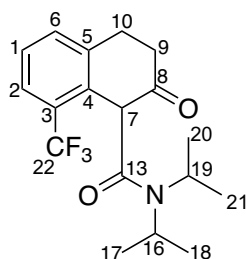
¹³C{¹H} NMR (126 MHz, CDCl₃) δ_C : 206.6 (C8), 166.6 (C11), 134.8 (C5), 132.8 (C2), 131.8 (C3), 130.0 (C4), 129.1 (C14), 128.1 (C1), 126.9 (C6), 126.6 (C16), 125.5 (C15),

122.4 (C17), 58.5 (C13), 58.4 (C7), 57.3 (C12), 37.7 (C9), 31.0 (CCy), 31.0 (CCy), 30.6 (C10), 29.7 (CCy), 29.5 (CCy), 26.7 (CCy), 26.7 (CCy), 26.0 (CCy), 25.8 (CCy), 25.4 (CCy), 25.3 (CCy).

FTIR (neat) ν/cm^{-1} = 2998, 2930, 1715, 1646, 1641, 1394, 1394, 1257, 1143, 954, 913, 745, 729.

HRMS (m/z , ESI⁺): calculated for C₂₇H₃₄NO₂ ([M+H]⁺) = 404.2584, found = 404.2585.

***N,N*-Diisopropyl-2-oxo-8-(trifluoromethyl)-1,2,3,4-tetrahydronaphthalene-1-carboxamide (122)**



Prepared according to **General Procedure E** with amide **132** (300 mg, 0.774 mmol) and KHMDS (2.3 mL, 0.5 M, 1.15 mmol) in anhydrous THF (7.0 mL). Purification by column chromatography, eluting with 10% ethyl acetate in petrol, yielded title compound **122** as a white solid (207 mg, 76%).

m.p. 110–113 °C

¹H NMR (500 MHz, CDCl₃) δ_H : 7.56 (d, J = 7.8 Hz, 1H, H2), 7.44 (d, J = 7.6 Hz, 1H, H6), 7.35 (t, J = 7.8 Hz, 1H, H1), 5.28 (s, 1H, H7), 4.76 (hept, J = 6.6 Hz, 1H, H16), 3.62 (ddd, J = 15.6, 11.1, 6.3 Hz, 1H, H10a), 3.40 (hept, J = 6.8 Hz, 1H, H19), 2.96 (ddd, J =

15.5, 6.7, 3.8 Hz, 1H, H10b), 2.88 (ddd, J = 17.3, 6.4, 3.8 Hz, 1H, H9a), 2.48 (ddd, J = 17.5, 11.1, 6.7 Hz, 1H, H9b), 1.33 (d, J = 6.7 Hz, 3H, H21), 1.28 (d, J = 6.8 Hz, 3H, H20), 1.26 (d, J = 6.6 Hz, 6H, H17 and H18).

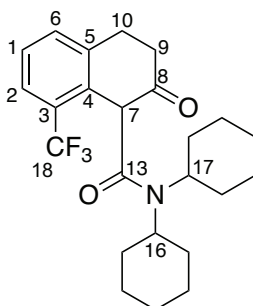
$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ_{C} : 205.6 (C8), 163.5 (C13), 140.8 (C5), 133.1 (C4), 132.2 (C6), 128.1 (q, J = 29.5 Hz, C3), 127.5 (C1), 124.5 (q, J = 274.1 Hz, C22), 124.5 (q, J = 5.8 Hz, C2), 57.0 (C7), 50.1 (C16), 46.9 (C19), 36.9 (C9), 28.4 (C10), 20.6 (C21), 20.3 (C20), 20.0 (C17 and C18).

^{19}F NMR (377 MHz, CDCl_3) δ_{F} : -59.4 (s, CF_3).

FTIR (neat) ν/cm^{-1} = 2980, 1716, 1643, 1381, 1315, 1251, 1158, 951.

HRMS (m/z , ESI^+): calculated for $\text{C}_{18}\text{H}_{22}\text{F}_3\text{NNaO}_2$ ($[\text{M}+\text{Na}]^+$) = 364.1495, found = 364.1493.

***N,N*-Dicyclohexyl-2-oxo-8-(trifluoromethyl)-1,2,3,4-tetrahydronaphthalene-1-carboxamide (123)**



Prepared according to **General Procedure E** with amide **133** (939 mg, 2.01 mmol) and KHMDS (6.0 mL, 0.5 M, 3.00 mmol) in anhydrous THF (20 mL). Purification by column chromatography, eluting with 10% ethyl acetate in petrol, yielded title compound **123** as a white solid (600 mg, 71%).

m.p. 161–163 °C

^1H NMR (500 MHz, CDCl_3) δ_H : 7.55 (d, J = 7.8 Hz, 1H, H2), 7.43 (d, J = 7.5 Hz, 1H, H6), 7.34 (t, J = 7.7 Hz, 1H, H1), 5.31 (s, 1H, H7), 4.36–4.23 (m, 1H, H16), 3.67–3.54 (m, 1H, H10a), 3.00–2.94 (m, 1H, H10b), 2.94–2.91 (m, 1H, H17), 2.91–2.83 (m, 1H, H9a), 2.47 (ddd, J = 17.5, 11.0, 6.7 Hz, 1H, H9b), 2.38 (qd, J = 12.5, 3.8 Hz, 1H, H*Cy*), 2.28 (qd, J = 12.7, 3.8 Hz, 1H, H*Cy*), 1.96–1.83 (m, 3H, H*Cy*), 1.83–1.78 (m, 1H, H*Cy*), 1.77–1.65 (m, 3H, H*Cy*), 1.57–1.31 (m, 7H, H*Cy*), 1.22–1.03 (m, 4H, H*Cy*).

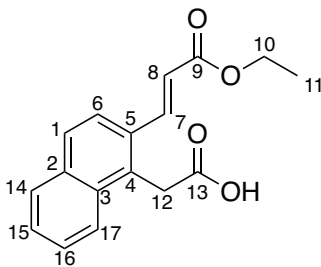
$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ_C : 205.5 (C8), 163.8 (C13), 140.9 (C5), 133.3 (C4), 132.2 (C6), 128.1 (q, J = 29.5 Hz, C3), 127.5 (C1), 124.5 (q, J = 274.2 Hz, C18), 124.5 (q, J = 5.9 Hz, C2), 58.8 (C16), 57.2 (C7), 57.2 (C17), 36.9 (C9), 31.1 (C*Cy*), 30.5 (C*Cy*), 29.6 (C*Cy*), 29.1 (C*Cy*), 28.4 (C10), 26.7 (C*Cy*), 26.6 (C*Cy*), 26.1 (C*Cy*), 25.8 (C*Cy*), 25.6 (C*Cy*), 25.4 (C*Cy*).

^{19}F NMR (377 MHz, CDCl_3) δ_F : –59.3 (s, CF_3).

FTIR (neat) ν/cm^{-1} = 2980, 1715, 1642, 1383, 1316, 1251, 1116, 954, 732.

HRMS (m/z , ESI⁺): calculated for $\text{C}_{24}\text{H}_{31}\text{F}_3\text{O}_2\text{N}$ ($[\text{M}+\text{H}]^+$) = 422.2301, found = 422.2295.

(*E*)-2-(2-(3-Ethoxy-3-oxoprop-1-en-1-yl)naphthalen-1-yl)acetic acid (124**)**



Prepared according to **General Procedure A** with 1-naphthylacetic acid (5.00 g, 26.9 mmol), potassium bicarbonate (5.40 g, 53.8 mmol), (*S*)-*N*-acetylalanine (705 mg, 5.38 mmol), palladium acetate (604 mg, 2.69 mmol) and ethyl acrylate (5.8 mL, 53.8 mmol) in *tert*-amyl alcohol (20 mL). Purification by column chromatography, eluting with 30% ethyl acetate, 1% acetic acid in petrol, yielded title compound **124** as a beige solid (7.05 g, 92%).

m.p. 161 °C

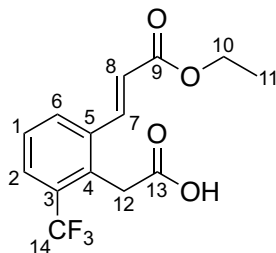
^1H NMR (500 MHz, CDCl_3) δ_{H} : 8.21 (d, J = 15.7 Hz, 1H, H7), 8.05 (d, J = 8.5 Hz, 1H, H17), 7.83 (d, J = 8.1 Hz, 1H, H14), 7.78 (d, J = 8.6 Hz, 1H, H1), 7.66 (d, J = 8.7 Hz, 1H, H6), 7.55 (dd, J = 8.4, 6.8 Hz, 1H, H16), 7.51 (dd, J = 8.0, 6.8 Hz, 1H, H15), 6.48 (d, J = 15.7 Hz, 1H, H8), 4.28 (q, J = 7.1 Hz, 2H, H10), 4.28 (s, 2H, H12), 1.34 (t, J = 7.1 Hz, 3H, H11).

$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ_{C} : 176.3 (C13), 167.0 (C9), 142.2 (C7), 134.3 (C2), 132.6 (C3), 131.9 (C5), 129.9 (C4), 128.8 (C14), 128.7 (C1), 127.4 (C16), 127.0 (C15), 124.6 (C17), 123.9 (C6), 121.7 (C8), 60.9 (C10), 34.0 (C12), 14.4 (C11).

FTIR (neat) ν/cm^{-1} = 3060, 1708, 1628, 1368, 1303. 1157, 1038, 979, 816.

HRMS (m/z , ESI⁺): calculated for C₁₇H₁₆O₄Na ([M+Na]⁺) = 307.0941, found = 307.0944.

(*E*)-2-(2-(3-Ethoxy-3-oxoprop-1-en-1-yl)-6-(trifluoromethyl)phenyl)acetic acid
(125)



Prepared according to **General Procedure A** with 2-(trifluoromethyl)phenylacetic acid (1.00 g, 4.90 mmol), potassium bicarbonate (981 mg, 9.80 mmol), (*S*)-*N*-acetylalanine (64 mg, 0.490 mmol), palladium acetate (55 mg, 0.245 mmol) and ethyl acrylate (1.1 mL, 9.80 mmol) in *tert*-amyl alcohol (20 mL). Purification by column chromatography, eluting with 30% ethyl acetate, 1% acetic acid in petrol, yielded title compound **125** as a beige solid (1.34 g, 92%).

m.p. 122–125 °C

¹H NMR (500 MHz, CDCl₃) δ_H : 7.90 (d, J = 15.7 Hz, 1H, H7), 7.74 (d, J = 7.9 Hz, 1H, H6), 7.71 (d, J = 7.8 Hz, 1H, H2), 7.44 (t, J = 7.9 Hz, 1H, H1), 6.37 (d, J = 15.7 Hz, 1H, H8), 4.27 (q, J = 7.1 Hz, 2H, H10), 4.01 (s, 2H, H12), 1.33 (t, J = 7.1 Hz, 3H, H11).

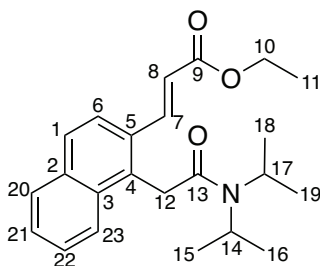
¹³C{¹H} NMR (126 MHz, CDCl₃) δ_C : 174.2 (C13), 166.4 (C9), 140.7 (C7), 137.4 (C5), 131.1 (C4), 130.8 (C6), 130.4 (q, J = 29.7 Hz, C3), 128.2 (C1), 127.4 (q, J = 5.8 Hz, C2), 124.2 (q, J = 274.2 Hz, C14), 123.4 (C8), 61.1 (C10), 34.2 (C12), 14.4 (C11).

^{19}F NMR (377 MHz, CDCl_3) δ_F : -59.7 (s, CF_3).

FTIR (neat) ν/cm^{-1} = 2987, 1715, 1455, 1396, 1325, 1161, 1121, 806.

HRMS (m/z , ESI^+): calculated for $\text{C}_{14}\text{H}_{13}\text{FO}_4$ ($[\text{M}+\text{H}]^+$) = 325.0658, found = 325.0660.

Ethyl (*E*)-3-(1-(2-(diisopropylamino)-2-oxoethyl)naphthalen-2-yl)acrylate
(126)



Prepared according to **General Procedure B** with acid **124** (7.85 g, 27.6 mmol), oxalyl chloride (11.3 mL, 55.2 mmol) and DMF (500 μL) in anhydrous dichloromethane (30 mL) followed by diisopropylamine (7.3 mL, 55.2 mmol) in anhydrous dichloromethane (30 mL). Purification by recrystallisation in hot ethyl acetate. The solid was filtered off to give a white solid (5.76 g) and the filtrate was purified by column chromatography, eluting with 10–20% ethyl acetate in petrol, to yield title compound **126** as a white solid (1.15 g, combined yield = 6.91 g, 68%).

m.p. 147–149 $^{\circ}\text{C}$

^1H NMR (500 MHz, CDCl_3) δ_H : 8.09 (d, J = 15.7 Hz, 1H, H7), 7.96 (d, J = 8.52 Hz, 1H, H23), 7.81 (d, J = 7.9, 1.7 Hz, 1H, H20), 7.75 (d, J = 8.6 Hz, 1H, H1), 7.65 (d, J = 8.7 Hz, 1H, H6), 7.55–7.45 (m, 2H, H21 and H22), 6.45 (d, J = 15.7 Hz, 1H, H8), 4.27 (q, J =

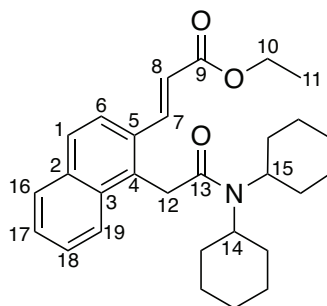
7.1 Hz, 3H, H10 and H17), 4.23 (s, 2H, H12), 3.56–3.42 (m, 1H, H14), 1.38 (d, J = 6.8 Hz, 6H, H15 and H16), 1.34 (t, J = 6.6 Hz, 3H, H11), 1.32 (d, J = 6.1 Hz, 6H, H19 and H19).

$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ_{C} : 168.5 (C13), 166.9 (C9), 142.5 (C7), 134.3 (C2), 133.1 (C3), 133.1 (C4), 131.4 (C5), 128.6 (C20), 127.8 (C1), 126.8 (C22), 126.5 (C21), 124.6 (C23), 123.8 (C6), 120.8 (C8), 60.5 (C11), 49.0 (C17), 46.2 (C14), 35.1 (C12), 21.1 (C18 and C19), 20.7 (C15 and C16), 14.4 (C10).

FTIR (neat) ν/cm^{-1} = 2963, 2933, 1713, 1626, 1438, 1341, 1299, 1278, 1175, 1154, 977, 817.

HRMS (m/z , ESI^+): calculated for $\text{C}_{23}\text{H}_{29}\text{O}_3\text{NNa}$ ($[\text{M}+\text{Na}]^+$) = 390.2040, found = 390.2028.

Ethyl (*E*)-3-(1-(2-(dicyclohexylamino)-2-oxoethyl)naphthalen-2-yl)acrylate
(127)



Prepared according to **General Procedure B** with acid **124** (4.60 g, 16.2 mmol), oxalyl chloride (6.60 mL, 32.4 mmol) and DMF (500 μL) in anhydrous dichloromethane (50 mL) followed by dicyclohexylamine (3.53 mL, 19.4 mmol) in anhydrous dichloromethane (50 mL). Purification by column chromatography, eluting with 10% ethyl acetate in petrol, yielded title compound **127** as a white solid (1.90 g, 26%).

m.p. 79–81 °C

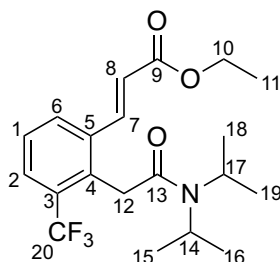
^1H NMR (500 MHz, CDCl_3) δ_{H} : 8.13 (d, J = 15.7 Hz, 1H, H7), 8.00 (d, J = 8.2 Hz, 1H, H19), 7.81 (dd, J = 7.8, 1.6 Hz, 1H, H16), 7.74 (d, J = 8.7 Hz, 1H, H1), 7.65 (d, J = 8.7 Hz, 1H, H6), 7.55–7.42 (m, 2H, H17 and H18), 6.46 (d, J = 15.7 Hz, 1H, H8), 4.28 (q, J = 7.1 Hz, 2H, H10), 4.25 (s, 2H, H12), 3.74–3.65 (m, 1H, H14), 2.96–2.92 (m, 1H, H15), 2.44–2.40 (m, 2H, H Cy), 1.86–1.78 (m, 2H, H Cy), 1.77–1.69 (m, 4H, H Cy), 1.73–1.57 (m, 3H, H Cy), 1.56–1.45 (m, 4H, H Cy), 1.34 (t, J = 7.1 Hz, 3H, H11), 1.31–1.03 (m, 5H, H Cy).

$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ_{C} : 169.1 (C13), 167.0 (C9), 142.6 (C7), 134.4 (C2), 133.4 (C4), 133.1 (C3), 131.4 (C5), 128.7 (C16), 127.9 (C1), 126.9 (C18), 126.7 (C17), 124.8 (C19), 123.8 (C6), 121.0 (C8), 60.6 (C10), 58.2 (C14), 56.6 (C15), 36.0 (C12), 31.5 ($2 \times \text{CCy}$), 30.0 ($2 \times \text{CCy}$), 26.8 ($2 \times \text{CCy}$), 26.1 ($2 \times \text{CCy}$), 25.5 (CCy), 25.4 (CCy), 14.5 (C11).

FTIR (neat) ν/cm^{-1} = 2928, 2852, 1708, 1630, 1432, 1364, 1261, 1261, 1175, 1038, 976, 894, 813, 747.

HRMS (m/z , ESI^+): calculated for $\text{C}_{29}\text{H}_{38}\text{NO}_3$ ($[\text{M}+\text{H}]^+$) = 448.2846, found = 448.2835.

Ethyl (*E*)-3-(2-(2-(diisopropylamino)-2-oxoethyl)-3-(trifluoromethyl)phenyl)acrylate (128**)**



Prepared according to **General Procedure B** with acid **125** (3.50 g, 11.6 mmol), oxalyl chloride (4.7 mL, 23.2 mmol) and DMF (500 μ L) in anhydrous dichloromethane (20 mL) followed by diisopropylamine (3.00 mL, 23.2 mmol) in anhydrous dichloromethane (20 mL). Purification by column chromatography, eluting with 10% ethyl acetate in petrol, yielded title compound **128** as a white solid (2.87 g, 64%).

m.p. 147–149 °C

^1H NMR (400 MHz, CDCl_3) δ_{H} : 7.80 (d, J = 15.7 Hz, 1H, H7), 7.71 (d, J = 7.8 Hz, 1H, H6), 7.67 (d, J = 7.9 Hz, 1H, H2), 7.37 (t, J = 7.9 Hz, 1H, H1), 6.34 (d, J = 15.8 Hz, 1H, H8), 4.24 (q, J = 7.2 Hz, 2H, H10), 4.12 (hept, J = 7.0 Hz, 1H, H17), 3.89 (s, 2H, H12), 3.46 (hept, J = 6.6 Hz, 1H, H14), 1.36 (d, J = 6.7 Hz, 6H, H15 and H16), 1.34–1.27 (m, 9H, H11, H18 and H19).

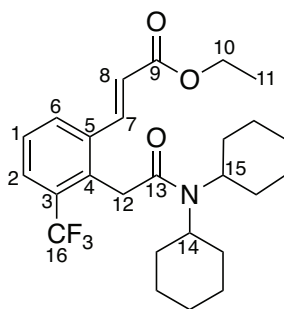
$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ_{C} : 167.1 (C13), 166.5 (C9), 141.7 (C7), 137.4 (C5), 134.4 (C4), 130.4 (C6), 130.1 (q, J = 29.7 Hz, C3), 127.2 (C1), 127.2 (q, J = 5.8 Hz, C2), 124.7 (q, J = 274.2 Hz, C20), 122.3 (C8), 60.7 (C10), 49.0 (C17), 46.2 (C14), 35.4 (C12), 21.0 (C18 and C19), 20.6 (C15 and C16), 14.4 (C11).

^{19}F NMR (377 MHz, CDCl_3) δ_{F} : –59.4 (s, CF_3).

FTIR (neat) ν/cm^{-1} = 2980, 1717, 1647, 1454, 1371, 1320, 1276, 1155, 1114, 1042, 956, 807.

HRMS (m/z , ESI⁺): calculated for C₂₀H₂₆F₃NNaO₃ ([M+Na]⁺) = 408.1757, found = 408.1751.

Ethyl (*E*)-3-(2-(2-(dicyclohexylamino)-2-oxoethyl)-3-(trifluoromethyl)phenyl)acrylate (129**)**



Prepared according to **General Procedure B** with acid **125** (887 mg, 2.94 mmol), oxalyl chloride (480 μL , 32.4 mmol) and DMF (50 μL) in anhydrous dichloromethane (10 mL) followed by dicyclohexylamine (1.20 mL, 5.87 mmol) in anhydrous dichloromethane (50 mL). Purification by column chromatography, eluting with 10% ethyl acetate in petrol, yielded title compound **129** as a white solid (1.05 g, 77%).

m.p. 129 °C

¹H NMR (500 MHz, CDCl₃) δ_H : 7.80 (d, J = 15.8 Hz, 1H, H7), 7.70 (d, J = 7.9 Hz, 1H, H6), 7.67 (d, J = 7.9 Hz, 1H, H2), 7.37 (t, J = 7.8 Hz, 1H, H1), 6.34 (d, J = 15.8 Hz, 1H, H8), 4.24 (q, J = 7.1 Hz, 2H, H10), 3.89 (s, 2H, H12), 3.63–3.54 (m, 1H, H14), 2.97–2.91 (m, 1H, H15), 2.43–2.38 (m, 2H, H_{Cy}), 1.94–1.84 (m, 4H, H_{Cy}), 1.76–1.67 (m, 3H, H_{Cy}), 1.63–1.59 (m, 2H, H_{Cy}), 1.56–1.44 (m, 3H, H_{Cy}), 1.43–1.33 (m, 2H, H_{Cy}), 1.31 (t, J = 7.2 Hz, 3H, H11), 1.27–1.02 (m, 4H, H_{Cy}).

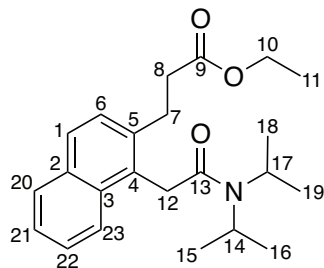
$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ_{C} : 167.5 (C13), 166.5 (C9), 141.7 (C7), 137.4 (C5), 134.6 (C4), 130.4 (C6), 130.0 (q, $J = 28.3$ Hz, C3), 127.2 (q, $J = 5.6$ Hz, C2), 127.1 (C1), 124.6 (q, $J = 274.3$ Hz, C16), 122.3 (C8), 60.7 (C10), 58.3 (C14), 56.5 (C15), 35.6 (C12), 31.3 ($2 \times \text{CCy}$), 29.8 ($2 \times \text{CCy}$), 26.8 ($2 \times \text{CCy}$), 26.2 ($2 \times \text{CCy}$), 25.5 (CCy), 25.4 (CCy), 14.4 (C11).

^{19}F NMR (377 MHz, CDCl_3) δ_{F} : -59.3 (CF_3).

FTIR (neat) $\nu/\text{cm}^{-1} = 2931, 2853, 1712, 1644, 1454, 1432, 1367, 1316, 1155, 1128, 1092, 808$.

HRMS (m/z , ESI^+): calculated for $\text{C}_{26}\text{H}_{35}\text{FNO}_3$ ($[\text{M}+\text{H}]^+$) = 466.2564, found = 466.2554.

Ethyl 3-(1-(2-(diisopropylamino)-2-oxoethyl)naphthalen-2-yl)propanoate (**130**)



Prepared according to **General Procedure D** with acrylate **126** (4.85 g, 13.2 mmol) and Pd/C (485 mg, 10% w/w) in methanol (30 mL), to yield title compound **130** as a white solid without need for further purification (4.50 g, 98%).

m.p. 74–78 °C

^1H NMR (500 MHz, CDCl_3) δ_{H} : 7.83 (d, $J = 8.4$ Hz, 1H, H23), 7.79 (d, $J = 8.1$ Hz, 1H, H11), 7.71 (d, $J = 8.4$ Hz, 1H, H1), 7.46 (dd, $J = 8.4, 6.7$ Hz, 1H, H22), 7.40 (dd, $J = 7.9,$

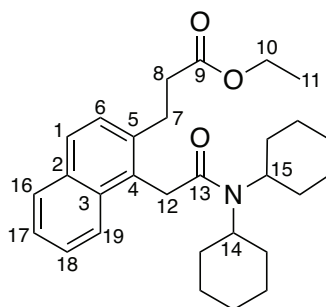
6.7 Hz, 1H, H21), 7.33 (d, J = 8.5 Hz, 1H, H6), 4.31 (hept, J = 6.8 Hz, 1H, H14), 4.17–4.10 (m, 4H, H10 and H12), 3.48 (hept, J = 7.1 Hz, 1H, H17), 3.13–3.05 (m, 2H, H7), 2.68–2.60 (m, 2H, H8), 1.38 (d, J = 6.8 Hz, 6H, H18 and H19), 1.31 (d, J = 6.7 Hz, 6H, H15 and H16), 1.24 (t, J = 7.2 Hz, 3H, H11).

$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ_{C} : 173.2 (C9), 169.1 (C13), 136.7 (C5), 133.4 (C3), 132.8 (C2), 130.0 (C4), 128.6 (C20), 127.6 (C6), 127.6 (C1), 126.3 (C22), 125.0 (C21), 123.9 (C23), 60.6 (C10), 48.9 (C14), 46.2 (C17), 35.6 (C8), 34.9 (C12), 29.4 (C7), 21.2 (C15 and C16), 20.8 (C18 and C19), 14.3 (C11).

FTIR (neat) ν/cm^{-1} = 2966, 2930, 1735, 1627, 1438, 1371, 1340, 1276, 1151, 1042, 819, 735.

HRMS (m/z , ESI^+): calculated for $\text{C}_{23}\text{H}_{32}\text{O}_3\text{N}$ ($[\text{M}+\text{H}]^+$) = 370.2377, found 370.2373.

Ethyl 3-(1-(2-(dicyclohexylamino)-2-oxoethyl)naphthalen-2-yl)propanoate
(**131**)



Prepared according to **General Procedure D** with acrylate **127** (1.85 g, 4.14 mmol) in methanol (10 mL) to yield title compound **131** as a white solid without need for further purification (1.80 g, 97%).

m.p. 75 °C

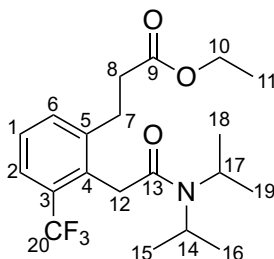
^1H NMR (600 MHz, CDCl_3) δ_{H} : 7.88 (dd, $J = 8.5$ Hz, 1.1, 1H, H19), 7.78 (dd, $J = 8.1$, 1.3 Hz, 1H, H16), 7.70 (d, $J = 8.4$ Hz, 1H, H1), 7.46 (ddd, $J = 8.4$, 6.7, 1.4 Hz, 1H, H18), 7.40 (ddd, $J = 8.0$, 6.7, 1.1 Hz, 1H, H17), 7.32 (d, $J = 8.4$ Hz, 1H, H6), 4.14 (s, 2H, H12), 4.14 (q, $J = 7.1$ Hz, 2H, H10), 3.76–3.72 (m, 1H, H14), 3.14–3.08 (m, 2H, H7), 3.00–2.86 (m, 1H, H15), 2.68–2.61 (m, 2H, H8), 2.51–2.33 (m, 2H, H Cy), 1.89–1.76 (m, 2H, H Cy), 1.76–1.69 (m, 4H, H Cy), 1.69–1.63 (m, 1H, H Cy), 1.62–1.50 (m, 3H, H Cy), 1.50–1.44 (m, 2H, H Cy), 1.24 (t, $J = 7.2$ Hz, 5H, H11 and H Cy), 1.21–1.17 (m, 2H, H Cy), 1.14–1.05 (m, 2H, H Cy).

$^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, CDCl_3) δ_{C} : 173.2 (C9), 169.6 (C13), 136.7 (C5), 133.3 (C3), 132.8 (C2), 130.2 (C4), 128.7 (C16), 127.7 (C6), 127.6 (C1), 126.3 (C18), 125.0 (C17), 124.0 (C19), 60.6 (C10), 58.1 (C14), 56.5 (C15), 35.6 (C12), 31.6 ($2 \times \text{CCy}$), 30.1 ($2 \times \text{CCy}$), 29.5 (C7), 26.8 ($2 \times \text{CCy}$), 26.2 ($2 \times \text{CCy}$), 25.5 (C Cy), 25.4 (C Cy), 14.4 (C11).

FTIR (neat) $\nu/\text{cm}^{-1} = 2972, 2931, 1732, 1503, 1453, 1369, 1367, 1268, 794, 738$.

HRMS (m/z , ESI^+): calculated for $\text{C}_{29}\text{H}_{40}\text{NO}_3$ ($[\text{M}+\text{H}]^+$) = 450.3003, found = 450.3008.

Ethyl 3-(2-(2-(diisopropylamino)-2-oxoethyl)-3-(trifluoromethyl)phenyl)propanoate (132)



Prepared according to **General Procedure D** with acrylate **128** (2.84 g, 7.37 mmol) and

Pd/C (284 mg, 10% w/w) in methanol (20 mL), to yield title compound **132** as a white solid without need for further purification (2.83 g, 99%).

m.p. 60–62 °C

^1H NMR (500 MHz, CDCl_3) δ_{H} : 7.52 (d, $J = 7.7$ Hz, 1H, H2), 7.39 (d, $J = 7.6$ Hz, 1H, H6), 7.29 (t, $J = 7.8$ Hz, 1H, H1), 4.20–4.12 (m, 1H, H14), 4.12 (q, $J = 7.1$ Hz, 2H, H10), 3.86 (s, 2H, H12), 3.44 (hept, $J = 6.3$ Hz, 1H, H17), 2.96–2.89 (m, 2H, H7), 2.68–2.60 (m, 2H, H8), 1.35 (d, $J = 6.8$ Hz, 6H, H18 and H19), 1.30 (d, $J = 6.7$ Hz, 6H, H15 and H16), 1.23 (t, $J = 7.1$ Hz, 3H, H11).

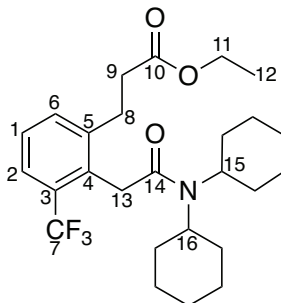
$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ_{C} : 173.1 (C9), 167.8 (C13), 142.2 (C5), 133.4 (C4), 132.5 (C6), 129.6 (q, $J = 28.8$ Hz, C3), 127.0 (C1), 124.8 (q, $J = 274.2$ Hz, C20), 124.3 (q, $J = 5.9$ Hz, C2), 60.6 (C10), 48.9 (C14), 46.1 (C17), 35.1 (C8), 34.9 (C12), 27.9 (C7), 20.9 (C15 and C16), 20.6 (C18 and C19), 14.3 (C11).

^{19}F NMR (377 MHz, CDCl_3) δ_{F} : -59.4 (s, CF_3).

FTIR (neat) $\nu/\text{cm}^{-1} = 2978, 1728, 1644, 1317, 1158, 1117, 907, 727$.

HRMS (m/z , ESI^+): calculated for $\text{C}_{20}\text{H}_{29}\text{F}_3\text{NO}_3$ ($[\text{M}+\text{H}]^+$) = 388.2094, found = 388.2089.

Ethyl 3-(2-(2-(dicyclohexylamino)-2-oxoethyl)-3-(trifluoromethyl)phenyl) propanoate (133**)**



Prepared according to **General Procedure D** with acrylate **129** (2.30 g, 4.94 mmol) and Pd/C (230 mg, 10% w/w) in methanol (30 mL), to yield title compound **133** as a white solid (2.31 g, quant.) without need for further purification.

m.p. 129 °C

^1H NMR (500 MHz, CDCl_3) δ_{H} : 7.52 (d, J = 8.0 Hz, 1H, H2), 7.38 (d, J = 7.7 Hz, 1H, H6), 7.28 (t, J = 7.7 Hz, 1H, H1), 4.12 (q, J = 7.1 Hz, 2H, H11), 3.85 (s, 2H, H13), 3.67–3.58 (m, 1H, H15), 3.13–2.82 (m, 3H, H8 and H16), 2.66–2.59 (m, 2H, H9), 2.41–2.39 (m, 2H, HCy), 1.93–1.82 (m, 4H, HCy), 1.77–1.68 (m, 3H, HCy), 1.63–1.49 (m, 3H, HCy), 1.48–1.41 (m, 2H, HCy), 1.41–1.31 (m, 2H, HCy), 1.23 (t, J = 7.1 Hz, 3H, H12), 1.21–1.03 (m, 4H, HCy).

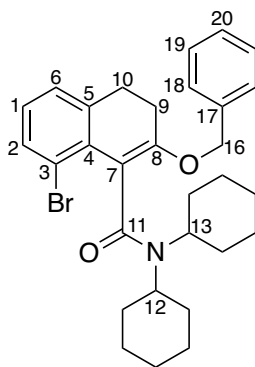
$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ_{C} : 172.9 (C10), 167.9 (C14), 142.0 (C5), 133.4 (C4), 132.3 (C6), 129.4 (q, J = 28.8 Hz, C3), 126.8 (C1), 124.9 (q, J = 274.2 Hz, C7), 124.2 (q, J = 5.9 Hz, C2), 60.5 (C11), 58.0 (C15), 56.2 (C16), 34.9 (C9), 34.9 (C13), 31.2 (2 $\times$ C Cy), 29.8 (2 $\times$ C Cy), 27.8, (C8) 26.7 (2 $\times$ C Cy), 26.1 (2 $\times$ C Cy), 25.3 (C Cy), 25.3 (C Cy), 14.2 (C12).

^{19}F NMR (377 MHz, CDCl_3) δ_F : -59.3 (s, CF_3).

FTIR (neat) ν/cm^{-1} = 2931, 2855, 1732, 1649, 1431, 1367, 1315, 1235, 1155, 1088.

HRMS (m/z , ESI^+): calculated for $\text{C}_{26}\text{H}_{37}\text{F}_3\text{NO}_3$ ($[\text{M}+\text{H}]^+$) = 468.2720, = found 468.2713.

2-(Benzyloxy)-8-bromo-*N,N*-dicyclohexyl-3,4-dihydronaphthalene-1-carboxamide (135)



Prepared according to **General Procedure F** with **87** (33 mg, 0.0764 mmol), TBAB (3 mg, 0.00764 mmol), 50% w/w aqueous potassium hydroxide (14 μL , 0.382 mmol) and benzyl bromide (36 μL , 0.306 mmol) in degassed dichloromethane (764 μL). Purification by column chromatography, eluting with 5–20% ethyl acetate in petrol, yielded title compound **135** as a white solid (7 mg, 20%).

m.p. > 215 $^{\circ}\text{C}$

^1H NMR (500 MHz, CDCl_3) δ_H : 7.43 (d, $J = 7.1$ Hz, 2H, H18), 7.38 (dd, $J = 8.1, 1.3$ Hz, 1H, H2), 7.34 (t, $J = 7.4$ Hz, 2H, H19), 7.31–7.28 (m, 1H, H20), 7.07 (dd, $J = 7.4, 1.3$ Hz, 1H, H6), 6.87 (t, $J = 7.7$ Hz, 1H, H1), 4.95 (s, 2H, H16), 3.37 (tt, $J = 11.9, 3.3$ Hz, 1H, H12), 3.01–2.91 (m, 1H, H13), 2.85–2.78 (m, 2H, H10), 2.75–2.61 (m, 2H, HCy), 2.47–2.40

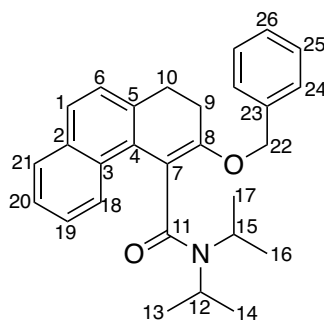
(m, 2H, H9), 1.84–1.78 (m, 1H, H*Cy*), 1.77–1.66 (m, 5H, H*Cy*), 1.64–1.50 (m, 2H, H*Cy*), 1.51–1.41 (m, 2H, H*Cy*), 1.37–1.15 (m, 5H, H*Cy*), 1.05–0.95 (m, 2H, H*Cy*), 0.77–0.65 (m, 1H, H*Cy*).

¹³C{¹H} NMR (126 MHz, CDCl₃) δ_C: 167.0 (C11), 157.7 (C8), 137.2 (C17), 136.6 (C5), 133.5 (C4), 133.2 (C2), 128.3 (C19), 127.8 (C20), 127.6 (C18), 126.6 (C1), 126.3 (C6), 120.0 (C3), 118.0 (C7), 70.6 (C16), 60.0 (C12), 56.2 (C13), 31.5 (C*Cy*), 30.5 (C10), 30.3 (C*Cy*), 30.1 (C*Cy*), 29.3 (C*Cy*), 26.8 (C*Cy*), 26.7 (C*Cy*), 26.4 (C*Cy*), 26.0 (C*Cy*), 25.5 (2 × C*Cy*), 23.7 (C9).

FTIR (neat) ν/cm⁻¹ = 2928, 2852, 1634, 1440, 1369, 1309, 1235, 1197, 1129, 1026, 732.

HRMS (*m/z*, ESI⁺): calculated for C₃₀H₃₇BrNO₂ ([M+H]⁺) = 522.2004, found = 522.2003.

3-(Benzyloxy)-*N,N*-diisopropyl-1,2-dihydrophenanthrene-4-carboxamide (**136**)



Prepared according to **General Procedure F** with **120** (238 mg, 0.736 mmol), TBAB (17 mg, 0.0736 mmol), 50% w/w aqueous potassium hydroxide (136 μL, 3.68 mmol) and benzyl bromide (350 μL, 2.94 mmol) in degassed dichloromethane (764 μL). Purification by column chromatography, eluting with 5–10% ethyl acetate in petrol, yielded title compound **136** as a white solid (90 mg, 30%).

m.p. 180–181 °C

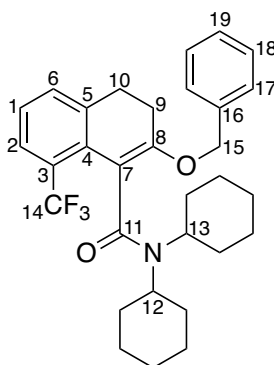
^1H NMR (500 MHz, CDCl_3) δ_{H} : 8.53–8.47 (m, 1H, H18), 7.77–7.70 (m, 1H, H21), 7.59 (d, J = 8.2 Hz, 1H, H1), 7.49 (d, J = 7.3 Hz, 2H, H24), 7.39–7.32 (m, 4H, H19, H20 and H25), 7.32–7.27 (m, 2H, H6 and H26), 5.03 (d, J = 11.7 Hz, 1H, H22a), 5.01 (d, J = 11.8 Hz, 1H, H22b), 3.81 (hept, J = 6.7 Hz, 1H, H12), 3.35 (hept, J = 6.7 Hz, 1H, H15), 3.10–2.90 (m, 2H, H10), 2.66–2.48 (m, 2H, H9), 1.59 (d, J = 6.8 Hz, 3H, H16), 1.54 (d, J = 6.8 Hz, 3H, H17), 1.02 (d, J = 6.7 Hz, 3H, H13), 0.41 (d, J = 6.6 Hz, 3H, H14).

$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ_{C} : 169.7 (C11), 156.3 (C8), 137.5 (C23), 133.5 (C4), 131.2 (C5), 130.1 (C3), 129.5 (C2), 128.5 (C25), 128.4 (C21), 127.9 (C26), 127.7 (C24), 126.6 (C1), 126.2 (C6), 125.9 (C18), 125.6 (C19), 125.0 (C20), 118.0 (C7), 70.9 (C22), 50.6 (C12), 46.0 (C15), 30.5 (C10), 23.9 (C9), 21.1 (C13), 21.1 (C17), 19.7 (C16), 19.6 (C14).

FTIR (neat) ν/cm^{-1} = 2974, 1628, 1596, 1453, 1370, 1336, 1267, 1154, 738.

HRMS (m/z , ESI^+): calculated for $\text{C}_{28}\text{H}_{32}\text{NO}_2$ ($[\text{M}+\text{H}]^+$) = 414.2432, found = 414.2428.

2-(Benzyloxy)-*N,N*-dicyclohexyl-8-(trifluoromethyl)-3,4-dihydronaphthalene-1-carboxamide (137)



Prepared according to **General Procedure F** with **123** (50 mg, 0.119 mmol), TBAB (4 mg, 0.0119 mmol), 50% w/w aqueous potassium hydroxide (22 μ L, 595 mmol) and benzyl bromide (56 μ L, 0.474 mmol) in degassed dichloromethane (238 μ L). Purification by column chromatography, eluting with 10–20% ethyl acetate in petrol, yielded title compound **137** as a white solid (43 mg, 73%).

m.p. 135–137 °C

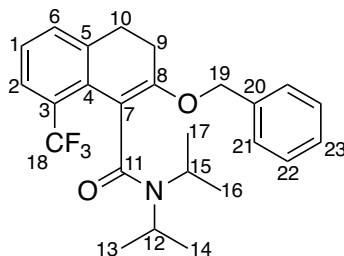
^1H NMR (500 MHz, CDCl_3) δ_{H} : 7.54 (dd, J = 8.0, 1.4 Hz, 1H, H2), 7.48–7.39 (m, 2H, H17), 7.39–7.31 (m, 3H, H6, H18), 7.31–7.27 (m, 1H, H19), 7.16 (t, J = 7.7 Hz, 1H, H1), 4.98 (d, J = 11.9 Hz, 1H, H15a), 4.97 (d, J = 11.9 Hz, 1H, H15b), 3.21–3.11 (m, 1H, H12), 2.87–2.75 (m, 3H, H10 and H13), 2.75–2.63 (m, 1H, H*Cy*), 2.62–2.50 (m, 1H, H*Cy*), 2.49–2.42 (m, 1H, H9a), 2.40–2.29 (m, 1H, H9b), 1.83–1.76 (m, 1H, H*Cy*), 1.75–1.65 (m, 3H, H*Cy*), 1.59–1.47 (m, 3H, H*Cy*), 1.47–1.36 (m, 2H, H*Cy*), 1.36–1.10 (m, 6H, H*Cy*), 1.06–0.86 (m, 2H, H*Cy*), 0.62–0.49 (m, 1H, H*Cy*).

$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ_{C} : 166.1 (C11), 158.1 (C8), 137.2 (C16), 137.0 (C5), 132.7 (C4), 130.8 (C6), 128.4 (C18), 127.9 (C19), 127.7 (C17), 125.8 (q, J = 31.6 Hz, C3), 125.8 (q, J = 6.2 Hz, C2), 125.5 (C1), 124.9 (q, J = 273.9 Hz, C14), 117.0 (C7), 70.8 (C15), 59.5 (C12), 56.2 (C13), 31.5 (C*Cy*), 30.7 (C*Cy*), 30.3 (C10), 30.0 (C*Cy*), 29.4 (C*Cy*), 27.0 (C*Cy*), 26.9 (C*Cy*), 26.6 (C*Cy*), 26.1 (C*Cy*), 25.6 (C*Cy*), 25.5 (C*Cy*), 23.6 (C9).

FTIR (neat) ν/cm^{-1} = 2980, 2929, 1635, 1446, 1367, 1309, 1234, 1158, 731.

HRMS (m/z , ESI^+): calculated for $\text{C}_{31}\text{H}_{37}\text{F}_3\text{NO}_2$ ($[\text{M}+\text{H}]^+$) = 512.2767, found 512.2771.

2-(Benzyloxy)-*N,N*-diisopropyl-8-(trifluoromethyl)-3,4-dihydronaphthalene-1-carboxamide (138)



Prepared according to **General Procedure F** with **122** (173 mg, 0.507 mmol), TBAB (16 mg, 0.0507 mmol), 50% w/w aqueous potassium hydroxide (93 μ L, 2.54 mmol) and benzyl bromide (241 μ L, 2.03 mmol) in degassed dichloromethane (764 μ L). Purification by column chromatography, eluting with 10–20% ethyl acetate in petrol, yielded title compound **138** as a white solid (162 mg, 74%).

m.p. 101–102 °C

^1H NMR (400 MHz, CDCl_3) δ_{H} : 7.54 (dd, J = 8.0, 1.4 Hz, 1H, H2), 7.45–7.41 (m, 2H, H21), 7.39–7.29 (m, 3H, H6 and H22), 7.31–7.27 (m, 1H, H23), 7.18–7.11 (m, 1H, H1), 5.04–4.92 (m, 2H, H19), 3.74 (hept, J = 6.6 Hz, 1H, H12), 3.34 (hept, J = 6.8 Hz, 1H, H15), 2.86–2.76 (m, 2H, H10), 2.48–2.35 (m, 2H, H9), 1.45 (d, J = 6.8 Hz, 3H, H14), 1.42 (d, J = 6.7 Hz, 3H, H13), 1.07 (d, J = 6.6 Hz, 3H, H16), 0.92 (d, J = 6.6 Hz, 3H, H17).

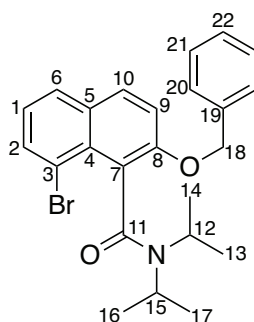
$^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ_{C} : 166.1 (C11), 158.2 (C8), 137.1 (C5 and C20), 132.7 (C4), 130.8 (C6), 128.5 (C22), 128.0 (C23), 127.7 (C21), 125.8 (q, J = 6.7 Hz, C2), 125.7 (q, J = 31.0 Hz, C3), 125.4 (C1), 124.5 (q, J = 273.7 Hz, C18), 116.6 (C7), 70.6 (C19), 50.3 (C12), 45.9 (C15), 30.3 (C10), 23.4 (C9), 21.2 (C16), 20.7 (C13), 20.3 (C17), 19.9 (C14).

^{19}F NMR (377 MHz, CDCl_3) δ_F : -59.4 (s, CF_3).

FTIR (neat) ν/cm^{-1} = 2980, 1639, 1613, 1368, 1339, 1311, 1133, 1039, 804, 737, 697.

HRMS (m/z , ESI^+): calculated for $\text{C}_{25}\text{H}_{29}\text{F}_3\text{NO}_2$ ($[\text{M}+\text{H}]^+$) = 432.2139, found = 432.2145.

2-(Benzyloxy)-8-bromo-*N,N*-diisopropyl-1-naphthamide (144)



Asymmetric: Prepared according to **General Procedure N** with naphthol **147** (70 mg, 0.200 mmol), benzyl iodide (130 mg, 0.600 mmol), **186** (8.4 mg, 0.0100 mmol), and 50% w/w aqueous caesium carbonate (385 μL , 1.00 mmol) in benzene (20.0 mL). Purification by column chromatography, eluting with 20–30% ethyl acetate in petrol, yielded title compound **144** (59 mg, 67%, 90:10 e.r.).

Racemic: Enol ether **109** (14 mg, 0.0316 mmol) was dissolved in dichloromethane. DDQ (14 mg, 0.0633 mmol) was added and the solution stirred at room temperature overnight then diluted with ethyl acetate and saturated aqueous sodium thiosulfate and stirred for 10 min. The mixture was washed three times with saturated aqueous sodium bicarbonate, dried with anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The crude was dissolved in dichloromethane and filtered through silica, eluting with 30% ethyl acetate in petrol to yield title compound **144** as a white solid (14 mg, quant.).

m.p. 188–192 °C

^1H NMR (500 MHz, CDCl_3) δ_H : 7.85–7.75 (2H, m, H2 and H10), 7.75 (d, J = 8.2 Hz, 1H, H6), 7.47 (d, J = 6.6 Hz, 1H, H20), 7.40–7.34 (m, 2H, H21), 7.33–7.30 (m, 2H, H9 and H22), 7.17 (t, J = 7.8 Hz, 1H, H1), 5.25–5.08 (m, 2H, H18), 3.67 (hept, J = 6.6 Hz, 1H, H15), 3.47 (hept, J = 6.8 Hz, 1H, H12), 1.61 (d, J = 6.8 Hz, 3H, H13), 1.36 (d, J = 6.8 Hz, 3H, H14), 1.16 (d, J = 6.7 Hz, 3H, H17), 1.02 (d, J = 6.6 Hz, 3H, H16).

$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ_C : 167.1 (C11), 154.8 (C8), 136.6 (C19), 134.0 (C2), 131.4 (C5), 130.9 (C10), 129.3 (C4), 128.9 (C6), 128.5 (C21), 128.2 (C20), 128.2 (C22), 124.4 (C1), 123.9 (C7), 118.6 (C3), 115.9 (C9), 72.4 (C18), 51.3 (C15), 46.0 (C12), 20.7 (C16), 20.3 (C14), 19.6 (C17), 19.4 (C13).

FTIR (neat) ν/cm^{-1} = 2980, 1630, 1505, 1379, 1308, 1257, 1153, 1060, 954, 818.

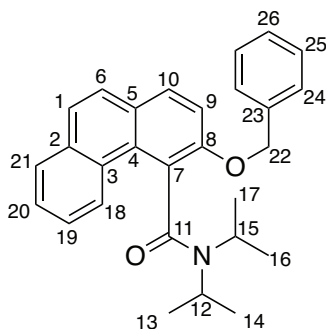
HRMS (m/z , ESI^+): calculated for $\text{C}_{24}\text{H}_{27}\text{BrNO}_2$ ($[\text{M}+\text{H}]^+$) = 440.1220, found = 440.1220.

$[\alpha]_D^{25} = -124.1^\circ$ (90:10 e.r., c = 0.5, CHCl_3).

Chiral HPLC: (Chiralpak ODH, 10% isopropanol, 90% hexane, 1.0 mL/min, λ = 240 nm)

τ_R (major) = 15.6 min, τ_R (minor) = 25.5 min.

3-(Benzyloxy)-*N,N*-diisopropylphenanthrene-4-carboxamide (145)



Asymmetric: Prepared according to **General Procedure N** with naphthol **148** (64 mg, 0.200 mmol), benzyl iodide (130 mg, 0.600 mmol), **186** (8.4 mg, 0.0100 mmol), and 50% w/w aqueous caesium carbonate (385 μ L, 1.00 mmol) in benzene (20.0 mL). Purification by column chromatography, eluting with 5–10% ethyl acetate in petrol, yielded title compound **145** (76 mg, 93%, 97:3 e.r.).

Racemic Method 1: Enol ether **136** (78 mg, 0.189 mmol) was dissolved in dichloromethane. DDQ (85 mg, 0.377 mmol) was added and the solution stirred at room temperature overnight, then diluted with ethyl acetate and saturated aqueous sodium thiosulfate and stirred for 10 min. The mixture was washed three times with saturated aqueous sodium bicarbonate, dried with anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude was dissolved in dichloromethane and filtered through silica eluting with 20% ethyl acetate in petrol, to yield title compound **145** as a white solid (53 mg, 99%).

Racemic Method 2: Prepared according to **General Procedure M** with naphthol **148** (55 mg, 0.171 mmol), benzyl bromide (61 μ L, 0.513 mmol), TBAB (5.5 mg, 0.0171 mmol), and 50% w/w aqueous potassium hydroxide (32 μ L, 0.856 mmol) in toluene (1.7 mL). Purification by column chromatography eluting with 10% ethyl acetate in petrol afforded title compound **145** as a white solid (55 mg, 78%).

m.p. 151–153 °C

^1H NMR (500 MHz, CDCl_3) δ_{H} : 9.00 (d, J = 8.5 Hz, 1H, H18), 7.84 (dd, J = 7.8, 1.6 Hz, 1H, H21), 7.83 (d, J = 8.7 Hz, 1H, H10), 7.65 (d, J = 8.8 Hz, 1H, H6), 7.61 (d, J = 8.7 Hz, 1H, H1), 7.57 (ddd, J = 7.9, 6.9, 1.3 Hz, 1H, H20), 7.54–7.49 (m, 3H, H19 and H24), 7.42–7.37 (m, 2H, H25), 7.36 (d, J = 8.8 Hz, 1H, H9), 7.35–7.31 (m, 1H, H26), 5.25 (d, J = 11.3 Hz, 1H, H22a), 5.17 (d, J = 11.3 Hz, 1H, H22b), 3.64 (hept, J = 6.6 Hz, 1H, H12),

3.53 (hept, $J = 6.9$ Hz, 1H, H15), 1.82 (d, $J = 6.9$ Hz, 3H, H17), 1.50 (d, $J = 6.8$ Hz, 3H, H16), 0.97 (d, $J = 6.7$ Hz, 3H, H14), 0.77 (d, $J = 6.7$ Hz, 3H, H13).

$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ_{C} : 169.7 (C11), 154.3 (C8), 136.8 (C17), 133.4 (C2), 130.2 (C10), 129.5 (C3), 128.6 (C21), 128.5 (C25), 128.1 (C4), 128.1 (C26), 128.0 (C24), 128.0 (C5), 127.3 (C6), 127.0 (C18), 126.9 (C20), 125.8 (C1), 125.7 (C19), 124.4 (C7), 113.9 (C9), 71.9 (C22), 51.3 (C12), 46.2 (C15), 20.6 (C13), 20.6 (C14), 20.4 (C16), 19.6 (C17).

FTIR (neat) $\nu/\text{cm}^{-1} = 2973, 1619, 1503, 1453, 1369, 1293, 1211, 1095, 831, 735$.

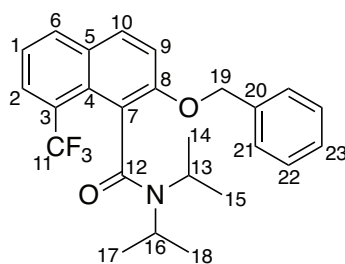
HRMS (m/z , ESI^+): calculated for $\text{C}_{28}\text{H}_{30}\text{NO}_2$ ($[\text{M}+\text{H}]^+$) = 412.2271, found = 412.2271.

$[\alpha]_D^{25} = -78.8^\circ$ (97:3 e.r., $c = 0.5$, CHCl_3).

Chiral HPLC: (Chiralpak ODH, 30% isopropanol, 70% hexane, 1.0 mL/min, $\lambda = 260$ nm)

τ_{R} (major) = 10.3 min, τ_{R} (minor) = 15.6 min.

2-(Benzyloxy)-*N,N*-diisopropyl-8-(trifluoromethyl)-1-naphthamide (146)



Asymmetric: Prepared according to **General Procedure N** with naphthol **149** (68 mg, 0.200 mmol), benzyl iodide (130 mg, 0.600 mmol), **186** (8.4 mg, 0.0100 mmol), and 50% w/w aqueous caesium carbonate (385 μL , 1.00 mmol) in benzene (20.0 mL). Purification

by column chromatography, eluting with 10–20% ethyl acetate in petrol, yielded title compound **146** as a white solid (85 mg, 99%, 95:5 e.r.).

Racemic: Enol ether **138** (134 mg, 0.310 mmol) was dissolved in dichloromethane (3.0 mL). DDQ (136 mg, 0.620 mmol) was added and the solution stirred at room temperature for 3 days, then diluted with ethyl acetate and saturated aqueous sodium thiosulfate and stirred for 10 min. The mixture was washed three times with saturated aqueous sodium bicarbonate, dried with anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude was purified by column chromatography, eluting with 20% ethyl acetate in petrol, to yield **146** as a white solid (60 mg, 45%).

m.p. 202–204 °C

^1H NMR (500 MHz, CDCl_3) δ_{H} : 8.00 (d, $J = 7.1$ Hz, 1H, H2), 7.97 (d, $J = 8.1$ Hz, 1H, H6), 7.88 (d, $J = 9.0$ Hz, 1H, H10), 7.47 (d, $J = 8.0$ Hz, 2H, H21), 7.41–7.38 (m, 2H, H1 and H9), 7.37–7.34 (m, 2H, H22), 7.34–7.29 (m, 1H, H23), 5.20 (d, $J = 11.4$ Hz, 1H, H19a), 5.15 (d, $J = 11.4$ Hz, 1H, H19b), 3.45 (hept, $J = 13.4, 6.7$ Hz, 1H, H16), 3.39 (hept, $J = 6.8$ Hz, 1H, H13), 1.55 (d, $J = 6.8$ Hz, 3H, H15), 1.31–1.21 (d, $J = 6.8$ Hz, 3H, H14), 0.99 (d, $J = 6.0$ Hz, 3H, H17), 0.97 (d, $J = 6.3$ Hz, 3H, H18).

$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ_{C} : 166.4 (C12), 155.6 (C8), 136.4 (C20), 134.5 (C6), 131.9 (C10), 130.9 (C5), 128.6 (C22), 128.5 (q, $J = 7.7$ Hz, H2), 128.4 (C21), 128.3 (C23), 126.7 (C4), 124.6 (q, $J = 273.3$ Hz, C11), 124.5 (q, $J = 30.9$ Hz, C3), 123.0 (C7), 122.3 (C1), 115.9 (C9), 72.5 (C19), 50.8 (C16), 46.2 (C13), 20.7 (C18), 20.4 (C15 and C17), 19.8 (C14).

^{19}F NMR (377 MHz, CDCl_3) δ_{F} : –55.0 (CF_3).

FTIR (neat) ν/cm^{-1} = 2974, 1632, 1515, 1437, 1295, 1258, 1146, 1059, 1013, 825.

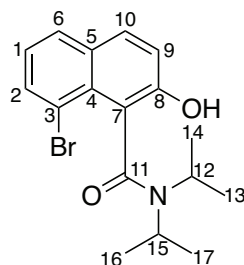
HRMS (m/z , ESI⁺): calculated for C₂₅H₂₇F₃NO₂ ([M+H]⁺) = 430.1988, found = 430.1974.

$[\alpha]_D^{25}$ = -38.6° (95:5 e.r., c = 0.5, CHCl₃).

Chiral HPLC: (Chiralpak ODH, 30% isopropanol, 70% hexane, 1.0 mL/min, λ = 240 nm)

τ_R (major) = 12.0 min, τ_R (minor) = 25.3 min.

8-Bromo-2-hydroxy-*N,N*-diisopropyl-1-naphthamide (147)



Method 1: Amide **144** (23 mg, 0.0522 mmol) was dissolved in a mixture of toluene (1.0 mL) and TFA (1.0 mL) and heated at reflux for 2 h. Water was added and the organic layer was extracted with dichloromethane, dried with anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to give the crude mixture. This was purified by column chromatography, eluting with 10–50% ethyl acetate in petrol to yield title compound **147** as a white solid (14 mg, 77%)

Method 2: Ester **107** (3.08 g, 8.03 mmol) was dissolved in anhydrous THF (30 mL) and cooled to 0 °C. KHMDS (32 mL, 0.5 M, 16.0 mmol) was added dropwise. The solution was warmed to room temperature and stirred for 4 h. TBDMSCl (2.42 g, 16.0 mmol) was added and the solution stirred for 30 min. Saturated aqueous ammonium chloride was added and the organic layer was extracted with diethyl ether. The organic layer was

separated, dried with anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude was purified by column chromatography, eluting with 5–10% diethyl ether in petrol, to yield intermediate **266** as a white solid (2.00 g, 54%)

Then, **266** (942 mg, 2.02 mmol) was dissolved in benzene (10 mL) and *N*-bromosuccinamide (396 mg, 2.22 mmol) was added and the solution was stirred at reflux overnight. The solution was cooled to 0 °C, filtered, and concentrated *in vacuo*. The crude mixture was purified by column chromatography, eluting with 20% ethyl acetate in petrol, to yield title compound **147** as a white solid (513 mg, 73%, combined yield = 39%).

m.p. 230–232 °C

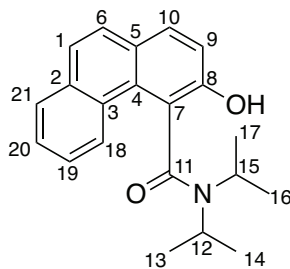
¹H NMR (500 MHz, CDCl₃) δ_H : 8.84 (s, 1H, OH), 7.74 (dd, J = 7.4, 1.3 Hz, 1H H2), 7.63 (dd, J = 8.1, 1.3 Hz, 1H, H6), 7.29 (d, J = 8.8 Hz, 1H, H10), 7.10 (t, J = 7.7 Hz, 1H, H1), 6.86 (d, J = 8.8 Hz, 1H, H9), 3.63 (hept, J = 6.7 Hz, 1H, H12), 3.53 (hept, J = 6.8 Hz, 1H, H15), 1.64 (d, J = 6.8 Hz, 3H, H17), 1.49 (d, J = 6.8 Hz, 3H, H16), 1.14 (d, J = 6.7 Hz, 3H, H13), 0.94 (d, J = 6.6 Hz, 3H, H14).

¹³C{¹H} NMR (126 MHz, CDCl₃) δ_C : 170.2 (C11), 154.5 (C8), 133.2 (C2), 130.7 (C10), 130.3 (C5), 129.3 (C4), 128.7 (C6), 123.4(C1), 120.1 (C9), 118.4 (C7), 117.9 (C3), 51.9 (C12), 46.5 (C15), 20.6 (C16), 20.5 (C14), 19.2 (C17), 19.2 (C13).

FTIR (neat) ν/cm^{-1} = 2975, 2931, 1590, 1507, 1428, 1338, 1295, 1210, 1162, 1052, 828.

HRMS (m/z , ESI⁺): calculated for C₁₇H₂₁BrNO₂ ([M+H]⁺) = 350.0750, found = 350.0751.

3-Hydroxy-*N,N*-diisopropylphenanthrene-4-carboxamide (**148**)



Method 1: Amide **145** (26 mg, 0.0632 mmol) was dissolved in toluene (0.5 mL). TFA (0.5 mL) was added and the mixture was heated at reflux for 4 h. Water was added and the organic layer was extracted with dichloromethane, dried with anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to give the crude mixture. This was purified by column chromatography, eluting with 30% ethyl acetate in petrol, to yield title compound **148** as a white solid (15 mg, 74%).

Method 2: Prepared according to **General Procedure J** with silylated naphthol **169** (2.67 g, 6.13 mmol) and potassium fluoride (710 mg, 12.3 mmol) in methanol (15 mL). Purification by trituration with ethyl acetate and washing with hexane yielded title compound **148** as a white solid (1.85 mg, 94%).

m.p. > 225 °C

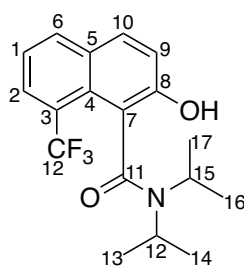
^1H NMR (500 MHz, CDCl_3) δ_{H} : 8.68 (d, J = 8.4 Hz, 1H, H18), 7.85 (d, J = 7.8 Hz, 1H, H21), 7.65 (d, J = 8.4 Hz, 1H, H10), 7.63 (d, J = 8.4 Hz, 1H, H6), 7.60 (d, J = 8.7 Hz, 1H, H1), 7.56 (dd, J = 7.9, 6.9 Hz, 1H, H6), 7.50 (dd, J = 8.4, 6.9 Hz, 1H, H19), 7.34 (s, 1H, OH), 7.16 (d, J = 8.6 Hz, 1H, H9), 3.54 (hept, J = 6.8 Hz, 1H, H15), 3.36 (hept, J = 6.6 Hz, 1H, H12), 1.80 (d, J = 6.9 Hz, 3H, H16), 1.69 (d, J = 6.8 Hz, 3H, H17), 0.86 (d, J = 6.6 Hz, 3H, H13), 0.51 (d, J = 6.6 Hz, 3H, H14).

$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ_{C} : 171.5 (C11), 153.3 (C8), 133.4 (C4), 130.6 (C10), 129.0 (C3), 128.5 (C21), 127.9 (C2), 127.2 (C18), 127.2 (C6), 127.0 (C20), 126.9 (C5), 125.5 (C19), 125.1 (C1), 119.4 (C7), 118.2 (C9), 51.5 (C12), 46.7 (C15), 21.2 (C17), 20.9 (C13), 19.3 (C14), 19.2 (C16).

FTIR (neat) ν/cm^{-1} = 2998, 1596, 1572, 1525, 1475, 1450, 1399, 1286, 1160, 1087, 969, 854.

HRMS (m/z , ESI^+): calculated for $\text{C}_{21}\text{H}_{24}\text{NO}_2$ ($[\text{M}+\text{H}]^+$) = 322.1802, found = 322.1803.

2-Hydroxy-*N,N*-diisopropyl-8-(trifluoromethyl)-1-naphthamide (149)



Method 1: Amide **146** (14 mg, 0.0340 mmol) was dissolved in MeOH (2.0 mL) with Pd/C (1 mg, 10% w/w). The flask was sealed and evacuated, then back-filled with hydrogen three times. The mixture was stirred overnight then filtered through celite, and concentrated *in vacuo*. The crude mixture was purified by column chromatography, eluting with 20% ethyl acetate in petrol, to yield title compound **149** as a white solid (10 mg, 90%).

Method 2: Prepared according to **General Procedure G** with **132** (2.79 g, 7.20 mmol) and KHMDS (29 mL, 0.5 M, 14.4 mmol) in anhydrous THF (30 mL) then TBDMSCl (2.17 g, 14.4 mmol). Purification by column chromatography, eluting with 5–10% diethyl ether in petrol, yielded intermediate **218** as a white solid (1.53 g, 47%)

Then, according to **General Procedure I** with **218** (1.10 g, 2.41 mmol) and *N*-bromosuccinamide (516 mg, 2.90 mmol) in benzene (20 mL). Purification by column chromatography, eluting with 20% ethyl acetate in petrol, yielded title compound **149** as a white solid (496 mg, 61%, combined yield = 29%).

m.p. 195–197 °C

^1H NMR (500 MHz, CDCl_3) δ_{H} : 8.34 (s, 1H, OH), 7.94 (d, J = 7.5 Hz, 1H, H2), 7.88 (d, J = 8.2 Hz, 1H, H6), 7.52 (d, J = 8.8 Hz, 1H, H10), 7.36 (t, J = 7.7 Hz, 1H, H1), 7.07 (d, J = 8.8 Hz, 1H, H9), 3.49 (hept, J = 6.8 Hz, 1H, H12), 3.30 (hept, J = 6.6 Hz, 1H, H15), 1.58 (d, J = 6.9 Hz, 3H, H14), 1.52 (d, J = 6.7 Hz, 3H, H13), 0.97 (d, J = 6.6 Hz, 3H, H16), 0.84 (d, J = 6.6 Hz, 3H, H17).

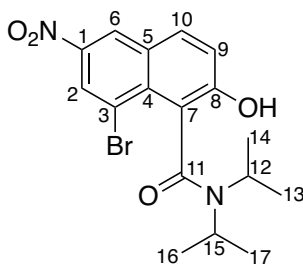
$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ_{C} : 169.4 (C11), 155.0 (C8), 134.1 (C6), 131.9 (C10), 129.7 (C5), 128.1 (q, J = 7.0 Hz, C2), 126.4 (C4), 124.9 (d, J = 272.8 Hz, C18), 123.6 (q, J = 30.8 Hz, C3), 121.7 (C1), 119.9 (C9), 117.2 (C7), 51.4 (C15), 46.7 (C12), 20.7 (C17), 20.6 (C13), 20.0 (C14), 19.7 (C16).

^{19}F NMR (MHz, CDCl_3) δ_{F} : −55.2 (CF_3).

FTIR (neat) ν/cm^{-1} = 2918, 2850, 1579, 1515, 1439, 1382, 1300, 1130, 1054, 839, 737.

HRMS (m/z , ESI^+): calculated for $\text{C}_{18}\text{H}_{21}\text{O}_2\text{NF}_3$ ($[\text{M}+\text{H}]^+$) = 340.1519, found = 340.1517.

8-Bromo-2-hydroxy-*N,N*-diisopropyl-6-nitro-1-naphthamide (161)



Naphthol **147** (200 mg, 0.571 mmol) and TBAB (20 mg 0.0571 mmol) were dissolved in 1,2-dichloroethane (1.1 mL). 1 M nitric acid was added (1.1 mL, 1.10 mmol) and the reaction was stirred vigorously at room temperature for 4 h. Ammonium chloride was added and the organic layer was extracted with dichloromethane, dried with anhydrous sodium sulfate, filtered, and concentrated under a stream of nitrogen. The crude was purified by column chromatography, eluting with 40% ethyl acetate in petrol, followed by trituration with ethyl acetate and washing with hexane to yield title compound **161** as a yellow solid (151 mg, 67%).

m.p. > 220 °C

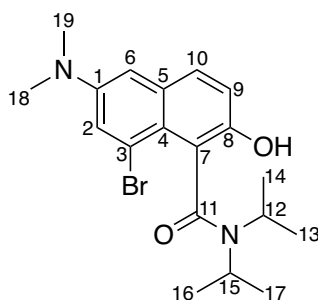
^1H NMR (500 MHz, CDCl_3) δ_{H} : 10.68 (s, 1H, OH), 8.60 (d, $J = 2.4$ Hz, 1H, H6), 8.51 (d, $J = 2.4$ Hz, 1H, H2), 7.62 (d, $J = 8.8$ Hz, 1H, H10), 7.20–7.07 (m, 1H, H9), 3.58–3.40 (m, 2H, H12 and H15), 1.61 (d, $J = 6.8$ Hz, 3H, H13), 1.31–1.26 (m, 3H, H14), 1.11 (d, $J = 6.7$ Hz, 3H, H16), 0.81 (d, $J = 6.6$ Hz, 3H, H17).

$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ_{C} : 169.2 (C11), 158.9 (C8), 142.2 (C1), 133.3 (C10), 132.3 (C4), 127.7 (C5), 126.4 (C2), 125.2 (C6), 121.8 (C9), 118.5 (C7), 117.9 (C3), 52.2 (C15), 46.7 (C12), 20.4 (C14), 20.2 (C17), 19.1 (C13), 19.1 (C16).

FTIR (neat) $\nu/\text{cm}^{-1} = 3155, 2081, 2980, 1772, 1691, 1294, 1189, 823$.

HRMS (m/z , ESI⁺): calculated for C₁₇H₂₀BrO₄N₂ ([M+H]⁺) = 395.0601, found = 395.0601.

8-Bromo-6-(dimethylamino)-2-hydroxy-*N,N*-diisopropyl-1-naphthamide (163)



Naphthol **148** (97 mg, 0.245 mmol) was dissolved in ethanol (10 mL) with conc. HCl (72 μ L) and tin (117 mg, 0.981 mmol) and heated to reflux until TLC analysis showed complete consumption of starting material. The mixture was filtered through cotton wool and ammonium chloride was added. The organic layer was extracted with dichloromethane, dried with anhydrous sodium sulfate and concentrated *in vacuo* to give intermediate **162** as a white solid (50 mg, 56%)

A mixture of **162** (45 mg, 0.124 mmol) and sodium borohydride (40 mg, 1.06 mmol) in THF (1.5 mL) was added dropwise over 10 min to a solution of 37% w/w aqueous formaldehyde (160 μ L, 2.15 mmol) and sulfuric acid (150 μ L, 3 M, 0.480 mmol) in THF (1.0 mL) and stirred for 1 h at room temperature. The THF was removed *in vacuo* and water was added. The solution was made basic with aqueous ammonium hydroxide solution and the organic layer was extracted with dichloromethane, dried with anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude mixture was purified by column chromatography, eluting with 50% ethyl acetate in petrol, to afford title compound **163** as a brown solid (18 mg, 37%, combined yield = 21%).

m.p. > 200 °C

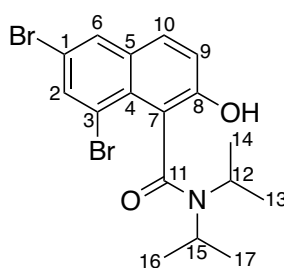
^1H NMR (500 MHz, CD_2Cl_2) δ_{H} : 7.47 (d, J = 2.7 Hz, 1H, H2), 7.45 (d, J = 8.8 Hz, 1H, H10), 6.99 (d, J = 8.8 Hz, 1H, H9), 6.88 (d, J = 2.7 Hz, 1H, H6), 6.65 (s, 1H, OH), 3.63–3.54 (m, 1H, H15), 3.54–3.47 (m, 1H, H12), 3.00 (s, 6H, H18 and H19), 1.62 (d, J = 6.9 Hz, 3H, H16), 1.59 (d, J = 6.8 Hz, 3H, H17), 1.16 (d, J = 6.7 Hz, 3H, H13), 0.94 (d, J = 6.7 Hz, 3H, H14).

$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CD_2Cl_2) δ_{C} : 169.6 (C11), 150.8 (C8), 147.6 (C1), 132.3 (C5), 129.7 (C10), 125.4 (C3), 123.4 (C2), 122.2 (C4), 120.2 (C9), 119.1 (C7), 108.5 (C6), 51.8 (C12), 46.8 (C15), 41.0 (C18 and C19), 21.3 (C17), 21.0 (C14), 19.4 (C13), 19.3 (C16).

FTIR (neat) ν/cm^{-1} = 2928, 1602, 1490, 1359, 1271, 1052, 766, 729, 636.

HRMS (m/z , ESI^+): calculated for $\text{C}_{19}\text{H}_{26}\text{BrN}_2\text{O}_2$ ($[\text{M}+\text{H}]^+$) = 393.1173, found = 393.1172.

6,8-Dibromo-2-hydroxy-*N,N*-diisopropyl-1-naphthamide (164)



Naphthol **147** (27 mg, 0.0770 mmol) was dissolved in acetic acid (2.0 mL). 1 M Bromine in acetic acid (1.5 mL, 0.150 mmol) was added and the solution was heated to 110 °C overnight. The reaction was cooled to room temperature and quenched with saturated aqueous sodium thiosulfate. The organic layer was extracted with ethyl acetate, dried

with anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude reaction mixture was purified by column chromatography, eluting with 10–20% ethyl acetate in petrol, to yield title compound **164** as a white solid (21 mg, 64%).

m.p. 161–162 °C

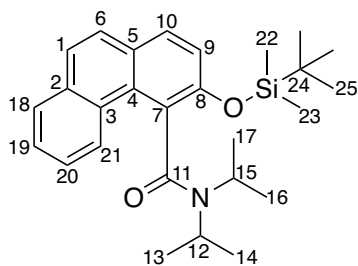
^1H NMR (500 MHz, CDCl_3) δ_{H} : 8.48 (s, 1H, OH), 7.86 (d, J = 2.1 Hz, 1H, H2), 7.81 (d, J = 2.1 Hz, 1H, H6), 7.29 (d, J = 8.9 Hz, 1H, H10), 6.92 (d, J = 8.8 Hz, 1H, H9), 3.61–3.47 (m, 2H, H12 and H15), 1.63 (d, J = 6.8 Hz, 3H, H13), 1.51 (d, J = 6.8 Hz, 3H, H14), 1.15 (d, J = 6.6 Hz, 3H, H16), 0.94 (d, J = 6.6 Hz, 3H, H17).

$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ_{C} : 169.4 (C11), 154.6 (C8), 135.5 (C2), 130.9 (C5), 130.6 (C6), 129.9 (C10), 128.0 (C4), 121.0 (C9), 118.8 (C7), 118.6 (C3), 115.8 (C1), 51.9 (C15), 46.7 (C12), 20.7 (C14 or C17), 20.5 (C14 or C17), 19.2 (C13 or C16), 19.1 (C13 or C16).

FTIR (neat) ν/cm^{-1} = 2926, 1583, 1492, 1369, 1294, 917.

HRMS (m/z , ESI^+): calculated for $\text{C}_{17}\text{H}_{20}\text{Br}_2\text{NO}_2$ ($[\text{M}+\text{H}]^+$) = 427.9855, found = 427.9856.

3-((*Tert*-butyldimethylsilyl)oxy)-*N,N*-diisopropylphenanthrene-4-carboxamide (169)



Prepared according to **General Procedure G** with amide **130** (2.54 g, 6.88 mmol) and KHMDS (27.5 mL, 0.5 M, 14.0 mmol) in anhydrous THF (20 mL). Followed by TBDMSCl (2.05 g, 13.8 mmol) Purification by column chromatography, eluting with 5–10% diethyl ether in petrol, yielded intermediate **168** as a white solid (1.80 g, 60%).

Then, according to **General Procedure H**, with intermediate **168** (1.70 g, 3.89 mmol) and DDQ (1.10 g, 5.07 mmol) in toluene (10 mL) for 30 min. Purification by column chromatography, eluting with 5–10% diethyl ether in petrol, yielded title compound **169** as a white solid (1.53 g, 90%, combined yield = 54%).

m.p. 182–184 °C

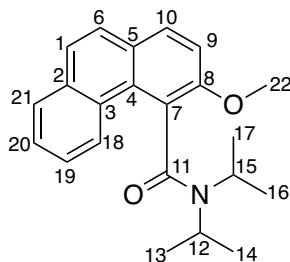
^1H NMR (500 MHz, CDCl_3) δ_{H} : 8.99 (d, J = 8.5 Hz, 1H, H21), 7.82 (dd, J = 7.8, 1.6 Hz, 1H, H18), 7.73 (d, J = 8.6 Hz, 1H, H10), 7.64 (d, J = 8.7 Hz, 1H, H6), 7.60 (d, J = 8.7 Hz, 1H, H1), 7.54 (ddd, J = 7.9, 6.9, 1.2 Hz, 1H, H19), 7.48 (ddd, J = 8.5, 6.9, 1.6 Hz, 1H, H20), 7.19 (d, J = 8.6 Hz, 1H, H9), 3.59 (hept, J = 6.9 Hz, 1H, H12), 3.41 (hept, J = 6.7 Hz, 1H, H15), 1.81 (d, J = 6.8 Hz, 3H, H14), 1.73 (d, J = 6.9 Hz, 3H, H13), 1.05 (s, 9H, H25), 1.01 (d, J = 6.7 Hz, 3H, H17), 0.60 (d, J = 6.7 Hz, 3H, H16), 0.40 (s, 3H, H22), 0.28 (s, 3H, H23).

$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ_{C} : 170.1 (C11), 151.7 (C8), 133.3 (C2), 129.7 (C10), 129.5 (C3), 128.5 (C18), 128.2 (C4), 127.8 (C5), 127.4 (C21), 127.2 (C6), 126.8 (C19), 125.7 (C1 and C7), 125.6 (C20), 120.2 (C9), 51.3 (C15), 46.3 (C12), 26.2 (C25), 21.7 (C13), 20.9 (C17), 20.3 (C16), 19.3 (C14), 18.8 (C24), -3.4 (C22), -3.8 (C23).

FTIR (neat) ν/cm^{-1} = 2930, 1617, 1501, 1454, 1422, 1326, 1269, 1212, 1091, 944, 841, 784.

HRMS (m/z , ESI⁺): calculated for C₂₇H₃₈NO₂Si ([M+H]⁺) = 436.2666, found = 436.2664.

***N,N*-Diisopropyl-3-methoxyphenanthrene-4-carboxamide (187)**



Prepared according to **General Procedure M** with **148** (50 mg, 0.156 mmol), TBAB (5 mg, 0.0156 mmol), 50% w/w aqueous caesium carbonate (150 μ L, 0.390 mmol), and methyl iodide (29 μ L, 0.468 mmol) in toluene (1.6 mL). Purification by column chromatography, eluting with 10–20% ethyl acetate in petrol, yielded title compound **187** as a white solid (15 mg, 29%).

m.p. 222–223 °C

¹H NMR (500 MHz, CDCl₃) δ_H : 8.96 (dd, J = 8.6, 1.0 Hz, 1H, H18), 7.85 (d, J = 8.8 Hz, 1H, H10), 7.83 (dd, J = 7.7, 1.4 Hz, 1H, H21), 7.65 (d, J = 8.8 Hz, 1H, H6), 7.60 (d, J = 8.7 Hz, 1H, H1), 7.55 (ddd, J = 7.9, 6.9, 1.3 Hz, 1H, H20), 7.51 (ddd, J = 8.5, 6.9, 1.6 Hz, 1H, H19), 7.31 (d, J = 8.7 Hz, 1H, H9), 3.95 (s, 3H, H22), 3.69–3.57 (m, 2H, H12 and H15), 1.84 (d, J = 6.9 Hz, 3H, H13), 1.72 (d, J = 6.8 Hz, 3H, H14), 1.04 (d, J = 6.6 Hz, 3H, H16), 0.83 (d, J = 6.7 Hz, 3H, H17).

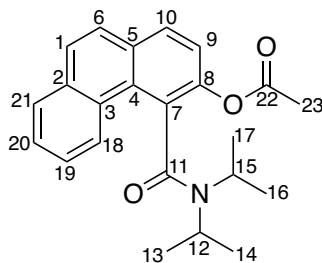
¹³C{¹H} NMR (126 MHz, CDCl₃) δ_C : 170.0 (C11), 154.9 (C8), 133.5 (C2), 130.3 (C10), 129.5 (C3), 128.7 (C21), 127.9 (C4), 127.9 (C5), 127.3 (C6), 126.9 (C20), 126.9 (C18),

125.8 (C19), 125.7 (C1), 123.7 (C7), 112.2 (C9), 56.6 (C22), 51.3 (C15), 46.3 (C12), 20.7 (C17), 20.6 (C14), 20.4 (C16), 19.7 (C13).

FTIR (neat) ν/cm^{-1} = 2980, 1616, 1267, 904, 832, 725, 689.

HRMS (m/z , ESI⁺): calculated for C₂₂H₂₆NO₂ ([M+H]⁺) = 336.1958, found = 336.1937.

4-(Diisopropylcarbamoyl)phenanthren-3-yl acetate (**188**)



Prepared according to **General Procedure M** with **148** (50 mg, 0.156 mmol), TBAB (5 mg, 0.0156 mmol), 50% w/w aqueous caesium carbonate (150 μ L, 0.390 mmol) and acetic anhydride (44 μ L, 0.468 mmol) in toluene (1.6 mL). Purification by column chromatography, eluting with 10–20% ethyl acetate in petrol, yielded title compound **188** as a white solid (16 mg, 28%).

m.p. > 215 °C

¹H NMR (500 MHz, CDCl₃) δ_H : 8.91 (dd, J = 8.4, 1.1 Hz, 1H, H18), 7.89 (d, J = 8.6 Hz, 1H, H10), 7.88 (d, J = 8.0 Hz, 1H, H21), 7.73 (d, J = 8.7 Hz, 1H, H6), 7.73 (d, J = 8.7 Hz, 1H, H1), 7.59 (ddd, J = 7.9, 6.9, 1.2 Hz, 1H, H20), 7.54 (ddd, J = 8.5, 6.9, 1.6 Hz, 1H, H19), 7.45 (d, J = 8.6 Hz, 1H, H9), 3.59 (hept, J = 6.8 Hz, 1H, H12), 3.40 (hept, J = 6.6 Hz, 1H, H17), 2.34 (s, 3H, H23), 1.84 (d, J = 6.9 Hz, 3H, H13), 1.71 (d, J = 6.8 Hz,

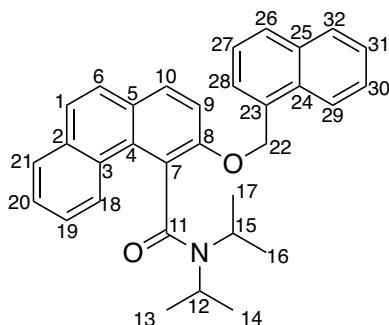
3H, H14), 0.98 (d, J = 6.7 Hz, 3H, H16), 0.66 (d, J = 6.7 Hz, 3H, H17).

$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ_{C} : 169.2 (C22), 168.4 (C11), 146.2 (C8), 133.1 (C2), 131.0 (C5), 129.8 (C10), 129.6 (C3), 128.8 (C21), 127.8 (C6), 127.6 (C4), 127.4 (C7), 127.3 (C20), 127.1 (C1), 126.9 (C18), 126.2 (C19), 122.1 (C9), 51.3 (C15), 46.4 (C12), 21.1 (C23), 20.9 (C14), 20.6 (C16), 20.3 (C17), 19.3 (C13).

FTIR (neat) ν/cm^{-1} = 2980, 2889, 1769, 1629, 1381, 1252, 1153, 1081, 954, 904, 725.

HRMS (m/z , ESI^+): calculated for $\text{C}_{23}\text{H}_{25}\text{NNaO}_3$ ($[\text{M}+\text{Na}]^+$) = 386.1727, found = 386.1722.

***N,N*-Diisopropyl-3-(naphthalen-1-ylmethoxy)phenanthrene-4-carboxamide**
(189)



Prepared according to **General Procedure M** with **148** (50 mg, 0.156 mmol), TBAB (5 mg, 0.0156 mmol), 50% w/w aqueous caesium carbonate (150 μL , 0.390 mmol), and 1-(bromomethyl)naphthylene (103 mg, 0.468 mmol) in toluene (1.6 mL). Purification by column chromatography, eluting with 10–20% ethyl acetate in petrol, yielded title compound **189** as a white solid (51 mg, 71%).

m.p. 195–196 °C

^1H NMR (500 MHz, CDCl_3) δ_{H} : 8.97 (d, J = 8.5 Hz, 1H, H18), 8.15 (d, J = 9.0 Hz, 1H,

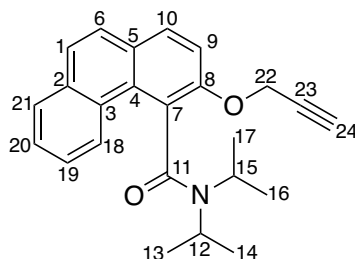
H29), 7.92–7.86 (m, 1H, H32), 7.87–7.83 (m, 3H, H10, H21 and H26), 7.70 (dd, J = 6.9, 1.1 Hz, 1H, H28), 7.67 (d, J = 8.8 Hz, 1H, H6), 7.62 (d, J = 8.8 Hz, 1H, H1), 7.60–7.55 (m, 2H, H20 and H30), 7.55–7.48 (m, 2H, H19 and H31), 7.47 (dd, J = 8.3, 7.0 Hz, 1H, H27), 7.45 (d, J = 8.7 Hz, 1H, H9), 5.71 (d, J = 11.6 Hz, 1H, H22a), 5.62 (d, J = 11.6 Hz, 1H, H22b), 3.64 (hept, J = 6.7 Hz, 1H, H12), 3.42 (hept, J = 6.8 Hz, 1H, H15), 1.74 (d, J = 6.8 Hz, 3H, H16), 1.17 (d, J = 6.8 Hz, 3H, H17), 0.90 (d, J = 6.6 Hz, 3H, H13), 0.75 (d, J = 6.7 Hz, 3H, H14).

$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ_{C} : 169.6 (C11), 154.4 (C8), 133.7 (C25), 133.4 (C2), 132.4 (C23), 131.5 (C24), 130.3 (C10), 129.5 (C3), 128.9 (C26), 128.7 (C21), 128.6 (C32), 128.3 (C5), 128.0 (C4), 127.3 (C6), 127.0 (C18), 127.0 (C30), 126.6 (C20 and C28), 126.0 (C31), 125.9 (C1), 125.7 (C19), 125.4 (C27), 124.6 (C7), 124.1 (C29), 114.2 (C9), 70.4 (C22), 51.3 (C12), 46.2 (C15), 20.7 (C14), 20.5 (C13), 19.8 (C17), 19.5 (C16).

FTIR (neat) ν/cm^{-1} = 2966, 1617, 1523, 1470, 1366, 1334, 1298, 1221, 1116, 1045, 995, 865, 830, 800, 777, 737.

HRMS (m/z , ESI^+): calculated for $\text{C}_{32}\text{H}_{32}\text{NO}_2$ ($[\text{M}+\text{H}]^+$) = 462.2428, found = 462.2528.

***N,N*-Diisopropyl-3-(prop-2-yn-1-yloxy)phenanthrene-4-carboxamide (190)**



Prepared according to **General Procedure M** with **148** (50 mg, 0.156 mmol), TBAB

(5 mg, 0.0156 mmol), 50% w/w aqueous caesium carbonate (150 μ L, 0.390 mmol), and propargyl bromide (52 μ L, 0.468 mmol) in toluene (1.6 mL). Purification by column chromatography, eluting with 10–20% ethyl acetate in petrol, yielded title compound **190** as a white solid (32 mg, 58%).

m.p. 215 °C

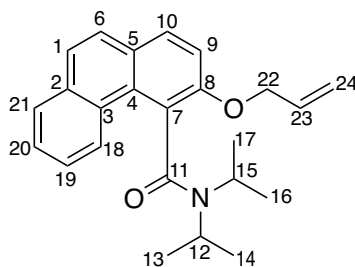
^1H NMR (500 MHz, CDCl_3) δ_{H} : 8.96 (dd, J = 8.6, 1.1 Hz, 1H, H18), 7.85 (d, J = 8.7 Hz, 1H, H10), 7.84 (dd, J = 7.8, 1.6 Hz, 1H, H21), 7.66 (d, J = 8.7 Hz, 1H, H6), 7.63 (d, J = 8.8 Hz, 1H, H1), 7.58–7.54 (m, 1H, H20), 7.52 (ddd, J = 8.5, 6.9, 1.6 Hz, 1H, H19), 7.42 (d, J = 8.8 Hz, 1H, H9), 4.91–4.76 (m, 2H, H22), 3.70–3.51 (m, 2H, H12 and H15), 2.53 (t, J = 2.4 Hz, 1H, H24), 1.84 (d, J = 6.8 Hz, 3H, H17), 1.74 (d, J = 6.8 Hz, 3H, H16), 1.11 (d, J = 6.6 Hz, 3H, H13), 0.82 (d, J = 6.7 Hz, 3H, H14).

$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ_{C} : 169.5 (C11), 152.9 (C8), 133.4 (C2), 130.1 (C10), 129.5 (C3), 128.7 (C21), 128.6 (C5), 127.9 (C4), 127.2 (C6), 127.0 (C20), 126.9 (C18), 126.2 (C1), 125.9 (C19), 124.8 (C7), 114.2 (C9), 78.8 (C23), 75.9 (C24), 57.6 (C22), 51.4 (C12), 46.3 (C15), 20.7 (C14), 20.6 (C13), 20.5 (C16), 19.7 (C17).

FTIR (neat) ν/cm^{-1} = 2971, 1619, 1502, 1453, 1369, 1337, 1268, 1223, 1112, 1096, 832, 733.

HRMS (m/z , ESI^+): calculated for $\text{C}_{24}\text{H}_{25}\text{NNaO}_2$ ($[\text{M}+\text{Na}]^+$) = 382.1770, found = 382.1778.

3-(Allyloxy)-*N,N*-diisopropylphenanthrene-4-carboxamide (**191**)



Prepared according to **General Procedure M** with **148** (50 mg, 0.156 mmol), TBAB (5 mg, 0.0156 mmol), 50% w/w aqueous caesium carbonate (150 μ L, 0.390 mmol), and allyl bromide (40 μ L, 0.468 mmol) in toluene (1.6 mL). Purification by column chromatography, eluting with 10–20% ethyl acetate in petrol, yielded title compound **191** as a white solid (37 mg, 66%).

m.p. 160–162 °C

^1H NMR (500 MHz, CDCl_3) δ_{H} : 8.98 (d, J = 8.3 Hz, 1H, H18), 7.85–7.82 (m, 1H, H21), 7.82 (d, J = 8.7 Hz, 1H, H10), 7.65 (d, J = 8.8 Hz, 1H, H6), 7.60 (d, J = 8.7 Hz, 1H, H1), 7.56 (ddd, J = 7.9, 6.9, 1.3 Hz, 1H, H20), 7.52 (ddd, J = 8.5, 6.9, 1.7 Hz, 1H, H19), 7.29 (d, J = 8.7 Hz, 1H, H9), 6.13 (dddd, J = 17.3, 10.7, 5.9, 5.0 Hz, 1H, H23), 5.46 (dq, J = 17.3, 1.6 Hz, 1H, H24a), 5.30 (dq, J = 10.5, 1.4 Hz, 1H, H24b), 4.73 (ddt, J = 12.2, 5.0, 1.6 Hz, 1H, H22a), 4.62 (ddt, J = 12.3, 6.0, 1.4 Hz, 1H, H22b), 3.70–3.56 (m, 2H, H12 and H15), 1.85 (d, J = 6.9 Hz, 3H, H17), 1.72 (d, J = 6.8 Hz, 3H, H16), 1.06 (d, J = 6.7 Hz, 3H, H13), 0.80 (d, J = 6.7 Hz, 3H, H14).

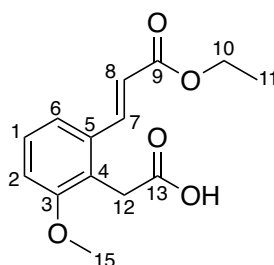
$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ_{C} : 169.7 (C11), 154.1 (C8), 133.4 (C23), 133.4 (C2), 130.2 (C10), 129.5 (C3), 128.6 (C21), 128.0 (C5), 127.9 (C4), 127.3 (C6), 127.0 (C18), 126.9 (C20), 125.8 (C1), 125.7 (C19), 124.3 (C7), 118.0 (C24), 113.8 (C9), 70.9 (C22),

51.3 (C12), 46.2 (C15), 20.7 (C14), 20.6 (C16), 20.5 (C13), 19.6 (C17).

FTIR (neat) ν/cm^{-1} = 2980, 1620, 1502, 1444, 1369, 1336, 1266, 1155, 1095, 832, 730.

HRMS (m/z , ESI⁺): calculated for C₂₄H₂₈NO₂ ([M+H]⁺) = 362.2109, found = 362.2115.

(*E*)-2-(2-(3-Ethoxy-3-oxoprop-1-en-1-yl)-6-methoxyphenyl)acetic acid (194**)**



Prepared according to **General Procedure A** with 2-methoxyphenylacetic acid (4.70 g, 28.3 mmol), potassium bicarbonate (5.70 g, 56.6 mmol), (*S*)-*N*-acetylalanine (742 mg, 5.66 mmol), palladium acetate (635 mg, 2.83 mmol) and ethyl acrylate (6.2 mL, 56.6 mmol) in *tert*-amyl alcohol (50 mL). Purification by column chromatography, eluting with 40% ethyl acetate, 1% acetic acid in petrol, yielded title compound **194** as a pale orange solid (6.44 g, 86%).

m.p. 96–98 °C

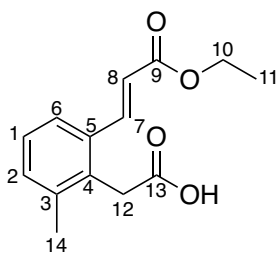
¹H NMR (500 MHz, CDCl₃) δ_H : 7.90 (d, J = 15.7 Hz, 1H, H7), 7.27 (t, J = 8.0 Hz, 1H, H1), 7.18 (d, J = 7.9 Hz, 1H, H6), 6.91 (d, J = 8.2 Hz, 1H, H2), 6.35 (d, J = 15.7 Hz, 1H, H8), 4.26 (q, J = 7.2 Hz, 2H, H10), 3.85 (s, 2H, H12), 3.83 (s, 3H, H15), 1.33 (t, J = 7.1 Hz, 3H, H11).

$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ_{C} : 177.3 (C13), 166.9 (C9), 158.0 (C3), 141.7 (C7), 135.5 (C5), 128.7 (C1), 122.3 (C4), 121.5 (C8), 119.1 (C6), 111.7 (C2), 60.8 (C10), 55.9 (C15), 31.5 (C12), 14.4 (C11).

FTIR (neat) ν/cm^{-1} = 2981, 1706, 1634, 1578, 1473, 1369, 1258, 1178, 1092, 1032, 976, 789, 731.

HRMS (m/z , ESI^+): calculated for $\text{C}_{14}\text{H}_{16}\text{NaO}_5$ ($[\text{M}+\text{Na}]^+$) = 287.0890, found = 287.0888.

(*E*)-2-(2-(3-Ethoxy-3-oxoprop-1-en-1-yl)-6-methylphenyl)acetic acid (AM-195)



This compound was prepared by Dr Aroonroj Mekareeya.

Prepared according to **General Procedure A** with 2-methylphenylacetic acid (2.00 g, 13.0 mmol), potassium bicarbonate (5.60 g, 56.0 mmol), (*S*)-*N*-acetylalanine (734 mg, 5.60 mmol), palladium acetate (629 mg, 2.80 mmol), and ethyl acrylate (2.5 mL, 26.0 mmol) in *tert*-amyl alcohol (50 mL). Purification by column chromatography, eluting with ethyl acetate, yielded title compound **AM-195** as a beige solid (1.70 g, 54%).

m.p. 124–125 °C

^1H NMR (500 MHz, CDCl_3) δ_{H} : 8.00 (d, J = 15.7 Hz, 1H, H7), 7.42 (dd, J = 6.9, 2.2 Hz, 1H, H6), 7.27–7.17 (m, 2H, H1 and H2), 6.33 (d, J = 15.7 Hz, 1H, H8), 4.26 (q, J = 7.2 Hz,

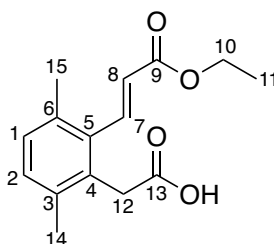
2H, H10), 3.84 (s, 2H, H12), 2.36 (s, 3H, H14), 1.33 (t, $J = 7.1$ Hz, 3H, H11).

$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ_{C} : 176.5 (C13), 167.0 (C9), 142.6 (C7), 138.2 (C3), 134.9 (C5), 132.1 (C2), 131.6 (C4), 127.9 (C1), 125.1 (C6), 121.3 (C8), 60.8 (C10), 34.8 (C12), 20.4 (C14), 14.4 (C11).

FTIR (neat) $\nu/\text{cm}^{-1} = 3071, 2987, 2942, 2873, 1706, 1690, 1633, 1590, 1472$.

HRMS (m/z , ESI $^+$): calculated for $\text{C}_{14}\text{H}_{16}\text{NaO}_4$ ($[\text{M}+\text{Na}]^+$) = 271.0940, found = 271.0941.

(*E*)-2-(2-(3-Ethoxy-3-oxoprop-1-en-1-yl)-3,6-dimethylphenyl)acetic acid
(AM-196)



This compound was prepared by Dr Aroonroj Mekareeya.

Prepared according to **General Procedure A** with (2,5-dimethylphenyl)acetic acid (2.00 g, 12.0 mmol), potassium bicarbonate (2.40 g, 24.0 mmol), (*S*)-*N*-acetylalanine (315 mg, 2.40 mmol), palladium acetate (269 mg, 1.20 mmol), and ethyl acrylate (2.4 mL, 24.0 mmol) in *tert*-amyl alcohol (50 mL). Purification by column chromatography, eluting with ethyl acetate, yielded title compound **AM-196** as a yellow oil (2.99 g, 95%).

^1H NMR (400 MHz, CDCl_3) δ_{H} : 7.88 (d, $J = 16.3$ Hz, 1H, H7), 7.23–7.05 (m, 2H, H1 and H2), 6.07 (d, $J = 16.3$ Hz, 1H, H8), 4.33 (q, $J = 7.2$ Hz, 2H, H10), 3.80 (s, 2H, H12), 2.35

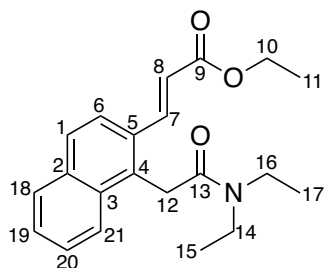
(s, 3H, H14), 2.32 (s, 3H, H15), 1.39 (t, $J = 7.1$ Hz, 3H, H11).

$^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ_{C} : 177.3 (C13), 166.5 (C9), 144.0 (C7), 135.8 (C5), 135.2 (C3), 134.0 (C6), 130.2 (C2), 130.2 (C4), 129.4 (C1), 125.3 (C8), 60.8 (C10), 36.2 (C12), 20.8 (C15), 20.0 (C14), 14.3 (C11).

FTIR (neat) $\nu/\text{cm}^{-1} = 3166, 2982, 2935, 2875, 1736, 1713, 1642, 1464$.

HRMS (m/z , ESI^+): calculated for $\text{C}_{15}\text{H}_{18}\text{NaO}_4$ ($[\text{M}+\text{Na}]^+$) = 285.1097, found = 285.1100.

Ethyl (*E*)-3-(1-(2-(diethylamino)-2-oxoethyl)naphthalen-2-yl)acrylate (197**)**



Prepared according to **General Procedure B** with acid **124** (2.50 g, 8.79 mmol), oxalyl chloride (3.6 mL, 17.6 mmol) and DMF (0.5 mL) in anhydrous dichloromethane (20 mL) followed by diethylamine (1.8 mL, 17.6 mmol) in anhydrous dichloromethane (20 mL). Purification by column chromatography, eluting with 10–20% ethyl acetate in petrol, yielded title compound **197** as a white solid (1.40 g, 47%).

m.p. 80–83 °C

^1H NMR (500 MHz, CDCl_3) δ_{H} : 8.11 (d, $J = 15.7$ Hz, 1H, H7), 7.95–7.90 (m, 1H, H21), 7.82 (d, $J = 7.7$ Hz, 1H, H18), 7.77 (d, $J = 8.6$ Hz, 1H, H1), 7.66 (d, $J = 8.6$ Hz, 1H, H6), 7.55–7.50 (m, 1H, H20), 7.50–7.46 (m, 1H, H19), 6.46 (d, $J = 15.7$ Hz, 1H, H8), 4.28 (q,

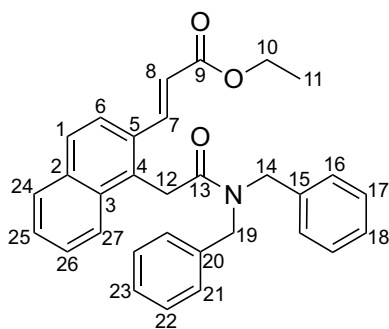
$J = 7.2$ Hz, 2H, H10), 4.27 (s, 2H, H12), 3.58 (q, $J = 7.1$ Hz, 2H, H14), 3.43 (q, $J = 7.1$ Hz, 2H, H16), 1.35 (t, $J = 7.2$ Hz, 3H, H15), 1.34 (t, $J = 7.2$ Hz, 3H, H11), 1.15 (t, $J = 7.1$ Hz, 3H, H17).

$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ_{C} : 168.9 (C13), 167.1 (C9), 142.6 (C7), 134.4 (C2), 133.2 (C3), 132.8 (C4), 131.6 (C5), 128.8 (C18), 128.1 (C1), 127.0 (C20), 126.7 (C19), 124.7 (C21), 123.8 (C6), 121.0 (C8), 60.7 (C10), 42.5 (C14), 40.8 (C16), 33.3 (C12), 14.6 (C15), 14.5 (C11), 13.2 (C17).

FTIR (neat) $\nu/\text{cm}^{-1} = 2080, 1708, 1640, 1457, 1426, 1381, 1297, 1257, 1176, 1155, 1137, 1089, 1039, 824$.

HRMS (m/z , ESI^+): calculated for $\text{C}_{21}\text{H}_{26}\text{NO}_3$ ($[\text{M}+\text{H}]^+$) = 340.1907, found = 340.1908.

Ethyl (*E*)-3-(1-(2-(dibenzylamino)-2-oxoethyl)naphthalen-2-yl)acrylate (198)



Prepared according to **General Procedure B** with acid **124** (2.20 g, 7.73 mmol), oxalyl chloride (3.1 mL 15.5 mmol) and DMF (0.5 mL) in anhydrous dichloromethane (20 mL) followed by dibenzylamine (3.0 mL, 15.5 mmol) in anhydrous dichloromethane (20 mL). Purification by column chromatography, eluting with 20% ethyl acetate in petrol, then

recrystallisation in hot ethyl acetate and washing with hexane yielded title compound **198** as a white solid (1.75 g, 49%).

m.p. 129–132 °C

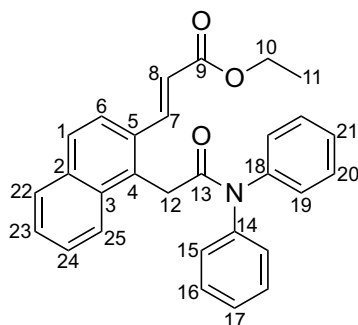
^1H NMR (500 MHz, CDCl_3) δ_{H} : 8.11 (d, J = 15.7 Hz, 1H, H7), 7.82 (dd, J = 7.1, 2.1 Hz, 1H, H24), 7.78 (d, J = 9.2 Hz, 1H, H27), 7.77 (d, J = 8.8 Hz, 1H, H1), 7.66 (d, J = 8.7 Hz, 1H, H6), 7.52–7.43 (m, 4H, H25, H26, and H22), 7.37 (t, J = 7.4 Hz, 1H, H23), 7.34–7.28 (m, 5H, H17, H18, and H21), 7.28–7.25 (m, 2H, H16), 6.47 (d, J = 15.7 Hz, 1H, H8), 4.72 (s, 2H, H19), 4.71 (s, 2H, H14), 4.34 (s, 2H, H12) 4.29 (q, J = 7.1 Hz, 2H, H10), 1.35 (t, J = 7.1 Hz, 3H, H11).

$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ_{C} : 170.7 (C13), 166.9 (C9), 142.4 (C7), 137.4 (C15), 136.6 (C20), 134.4 (C2), 133.0 (C3), 132.1 (C4), 131.9 (C5), 129.4 (C17), 128.9 (C24), 128.8 (C22), 128.6 (C16), 128.2 (C1), 128.0 (C23), 127.7 (C18), 127.0 (C26), 126.7 (C25), 126.6 (C21), 124.6 (C27), 123.9 (C6), 121.3 (C8), 60.7 (C10), 50.6 (C19), 49.3 (C14), 33.5 (C12), 14.5 (C11).

FTIR (neat) ν/cm^{-1} = 3026, 1709, 1649, 1495, 1448, 1418, 1364, 1299, 1260, 1241, 1177, 1038, 838, 812, 730, 699.

HRMS (m/z , ESI^+): calculated for $\text{C}_{31}\text{H}_{30}\text{NO}_3$ ($[\text{M}+\text{H}]^+$) = 464.2220, found = 464.2219.

Ethyl (*E*)-3-(1-(2-(diphenylamino)-2-oxoethyl)naphthalen-2-yl)acrylate (199**)**



Prepared according to **General Procedure B** with acid **124** (2.20 g, 7.73 mmol), oxalyl chloride (3.1 mL 15.5 mmol) and DMF (0.5 mL) in anhydrous dichloromethane (20 mL) followed by diphenylamine (2.60 g, 15.5 mmol) in anhydrous dichloromethane (20 mL). Purification by column chromatography eluting with 10% ethyl acetate in petrol yielded title compound **199** as a white solid (1.46 g, 43%).

m.p. 129–132 °C

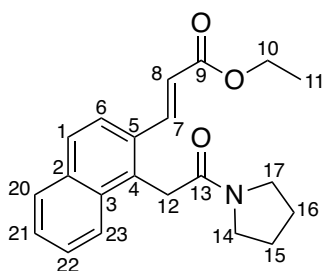
^1H NMR (500 MHz, CDCl_3) δ_{H} : 8.09 (d, J = 15.6 Hz, 1H, H7), 7.98 (d, J = 8.4 Hz, 1H, H25), 7.81 (dd, J = 8.1, 1.4 Hz, 1H, H22), 7.76 (d, J = 8.7 Hz, 1H, H1), 7.63 (d, J = 8.7 Hz, 1H, H6), 7.58–7.51 (m, 1H, H24), 7.52–7.46 (m, 1H, H23), 7.46–7.35 (m, 2H, *ArH*), 7.27 (d, J = 13.0 Hz, 5H, H16 and *ArH*), 7.21–7.15 (m, 1H, *ArH*), 7.14–7.10 (m, 1H, *ArH*), 6.84–6.77 (m, 1H, *ArH*), 6.46 (d, J = 15.7 Hz, 1H, H8), 4.31 (q, J = 7.1 Hz, 2H, H10), 4.19 (s, 2H, H12), 1.37 (t, J = 7.1 Hz, 3H, H11).

$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ_{C} : 170.3 (C13), 167.1 (C9), 142.6 (C7), 140.8 (C14), 140.0 (C18), 134.4 (C2), 132.9 (C3), 132.7 (C4), 131.8 (C5), 129.3 (*ArC*), 129.2 (*ArC*), 128.8 (C22), 128.6 (*ArC*), 128.3 (*ArC*), 128.2 (C1), 127.2 (*ArC*), 127.0 (C24), 126.7 (C23), 126.4 (*ArC*), 124.6 (C25), 123.8 (C6), 121.1 (C8), 60.7(C10), 35.7 (C12), 14.6 (C11).

FTIR (neat) ν/cm^{-1} = 3064, 1699, 1669, 1626, 1593, 1490, 1490, 1346, 1299, 1262, 1178, 913, 980, 822, 757, 693.

HRMS (m/z , ESI⁺): calculated for C₂₉H₂₅O₃NNa ([M+Na]⁺) = 458.1727, found = 458.1725.

Ethyl (*E*)-3-(1-(2-oxo-2-(pyrrolidin-1-yl)ethyl)naphthalen-2-yl)acrylate
(AM-200)



This compound was prepared by Dr Aroonroj Mekareeya.

Prepared according to **General Procedure C** with acid **124** (250 mg, 0.880 mmol), Mukaiyama's reagent (337 mg, 1.32 mmol) and pyrrolidine (220 μL , 2.64 mmol) in dichloromethane (6 mL). Purification by column chromatography, eluting with ethyl acetate, yielded title compound **AM-200** as an off-white solid (202 mg, 68%).

m.p. 110–112 °C

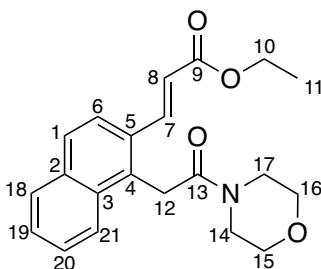
¹H NMR (500 MHz, CDCl₃) δ_H : 8.10 (d, J = 15.7 Hz, 1H, H7), 7.91 (d, J = 8.3 Hz, 1H, H23), 7.78 (d, J = 7.8 Hz, 1H, H20), 7.72 (d, J = 8.6 Hz, 1H, H1), 7.62 (d, J = 8.6 Hz, 1H, H6), 7.53–7.42 (m, 2H, H21 and H22), 6.45 (d, J = 15.6 Hz, 1H, H8), 4.27 (q, J = 7.1 Hz, 2H, H10), 4.12 (s, 2H, H12), 3.60 (t, J = 6.6 Hz, 2H, H14), 3.48 (t, J = 6.9 Hz, 2H, H17), 2.06–1.96 (m, 2H, H15), 1.91–1.81 (m, 2H, H16), 1.33 (t, J = 7.2 Hz, 3H, H11).

$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ_{C} : 168.1 (C13), 166.9 (C9), 142.5 (C7), 134.2 (C2), 132.9 (C3), 132.3 (C4), 131.3 (C5), 128.5 (C20), 127.9 (C1), 126.8 (C22), 126.5 (C21), 124.7 (C23), 123.6 (C6), 120.6 (C8), 60.4 (C10), 46.8 (C14), 46.0 (C17), 34.3 (C12), 26.2 (C15), 24.3 (C16), 14.3 (C11).

FTIR (neat) ν/cm^{-1} = 2983, 2965, 2878, 2161, 2033, 1978, 1704, 1628, 1424.

HRMS (m/z , ESI^+): calculated for $\text{C}_{21}\text{H}_{24}\text{NO}_3$ ($[\text{M}+\text{H}]^+$) = 338.1751, found = 338.1754.

Ethyl (*E*)-3-(1-(2-morpholino-2-oxoethyl)naphthalen-2-yl)acrylate (AM-201)



This compound was prepared by Dr Aroonroj Mekareeya.

Prepared according to **General Procedure C** with acid **124** (250 mg, 0.880 mmol), Mukaiyama's reagent (337 mg, 1.32 mmol) and morpholine (0.23 mL, 2.64 mmol) in dichloromethane (6 mL). Purification by column chromatography, eluting with ethyl acetate, yielded title compound **AM-201** as an off-white solid (203 mg, 65%).

m.p. 137–139 °C

^1H NMR (500 MHz, CDCl_3) δ_{H} : 8.08 (d, J = 15.7 Hz, 1H, H7), 7.92–7.85 (m, 1H, H21), 7.84 (dd, J = 7.5, 1.8 Hz, 1H, H18), 7.79 (d, J = 8.7 Hz, 1H, H1), 7.67 (d, J = 8.7 Hz, 1H, H6), 7.58–7.47 (m, 2H, H19 and H20), 6.48 (d, J = 15.7 Hz, 1H, H8), 4.31 (q, J = 7.1 Hz,

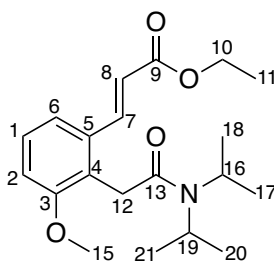
2H, H10), 4.22 (s, 2H, H12), 3.82–3.60 (m, 8H, H14, H15, H16, and H17), 1.38 (t, $J = 7.1$ Hz, 3H, H11).

$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ_{C} : 168.7 (C13), 167.0 (C9), 142.2 (C7), 134.3 (C2), 133.0 (C3), 132.1 (C4), 131.5 (C5), 128.8 (C18), 128.2 (C1), 127.1 (C20), 126.8 (C19), 124.5 (C21), 123.8 (C6), 121.1 (C8), 67.1 (C15 or C16), 66.8 (C15 or C16), 60.7 (C10), 46.3 (C14), 42.5 (C17), 32.6 (C12), 14.5 (C11).

FTIR (neat) $\nu/\text{cm}^{-1} = 2979, 2925, 2844, 2161, 2030, 1978, 1710, 1634, 1626, 1455, 1428$.

HRMS (m/z , ESI^+): calculated for $\text{C}_{21}\text{H}_{24}\text{NO}_4$ ($[\text{M}+\text{H}]^+$) = 354.1700, found = 354.1700.

Ethyl (*E*)-3-(2-(2-(diisopropylamino)-2-oxoethyl)-3-methoxyphenyl)acrylate
(202)



Prepared according to **General Procedure B** with acid **194** (3.00 g, 11.4 mmol), oxalyl chloride (4.6 mL, 22.7 mmol) and DMF (0.5 mL) in anhydrous dichloromethane (20 mL) followed by diisopropylamine (2.3 mL, 22.7 mmol) in anhydrous dichloromethane (20 mL). Purification by column chromatography, eluting with 10–20% ethyl acetate in petrol, yielded title compound **202** as a white solid (1.96 g, 50%).

m.p. 121–123 °C

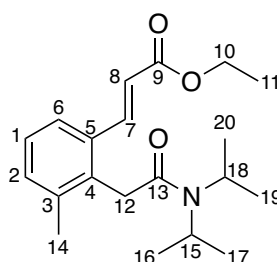
^1H NMR (500 MHz, CDCl_3) δ_H : 7.84 (d, J = 15.8 Hz, 1H, H7), 7.22 (t, J = 7.9 Hz, 1H, H1), 7.19 (d, J = 7.9 Hz, 1H, H6), 6.89 (d, J = 7.9 Hz, 1H, H2), 6.33 (d, J = 15.8 Hz, 1H, H8), 4.23 (q, J = 7.1 Hz, 2H, H10), 4.21–4.09 (m, 1H, H16), 3.81 (s, 3H, H15), 3.80 (s, 2H, H12), 3.51–3.47 (m, 1H, H19), 1.37 (d, J = 6.8 Hz, 6H, H20 and H21), 1.31 (t, J = 7.1 Hz, 3H, H11), 1.27 (d, J = 6.7 Hz, 6H, H17 and H18).

$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ_C : 169.2 (C13), 167.0 (C9), 157.7 (C3), 142.6 (C7), 135.7 (C5), 127.8 (C1), 125.4 (C4), 120.6 (C8), 119.1 (C6), 111.8 (C2), 60.5 (C10), 55.9 (C15), 48.7 (C16), 46.0 (C19), 32.2 (C12), 21.1 (C17 and C18), 20.8 (C20 and C21), 14.5 (C11).

FTIR (neat) ν/cm^{-1} = 2967, 1710, 1636, 1578, 1473, 1441, 1369, 1333, 1256, 1177, 1072, 1041, 980, 795.

HRMS (m/z , ESI^+): calculated for $\text{C}_{20}\text{H}_{29}\text{NNaO}_4$ ($[\text{M}+\text{Na}]^+$) = 370.1989, found = 370.1989.

Ethyl (*E*)-3-(2-(2-(diisopropylamino)-2-oxoethyl)-3-methylphenyl)acrylate
(AM-203)



This compound was prepared by Dr Aroonroj Mekareeya.

Prepared according to **General Procedure C** with **AM-195** (218 mg, 0.880 mmol),

Mukaiyama's reagent (337 mg, 1.32 mmol) and morpholine (0.23 mL, 2.64 mmol) in dichloromethane (6 mL). Purification by column chromatography, eluting with 40–100% ethyl acetate, in petrol yielded title compound **AM-203** as an off-white solid (216 mg, 74%).

m.p. 112–115 °C

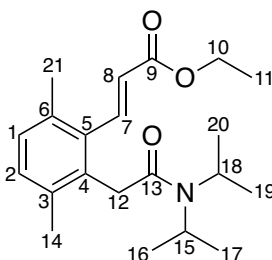
^1H NMR (400 MHz, CDCl_3) δ_{H} : 7.85 (d, J = 15.7 Hz, 1H, H7), 7.39 (dd, J = 7.4, 1.6 Hz, 1H, H6), 7.23–7.11 (m, 2H, H1 and H2), 6.29 (d, J = 15.7 Hz, 1H, H8), 4.23 (q, J = 7.1 Hz, 2H, H10), 4.16 (hept, J = 7.6 Hz, 1H, H15), 3.74 (s, 2H, H12), 3.47 (hept, J = 7.5 Hz, 1H, H18), 2.29 (s, 3H, H14), 1.39 (d, J = 6.8 Hz, 6H, H19 and H20), 1.35–1.27 (m, 9H, H11, H16 and H17).

$^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ_{C} : 168.2 (C13), 167.0 (C9), 143.3 (C7), 137.8 (C3), 134.8 (C4), 134.7 (C5), 131.9 (C2), 127.0 (C1), 124.9 (C6), 120.5 (C8), 60.5 (C10), 48.8 (C15), 46.2 (C18), 35.7 (C12), 21.1 (C16 and C17), 20.8 (C19 and C20), 20.4 (C14), 14.5 (C11).

FTIR (neat) ν/cm^{-1} = 2969, 2870, 2161, 2032, 1798, 1594, 1476, 1460, 1444.

HRMS (m/z , ESI^+): calculated for $\text{C}_{20}\text{H}_{29}\text{NNaO}_3$ ($[\text{M}+\text{Na}]^+$) = 354.2044, found = 354.2040.

Ethyl (*E*)-3-(2-(2-(diisopropylamino)-2-oxoethyl)-3,6-dimethylphenyl)acrylate
(AM-204)



This compound was prepared by Dr Aroonroj Mekareeya.

Prepared according to **General Procedure C** with **AM-196** (231 mg, 0.880 mmol), Mukaiyama's reagent (337 mg, 1.32 mmol) and diisopropylamine (0.36 mL, 2.64 mmol) in dichloromethane (6 mL). Purification by column chromatography, eluting with 20–40% ethyl acetate in petrol, yielded title compound **AM-204** as an off-white solid (258 mg, 85%).

m.p. 115–117 °C

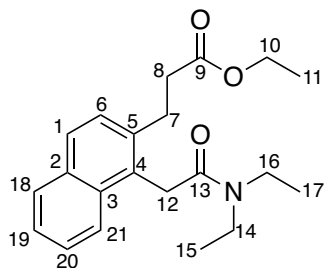
^1H NMR (400 MHz, CDCl_3) δ_{H} : 7.73 (d, $J = 16.3$ Hz, 1H, H7), 7.00 (d, $J = 7.7$ Hz, 1H, H2), 6.95 (d, $J = 7.8$ Hz, 1H, H1), 5.94 (d, $J = 16.3$ Hz, 1H, H8), 4.20 (q, $J = 7.1$ Hz, 2H, H10), 4.12–3.99 (m, 1H, H15), 3.54 (s, 2H, H12), 3.45–3.33 (m, 1H, H18), 2.21 (s, 3H, H21), 2.18 (s, 3H, H14), 1.38 (d, $J = 6.8$ Hz, 6H, H19 and H20), 1.26 (t, $J = 7.1$ Hz, 3H, H11), 1.19 (d, $J = 6.7$ Hz, 6H, H16 and H17).

$^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ_{C} : 168.3 (C13), 166.2 (C9), 144.0 (C7), 135.0 (C5 or C6), 134.9 (C5 or C6), 133.4 (C4), 132.8 (C3), 129.8 (C2), 128.2 (C1), 124.1 (C8), 60.1 (C10), 48.3 (C15), 45.7 (C19), 36.9 (C12), 20.6 (C16 and C17), 20.3 (C19, C20, and C21), 19.7 (C14), 14.1 (C11).

FTIR (neat) ν/cm^{-1} = 2970, 2923, 2161, 2031, 1978, 1710, 1644, 1439.

HRMS (m/z , ESI⁺): calculated for C₂₁H₃₁NNaO₃ ([M+Na]⁺) = 368.2201, found = 368.2202.

Ethyl 3-(1-(2-(diethylamino)-2-oxoethyl)naphthalen-2-yl)propanoate (205)



Prepared according to **General Procedure D** with acrylate **197** (1.35 g, 3.98 mmol) and Pd/C (135 mg, 10% w/w) in methanol (30 mL). Purification by column chromatography, eluting with 20% ethyl acetate in petrol, yielded title compound **205** as a white solid (1.10 g, 81%).

m.p. 69–71 °C

¹H NMR (500 MHz, CDCl₃) δ_H : 7.80 (d, J = 4.5 Hz, 1H, H21), 7.79 (d, J = 4.1 Hz, 1H, H18), 7.72 (d, J = 8.5 Hz, 1H, H1), 7.47 (dd, J = 8.5, 6.8 Hz, 1H, H20), 7.41 (dd, J = 8.0, 6.7, 1.1 Hz, 1H, H19), 7.34 (d, J = 8.4 Hz, 1H, H6), 4.17 (s, 2H, H12), 4.13 (q, J = 7.1 Hz, 2H, H10), 3.59 (q, J = 7.1 Hz, 2H, H14), 3.43 (q, J = 7.1 Hz, 2H, H16), 3.15–3.06 (m, 2H, H7), 2.73–2.60 (m, 2H, H8), 1.35 (t, J = 7.2 Hz, 3H, H15), 1.24 (t, J = 7.1 Hz, 3H, H11), 1.14 (t, J = 7.1 Hz, 3H, H17).

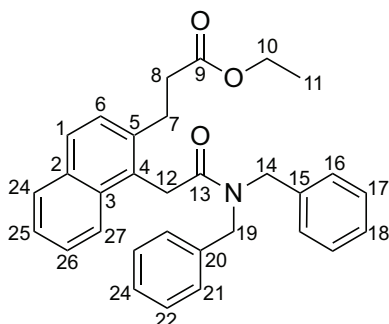
¹³C{¹H} NMR (126 MHz, CDCl₃) δ_C : 173.2 (C9), 169.6 (C13), 137.0 (C5), 133.3 (C3), 132.8 (C2), 129.6 (C4), 128.7 (C18), 127.8 (C1), 127.6 (C6), 126.4 (C20), 125.0 (C19),

123.8 (C21), 60.6 (C10), 42.5 (C14), 40.8 (C16), 35.7 (C8), 32.9 (C12), 29.4 (C7), 14.6 (C15), 14.4 (C11), 13.3 (C17).

FTIR (neat) ν/cm^{-1} = 2933, 1730, 1641, 1426, 1375, 1253, 1253, 1220, 1179, 1097, 1036, 860, 824, 787, 744.

HRMS (m/z , ESI⁺): calculated for C₂₁H₂₈NO₃ ([M+H]⁺) = 342.2064, found = 342.2064.

Ethyl 3-(1-(2-(dibenzylamino)-2-oxoethyl)naphthalen-2-yl)propanoate (206)



Prepared according to **General Procedure D** with acrylate **198** (1.70 g, 3.77 mmol) and Pd/C (170 mg, 10% w/w) in methanol (30 mL). Purification by filtration through celite yielded title compound **206** as a colourless semi-solid (1.74 g, 99%).

¹H NMR (500 MHz, CDCl₃) δ_H : 7.80 (d, J = 7.1 Hz, 1H, H24), 7.73 (d, J = 8.4 Hz, 1H, H1), 7.68 (d, J = 7.6 Hz, 1H, H27), 7.50–7.45 (m, 2H, H17), 7.45–7.41 (m, 2H, H25 and H26), 7.40–7.37 (m, 1H, H18), 7.37–7.32 (m, 5H, H6, H16, and H22), 7.32–7.27 (m, 3H, H21 and H24), 4.75 (s, 2H, H14), 4.73 (s, 2H, H19), 4.23 (s, 2H, H12), 4.14 (q, J = 7.1 Hz, 2H, H10), 3.12–3.02 (m, 2H, H7), 2.69–2.57 (m, 2H, H8), 1.25 (t, J = 7.1 Hz, 3H, H11).

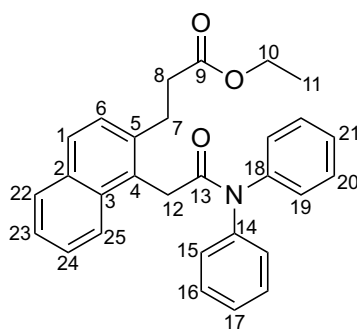
¹³C{¹H} NMR (126 MHz, CDCl₃) δ_C : 173.1 (C9), 171.2 (C13), 137.7 (C20), 137.3 (C5),

136.9 (C15), 133.2 (C3), 132.8 (C2), 129.3 (C17), 129.1 (C4), 128.8 (C22), 128.7 (C24), 128.7 (C21), 127.9 (C1 and C18), 127.7 (C24), 127.6 (C6), 126.6 (C16), 126.4 (C26), 125.0 (C25), 123.7 (C27), 60.6 (C10), 50.5 (C14), 49.4 (C19), 35.6 (C8), 33.2 (C12), 29.4 (C7), 14.4 (C11).

FTIR (neat) ν/cm^{-1} = 2980, 1729, 1650, 1417, 1369, 1206, 1030, 815, 738, 699.

HRMS (m/z , ESI⁺): calculated for C₃₁H₃₁O₃NNa ([M+Na]⁺) = 488.2196, found = 488.2190.

Ethyl 3-(1-(2-(diphenylamino)-2-oxoethyl)naphthalen-2-yl)propanoate (**207**)



Prepared according to **General Procedure D** with acrylate **199** (1.43 g, 3.28 mmol) and Pd/C (143 mg, 10% w/w) in methanol (20 mL). Purification by column chromatography, eluting with 20% ethyl acetate in petrol, yielded title compound **207** as a white solid (1.41 g, 98%).

m.p. 115–117 °C

¹H NMR (500 MHz, CDCl₃) δ_H : 7.87 (d, J = 8.5 Hz, 1H, H25), 7.79 (d, J = 8.1 Hz, 1H, H22), 7.70 (d, J = 8.4 Hz, 1H, H1), 7.50 (dd, J = 8.5, 6.8 Hz, 1H, H24), 7.45–7.39 (m, 4H, H20, H21, and H23), 7.31 (d, J = 8.4 Hz, 1H, H6), 7.25 (dd, J = 8.4, 6.9 Hz, 2H, H16),

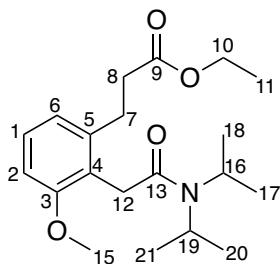
7.22–7.15 (m, 1H, H17), 7.15–7.10 (m, 2H, H19), 6.84–6.77 (m, 2H, H15), 4.14 (q, $J=7.2$ Hz, 2H, H10), 4.08 (s, 2H, H12), 3.13–3.05 (m, 2H, H7), 2.69–2.62 (m, 2H, H8), 1.25 (t, $J=7.1$ Hz, 3H, H11).

$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ_{C} : 173.2 (C9), 171.0 (C13), 140.8 (C14), 140.0 (C18), 137.4 (C5), 133.0 (C3), 132.8 (C2), 129.7 (C4), 129.3 (C20), 129.2 (C16), 128.8 (C22), 128.6 (C19), 128.3 (C21), 127.9 (C1), 127.7 (C6), 127.2 (C17), 126.4 (C24), 126.4 (C15), 125.1 (C23), 123.7 (C25), 60.6 (C10), 35.8 (C8), 35.7 (C12), 29.5 (C7), 14.4 (C11).

FTIR (neat) $\nu/\text{cm}^{-1} = 2981, 1727, 1671, 1593, 1490, 1452, 1349, 1255, 1176, 1073, 1033, 858, 823, 757, 694$.

HRMS (m/z , ESI^+): calculated for $\text{C}_{29}\text{H}_{28}\text{NO}_2$ ($[\text{M}+\text{H}]^+$) = 438.2064, found = 438.2064.

Ethyl 3-(2-(2-(diisopropylamino)-2-oxoethyl)-3-methoxyphenyl)propanoate
(208)



Prepared according to **General Procedure D** with acrylate **202** (1.93 g, 5.55 mmol) and Pd/C (193 mg, 10% w/w) in methanol (30 mL) to yield title compound **208** as a white solid without need for further purification (1.90 g, 99%).

m.p. 84–86 °C

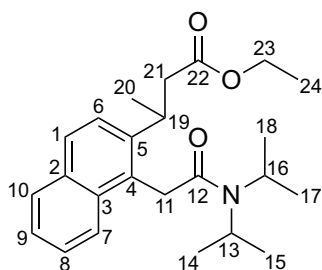
^1H NMR (500 MHz, CDCl_3) δ_{H} : 7.14 (t, J = 8.0 Hz, 1H, H1), 6.80 (d, J = 7.7 Hz, 1H, H6), 6.74 (d, J = 8.2 Hz, 1H, H2), 4.19 (hept, J = 6.7 Hz, 1H, H16), 4.12 (q, J = 7.1 Hz, 2H, H10), 3.77 (s, 3H, H15), 3.69 (s, 2H, H12), 3.50–3.44 (m, 1H, H19), 2.97–2.87 (m, 2H, H7), 2.62–2.53 (m, 2H, H8), 1.35 (d, J = 6.9 Hz, 6H, H20 and H21), 1.25 (d, J = 6.8 Hz, 6H, H17 and H18), 1.23 (t, J = 7.1 Hz, 3H, H11).

$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ_{C} : 173.3 (C9), 169.8 (13), 157.7 (C3), 140.8 (C5), 127.5 (C1), 123.9 (C4), 121.3 (C6), 108.7 (C2), 60.4 (C10), 55.7 (C15), 48.6 (C16), 45.9 (C19), 35.4 (C8), 32.3 (C12), 28.4 (C7), 21.0 (C17 and 18), 20.8 (C20 and 21), 14.3 (C11).

FTIR (neat) ν/cm^{-1} = 2968, 1725, 1644, 1583, 1435, 1372, 1335, 1282, 1257, 1192, 1159, 1086, 1044, 1026, 800, 775, 758.

HRMS (m/z , ESI^+): calculated for $\text{C}_{20}\text{H}_{32}\text{NO}_4$ ($[\text{M}+\text{H}]^+$) = 350.2326, found = 350.2322.

Ethyl 3-(1-(2-(diisopropylamino)-2-oxoethyl)naphthalen-2-yl)butanoate (**209**)



In a flame-dried two-necked flask under argon was added copper iodide (2.80 g, 14.7 mmol), sodium iodide (4.08 g, 27.2 mmol) and dimethyl sulphide (9.0 mL, 0.6 mL/mmol CuI) in anhydrous dichloromethane (30 mL). The solution was cooled to $-78\text{ }^\circ\text{C}$ and MeLi (8.5 mL, 1.6 M, 13.6 mmol) was added followed by TMSCl (3.45 mL, 27.2 mmol) and stirred for 20 min. Amide **126** (1.00 g, 2.72 mmol) in anhydrous dichloromethane (20 mL) was

added and the solution warmed to 0 °C and stirred for 9 h. The reaction was quenched with ammonium chloride and filtered. The organic layer was extracted with ethyl acetate and washed with sodium thiosulfate then brine before being dried with anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude was purified by column chromatography, eluting with 10% ethyl acetate in petrol, to yield title compound **209** as a white solid (631 mg, 61%).

m.p. 92–94 °C

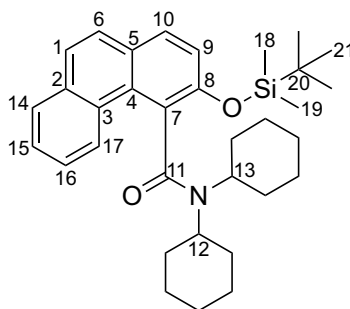
^1H NMR (500 MHz, CDCl_3) δ_{H} : 7.89 (d, J = 8.6 Hz, 1H, H7), 7.78 (d, J = 8.1 Hz, 1H, H10), 7.76 (d, J = 8.6 Hz, 1H, H1), 7.47 (ddd, J = 8.4, 6.8, 1.4 Hz, 1H, H8), 7.40 (ddd, J = 8.0, 6.8, 1.1 Hz, 1H, H9), 7.39 (d, J = 8.6 Hz, 1H, H6), 4.36 (hept, J = 6.7 Hz, 1H, H13), 4.28 (d, J = 16.7 Hz, 1H, H11a), 4.19 (d, J = 16.8 Hz, 1H, H11b), 4.07 (qd, J = 7.1, 2.1 Hz, 2H, H23), 3.63 (dp, J = 8.4, 6.7 Hz, 1H, H19), 3.48 (hept, J = 6.8 Hz, 1H, H16), 2.72 (dd, J = 15.5, 6.4 Hz, 1H, H21a), 2.61 (dd, J = 15.5, 8.4 Hz, 1H, H21b), 1.39 (d, J = 3.7 Hz, 3H, H17), 1.38 (d, J = 3.7 Hz, 3H, H18), 1.34 (d, J = 6.8 Hz, 3H, H20), 1.34 (d, J = 6.6 Hz, 6H, H14 and H15), 1.17 (t, J = 7.1 Hz, 3H, H24).

$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ_{C} : 172.7 (C22), 169.1 (C12), 141.5 (C5), 133.3 (C3), 132.6 (C2), 129.2 (C4), 128.6 (C10), 127.8 (C1), 126.2 (C8), 124.9 (C9), 124.2 (C7), 123.7 (C6), 60.4 (C23), 48.9 (C13), 46.1 (C16), 42.7 (C21), 34.4 (C11), 32.3 (C19), 21.5 (C20), 21.2 (C14 or C15), 21.1 (C14 or C15), 20.8 (C17 or C18), 20.8 (C17 or C18), 14.3 (C24).

FTIR (neat) ν/cm^{-1} = 2967, 1731, 1643, 1446, 1371, 1446, 1371, 1330, 1176, 1154, 1040, 820, 745.

HRMS (m/z , ESI⁺): calculated for C₂₄H₃₄NO₃ ([M+H]⁺) = 384.2533, found = 384.2541.

**3-((*Tert*-butyldimethylsilyl)oxy)-*N,N*-dicyclohexylphenanthrene-4-carboxamide
(210)**



Prepared according to **General Procedure G** with amide **131** (1.79 g, 3.98 mmol) and KHMDS (16 mL, 0.5 M, 7.97 mmol) in anhydrous THF (10 mL), followed by TBDMSCl (1.20 g, 7.97 mmol). Purification by column chromatography, eluting with 5–10% diethyl ether in petrol, yielded intermediate **267** as a white solid (1.21 g, 59%).

Then, according to **General Procedure H** with intermediate **267** (1.19 g, 2.30 mmol) and DDQ (657 mg, 2.99 mmol) in toluene (10 mL) for 30 min. Purification by column chromatography, eluting with 5–10% diethyl ether in petrol, yielded title compound **210** as a white solid (905 mg, 76%, combined yield = 45%).

m.p. 105–110 °C

¹H NMR (500 MHz, CDCl₃) δ_H : 9.03 (d, J = 8.9 Hz, 1H, H17), 7.81 (dd, J = 7.8, 1.5 Hz, 1H, H14), 7.73 (d, J = 8.7 Hz, 1H, H10), 7.63 (d, J = 8.8 Hz, 1H, H6), 7.59 (d, J = 8.7 Hz, 1H, H1), 7.53 (ddd, J = 7.9, 6.9, 1.2 Hz, 1H, H15), 7.48 (ddd, J = 8.5, 6.9, 1.6 Hz, 1H, H16), 7.18 (d, J = 8.6 Hz, 1H, H9), 3.21–3.03 (m, 1H, H13), 2.96–2.86 (m, 1H, H12),

2.02–1.94 (m, 1H, *HCy*), 1.97–1.86 (m, 2H, *HCy*), 1.86–1.74 (m, 3H, *HCy*), 1.73–1.66 (m 1H, *HCy*), 1.61–1.52 (m, 1H, *HCy*), 1.48–1.16 (m, 8H, *HCy*), 1.19–1.04 (m 1H, *HCy*), 1.06 (s, 9H, H21), 0.99–0.93 (m, 1H, *HCy*), 0.88–0.67 (m, 2H, *HCy*), 0.38 (s, 3H, H18), 0.27 (s, 3H, H19).

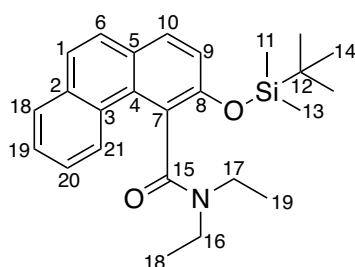
$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ_{C} : 170.3 (C11), 151.6 (C8), 133.2 (C2), 129.7 (C10), 129.5 (C3), 128.4 (C14), 128.2 (C4), 127.7 (C5), 127.6 (C17), 127.2 (C6), 126.7 (C15), 125.8 (C7), 125.6 (C1), 125.5 (C16), 120.0 (C9), 60.5 (C12), 56.5 (C13), 31.4 (*CCy*), 31.1 (*CCy*), 30.7 (*CCy*), 29.1 (*CCy*), 27.0 (*CCy*), 27.0 (*CCy*), 26.2 (C21), 25.8 (*CCy*), 25.6 (*CCy*), 25.5 (*CCy*), 25.2 (*CCy*), 18.8 (C20), –3.4 (C18), –3.9 (C19).

FTIR (neat) ν/cm^{-1} = 2929, 2855, 1627, 1503, 1453, 1290, 1229, 1098, 946, 839, 731.

HRMS (m/z , ESI^+): calculated for $\text{C}_{33}\text{H}_{46}\text{NO}_2\text{Si}$ ($[\text{M}+\text{H}]^+$) = 516.3292, found = 516.3291.

3-((*Tert*-butyldimethylsilyl)oxy)-*N,N*-diethylphenanthrene-4-carboxamide

(211)



Prepared according to **General Procedure G** with amide **205** (1.06 g, 3.10 mmol) and KHMDS (12.4 mL, 0.5 M, 6.21 mmol) in anhydrous THF (10 mL), followed by TBDMSCl (1.20 g, 7.97 mmol). Purification by column chromatography, eluting with 5–10% diethyl ether in petrol, yielded intermediate **268** as a white solid (284 mg, 22%).

Then, according to **General Procedure H** with intermediate **268** (236 mg, 0.576 mmol) and DDQ (170 mg, 0.749 mmol) in toluene (10 mL) for 40 min. Purification by column chromatography, eluting with 5–10% diethyl ether in petrol, yielded title compound **211** as a white solid (262 mg, 97%, combined yield = 21%).

m.p. 99–101 °C

^1H NMR (500 MHz, CDCl_3) δ_{H} : 8.74 (d, J = 8.6 Hz, 1H, H21), 7.84 (d, J = 7.9 Hz, 1H, H18), 7.77 (d, J = 8.6 Hz, 1H, H10), 7.65 (d, J = 8.7 Hz, 1H, H6), 7.61 (d, J = 8.7 Hz, 1H, H1), 7.55 (dd, J = 8.0, 6.8 Hz, 1H, H19), 7.49 (dd, J = 8.5, 6.9 Hz, 1H, H20), 7.18 (d, J = 8.6 Hz, 1H, H9), 4.15 (dq, J = 14.2, 7.2 Hz, 1H, H16a), 3.34 (dq, J = 14.2, 7.1 Hz, 1H, H16b), 3.02 (q, J = 7.2 Hz, 2H, H17), 1.43 (t, J = 7.1 Hz, 3H, H18), 1.04 (s, 9H, H14), 0.86 (t, J = 7.1 Hz, 3H, H19), 0.32 (s, 3H, H11), 0.31 (s, 3H, H13).

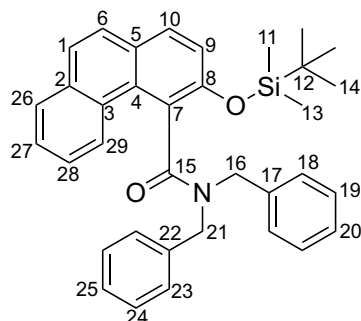
$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ_{C} : 170.4 (C14), 151.4 (C8), 133.4 (C2), 130.4 (C10), 129.4 (C3), 128.7 (C18), 128.4 (C4), 127.9 (C5), 127.3 (C6), 126.8 (C19), 126.3 (C21), 125.9 (C20), 125.8 (C1), 124.5 (C7), 119.4 (C9), 43.0 (C17), 39.3 (C16), 25.9 (C14), 18.4 (C12), 13.5 (C19), 12.2 (C18), -3.6 (C13), -4.2 (C11).

FTIR (neat) ν/cm^{-1} = 2930, 2857, 1632, 1596, 1521, 1503, 1454, 1325, 1276, 1233, 1089, 948, 840.

HRMS (m/z , ESI^+): calculated for $\text{C}_{25}\text{H}_{34}\text{NO}_2\text{Si}$ ($[\text{M}+\text{H}]^+$) = 408.2353, found 408.2353.

***N,N*-Dibenzyl-3-((tert-butyldimethylsilyl)oxy)phenanthrene-4-carboxamide**

(212)



Prepared according to **General Procedure G** with amide **206** (1.70 g, 3.65 mmol) and KHMDS (14.6 mL, 0.5 M, 7.30 mmol) in anhydrous THF (20 mL), followed by TBDMSCl (1.10 g, 7.30 mmol). Purification by column chromatography, eluting with 5% diethyl ether in petrol, yielded intermediate **269** as a white solid (1.38 g, 71%).

Then, according to **General Procedure H** with intermediate **269** (1.33 g, 2.49 mmol) and DDQ (712 mg, 3.24 mmol) in toluene (15 mL) for 30 min. Purification by column chromatography, eluting with 5% diethyl ether in petrol, yielded title compound **212** as a white solid (973 mg, 73%, combined yield = 52%).

m.p. 123–125 °C

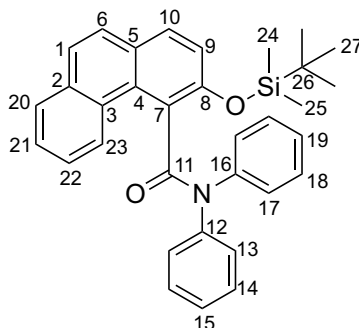
^1H NMR (500 MHz, CDCl_3) δ_{H} : 8.39 (d, J = 8.5 Hz, 1H, H29), 7.79 (d, J = 7.9 Hz, 1H, H26), 7.77 (d, J = 8.7 Hz, 1H, H10), 7.65–7.55 (m, 4H, H1, H6, and H18), 7.49–7.38 (m, 4H, H27, H19 and H20), 7.26–7.16 (m, 6H, H9, H23, H24, H25), 6.94 (ddd, J = 8.5, 6.9, 1.5 Hz, 1H, H28), 5.63 (d, J = 13.8 Hz, 1H, H16a), 4.27 (d, J = 15.5 Hz, 1H, H21a), 3.88 (d, J = 15.5 Hz, 1H, H21b), 3.86 (d, J = 13.8 Hz, 1H, H16b), 1.13 (s, 9H, H14), 0.39 (s, 3H, H13), 0.38 (s, 3H, H11).

$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ_{C} : 171.0 (C15), 151.6 (C8), 136.2 (C22), 135.8 (C17), 133.3 (C2), 130.7 (C18), 130.7 (C10), 129.2 (C3), 128.8 (C24 and C19), 128.7 (C26), 128.6 (C5), 128.6 (C23), 127.9 (C20), 127.9 (C4), 127.6 (C25), 127.2 (C1), 126.8 (C27), 126.3 (C28), 125.9 (C6), 125.7 (C29), 124.0 (C7), 120.2 (C9), 51.0 (C21), 46.6 (C16), 26.1 (C14), 18.6 (C12), -3.6 (C11), -4.2 (C13).

FTIR (neat) ν/cm^{-1} = 2929, 2857, 1636, 1595, 1502, 1471, 1452, 1412, 1325, 1273, 1215, 1098, 1077, 946, 840, 807, 784, 753, 734.

HRMS (m/z , ESI^+): calculated for $\text{C}_{35}\text{H}_{38}\text{O}_2\text{NSi}$ ($[\text{M}+\text{H}]^+$) = 532.2666, found = 532.2664.

**3-((*Tert*-butyldimethylsilyl)oxy)-*N,N*-diphenylphenanthrene-4-carboxamide
(213)**



Prepared according to **General Procedure G** with amide **207** (1.28 g, 2.92 mmol) and KHMDS (11.7 mL, 0.5 M, 5.87 mmol) in anhydrous THF (10 mL), followed by TBDMSCl (878 mg, 5.85 mmol). Purification by column chromatography, eluting with 5–10% diethyl ether in petrol, yielded intermediate **270** as a white solid (755 g, 51%).

Then, according to **General Procedure H** with intermediate **270** (736 mg, 1.46 mmol) and DDQ (416 mg, 1.89 mmol) in toluene (10 mL) for 30 min. Purification by column

chromatography, eluting with 5–10% diethyl ether in petrol, yielded title compound **213** as a white solid (653 mg, 89%, combined yield = 45%).

m.p. 53–55 °C

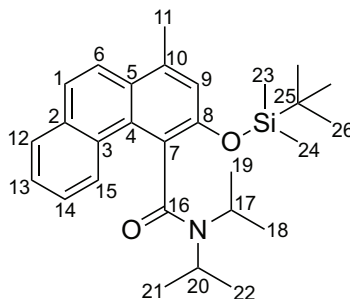
^1H NMR (500 MHz, CDCl_3) δ_{H} : 9.16 (dd, J = 8.4, 1.0 Hz, 1H, H23), 7.85 (dd, J = 7.8, 1.5 Hz, 1H, H20), 7.68 (ddd, J = 8.5, 6.9, 1.6 Hz, 1H, H22), 7.65–7.58 (m, 3H, H21 and H13), 7.56 (d, J = 8.6 Hz, 1H, H10), 7.51 (d, J = 8.7 Hz, 1H, H1), 7.46 (d, J = 8.7 Hz, 1H, H6), 7.43 (dd, J = 8.5, 7.4 Hz, 2H, H14), 7.26 (t, J = 7.4 Hz, 1H, H15), 7.01 (d, J = 8.6 Hz, 1H, H9), 6.87–6.82 (m, 2H, H17), 6.82–6.76 (m, 1H, H19), 6.76–6.69 (m, 2H, H18), 1.11 (s, 9H, H27), 0.38 (s, 3H, H24), 0.38 (s, 3H, H23).

$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ_{C} : 170.4 (C11), 151.6 (C8), 142.8 (C12), 142.3 (C16), 133.4 (C2), 130.5 (C10), 129.6 (C3), 129.1 (C14), 128.8 (C20), 128.5 (C4), 128.1 (C18), 127.4 (C5), 127.4 (C17), 127.3 (C19), 127.0 (C6), 126.9 (C21), 126.5 (C23), 126.3 (C13 and C15), 126.2 (C22), 125.5 (C1), 124.9 (C7), 119.1 (C9), 26.1 (C27), 18.6 (C26), –3.5 (C24), –3.9 (C25).

FTIR (neat) ν/cm^{-1} = 2954, 2857, 1664, 1595, 1492, 1453, 1326, 1277, 1094, 945, 839, 756, 698.

HRMS (m/z , ESI^+): calculated for $\text{C}_{33}\text{H}_{34}\text{NO}_2\text{Si}$ ($[\text{M}+\text{H}]^+$) = 504.2343, found = 504.2346.

3-((*Tert*-butyldimethylsilyl)oxy)-*N,N*-diisopropyl-1-methylphenanthrene-4-carboxamide (214**)**



Prepared according to **General Procedure G** with amide **209** (682 mg, 1.78 mmol) and KHMDS (7.1 mL, 0.5 M, 3.56 mmol) in anhydrous THF (5 mL), followed by TBDMSCl (536 mg, 3.56 mmol). Purification by column chromatography, eluting with 5% diethyl ether in petrol, yielded intermediate **271** as a white solid (181 mg, 23%).

Then, according to **General Procedure H** with intermediate **271** (200 mg, 0.458 mmol) and DDQ (135 mg, 0.595 mmol) in toluene (10 mL) for 30 min. Purification by column chromatography, eluting with 5–10% diethyl ether in petrol, yielded title compound **214** as a white solid (158 mg, 36%, combined yield = 8%).

m.p. 166–167 °C

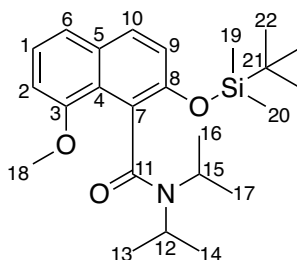
^1H NMR (400 MHz, CDCl_3) δ_{H} : 9.03 (d, J = 8.5 Hz, 1H, H15), 7.86 (d, J = 9.0 Hz, 1H, H6), 7.82 (d, J = 7.8 Hz, 1H, H12), 7.63 (d, J = 9.0 Hz, 1H, H1), 7.53 (t, J = 7.0 Hz, 1H, H13), 7.47 (dd, J = 8.5, 6.9 Hz, 1H, H14), 7.07 (s, 1H, H9), 3.56 (hept, J = 6.6 Hz, 1H, H20), 3.38 (hept, J = 6.7 Hz, 1H, H17), 2.72 (s, 3H, H11), 1.80 (d, J = 6.9 Hz, 3H, H21), 1.72 (d, J = 6.8 Hz, 3H, H22), 1.07 (s, 9H, H26), 0.99 (d, J = 6.7 Hz, 3H, H19), 0.54 (d, J = 6.7 Hz, 3H, H18), 0.40 (s, 3H, H23), 0.29 (s, 3H, H24).

$^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ_{C} : 170.3 (C16), 151.1 (C8), 135.9 (C10), 133.0 (C2), 129.9 (C3), 128.5 (C4), 128.3 (C12), 127.8 (C15), 126.6 (C13), 126.5 (C5), 125.5 (C1), 125.5 (C14), 124.0 (C7), 122.8 (C6), 121.7 (C9), 51.2 (C17), 46.2 (C20), 26.2 (C26), 21.8 (C22), 20.9 (C19), 20.8 (C11), 20.1 (C18), 19.3 (C21), 18.8 (C25), -3.4 (C23), -3.8 (C24).

FTIR (neat) ν/cm^{-1} = 2930, 1623, 1461, 1372, 1328, 1151, 834, 730.

HRMS (m/z , ESI^+): calculated for $\text{C}_{28}\text{H}_{40}\text{NO}_2\text{Si}$ ($[\text{M}+\text{H}]^+$) = 450.2823, found = 450.2814.

2-((*Tert*-butyldimethylsilyl)oxy)-*N,N*-diisopropyl-8-methoxy-1-naphthamide
(215)



Prepared according to **General Procedure G** with amide **208** (1.85 g, 5.29 mmol) and KHMDS (21.2 mL, 0.5 M, 10.6 mmol) in anhydrous THF (10 mL), followed by TBDMSCl (1.60 g, 10.6 mmol). Purification by column chromatography, eluting with 10% diethyl ether in petrol, yielded intermediate **272** as a white solid (1.22 g, 55%).

Then, according to **General Procedure H** with intermediate **272** (1.20 g, 2.87 mmol) and DDQ (486 mg, 2.21 mmol) in toluene (10 mL) for 30 min. Purification by column chromatography, eluting with 10% diethyl ether in petrol, yielded title compound **215** as a white solid (403 mg, 34%, combined yield = 19%).

m.p. 159–162 °C

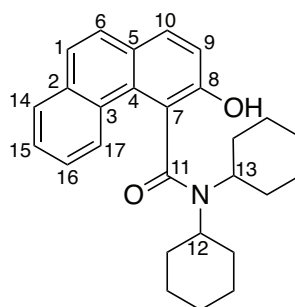
^1H NMR (500 MHz, CDCl_3) δ_{H} : 7.63 (d, J = 8.9 Hz, 1H, H10), 7.34 (d, J = 8.2 Hz, 1H, H6), 7.24 (t, J = 7.9 Hz, 1H, H1), 7.07 (d, J = 8.9 Hz, 1H, H9), 6.80 (d, J = 7.7 Hz, 1H, H2), 3.88 (s, 3H, H18), 3.54 (h, J = 6.7 Hz, 2H, H12 and H15), 1.64 (d, J = 6.8 Hz, 6H, H13 and H14), 1.07 (d, J = 6.6 Hz, 3H, H17), 1.01 (s, 9H H22), 0.93 (d, J = 6.7 Hz, 3H, H16), 0.33 (s, 3H, H20), 0.21 (s, 3H, H19).

$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ_{C} : 168.6 (C11), 155.3 (C3), 150.0 (C8), 130.8 (C5), 128.8 (C10), 124.1 (C1), 123.2 (C4), 122.7 (C7), 121.5 (C9), 120.8 (C6), 106.3 (C2), 55.4 (C18), 50.9 (C12), 45.7 (C15), 26.2 (C22), 21.7 (C13), 21.1 (C17), 20.4 (C14), 19.9 (C16), 18.8 (C21), -3.4 (C20), -3.8 (C19).

FTIR (neat) ν/cm^{-1} = 2929, 1630, 1461, 1313, 1255, 989, 830, 779.

HRMS (m/z , ESI^+): calculated for $\text{C}_{24}\text{H}_{33}\text{NO}_3\text{Si}$ ($[\text{M}+\text{H}]^+$) = 416.2616, found = 416.2624.

N,N-Dicyclohexyl-3-hydroxyphenanthrene-4-carboxamide (**221**)



Prepared according to **General Procedure J** with silylated naphthol **210** (960 mg, 1.86 mmol) and potassium fluoride (216 mg, 3.72 mmol) in methanol (20 mL). Purification

by trituration with ethyl acetate and washing with hexane yielded title compound **221** as a white solid (697 mg, 97%).

m.p. > 225 °C

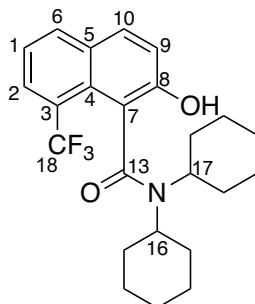
^1H NMR (500 MHz, CDCl_3) δ_{H} : 8.74 (d, J = 8.4 Hz, 1H, H17), 7.86 (d, J = 7.9 Hz, 1H, H14), 7.83 (s, 1H, OH), 7.64 (d, J = 8.7 Hz, 1H, H6), 7.62 (d, J = 8.5 Hz, 1H, H10), 7.60 (d, J = 8.7 Hz, 1H, H1), 7.57 (dd, J = 7.9, 6.8 Hz, 1H, H15), 7.50 (dd, J = 8.4, 6.9 Hz, 1H, H16), 7.13 (d, J = 8.5 Hz, 1H, H9), 3.15–3.05 (m, 1H, H12), 3.01–2.83 (m, 3H, H3 and H*Cy*), 2.05–1.85 (m, 3H, H*Cy*), 1.82–1.71 (m, 2H, H*Cy*), 1.70–1.63 (m, 1H, H*Cy*), 1.55–1.47 (m, 1H, H*Cy*), 1.47–1.28 (m, 3H, H*Cy*), 1.27–1.21 (m, 2H, H*Cy*), 1.21–1.06 (m, 2H, H*Cy*), 0.93–0.87 (m, 1H, H*Cy*), 0.85–0.72 (m, 1H, H*Cy*), 0.63–0.50 (m, 1H, H*Cy*), 0.29–0.17 (m, 1H, H*Cy*).

$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ_{C} : 171.8 (C11), 153.2 (C8), 133.2 (C2), 130.3 (C10), 128.9 (C3), 128.3 (C14), 127.8 (C4), 127.2 (C6), 127.1 (C17), 126.7 (C15), 126.5 (C5), 125.3 (C16), 124.7 (C1), 119.3 (C7), 118.0 (C9), 60.6 (C13), 56.8 (C12), 31.0 (C*Cy*), 29.9 (C*Cy*), 29.9 (C*Cy*), 28.7 (C*Cy*), 26.7 ($2 \times$ C*Cy*), 25.5 (C*Cy*), 25.5 (C*Cy*), 25.3 (C*Cy*), 25.0 (C*Cy*).

FTIR (neat) ν/cm^{-1} = 3138, 2927, 2849, 1611, 1590, 1573, 1509, 1472, 1283, 1230, 833, 714.

HRMS (m/z , ESI $^+$): calculated for $\text{C}_{27}\text{H}_{32}\text{NO}_2$ ($[\text{M}+\text{H}]^+$) = 402.2428, found = 402.2423.

***N,N*-Dicyclohexyl-2-hydroxy-8-(trifluoromethyl)-1-naphthamide (222)**



Prepared according to **General Procedure G** with **131** (2.28 g, 4.88 mmol) and KHMDS (19.5 mL, 0.5 M, 9.75 mmol) in anhydrous THF (20 mL), followed by TBDMSCl (1.46 g, 9.75 mmol). Purification by column chromatography, eluting with 5% diethyl ether in petrol, yielded intermediate **273** as a white solid (1.05 g, 40%)

Then, according to **General Procedure I** with intermediate **273** (1.00 g, 1.87 mmol) and *N*-bromosuccinamide (399 mg, 2.24 mmol) in benzene (10 mL). Purification by column chromatography eluting with 5–40% ethyl acetate in petrol then trituration with hexane and a small amount of dichloromethane yielded title compound **222** as a white solid (229 mg, 29%).

m.p. > 230 °C

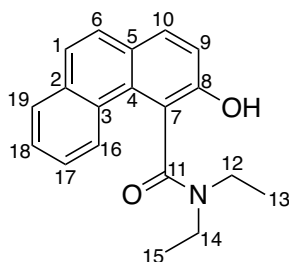
¹H NMR (400 MHz, CDCl₃) δ_H : 7.97–7.90 (m, 2H, C2 and C6), 7.68 (d, J = 8.8 Hz, 1H, H10), 7.65 (s, 1H, OH), 7.39 (t, J = 7.7 Hz, 1H, H1), 7.18 (d, J = 8.8 Hz, 1H, H9), 3.11–3.02 (m, 1H, H17), 2.85–2.74 (m, 1H, H_{Cy}), 2.73–2.61 (m, 1H, H16), 2.63–2.54 (m, 1H, H_{Cy}), 1.92–1.81 (m, 2H, H_{Cy}), 1.81–1.74 (m, 1H, H_{Cy}), 1.73–1.64 (m, 2H, H_{Cy}), 1.57–1.50 (m, 2H, H_{Cy}), 1.49–1.38 (m, 2H, H_{Cy}), 1.35–1.19 (m, 5H, H_{Cy}), 1.22–1.11 (m, 1H, H_{Cy}), 0.92–0.80 (m, 1H, H_{Cy}), 0.60–0.39 (m, 2H, H_{Cy}).

$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ_{C} : 169.1 (C13), 154.5 (C8), 134.0 (C6), 131.9 (C10), 129.5 (C5), 128.3 (q, $J = 6.9$ Hz, C2), 126.4 (C4), 125.4 (q, $J = 275.0$ Hz, C18), 123.8 (q, $J = 31.0$ Hz, C3), 122.1 (C1), 119.6 (C9), 117.1 (C7), 60.7 (C16), 57.0 (C17), 31.5 (CCy), 29.9 ($2 \times \text{CCy}$), 29.4 (CCy), 26.9 (CCy), 26.8 (CCy), 25.9 (CCy), 25.8 (CCy), 25.6 (CCy), 25.3 (CCy).

FTIR (neat) $\nu/\text{cm}^{-1} = 2981, 1597, 1512, 1444, 1381, 1299, 1129, 831$.

HRMS (m/z , ESI^+): calculated for $\text{C}_{24}\text{H}_{29}\text{F}_3\text{NO}_2$ ($[\text{M}+\text{H}]^+$) = 420.2145, found = 420.2142.

***N,N*-Diethyl-3-hydroxyphenanthrene-4-carboxamide (**223**)**



Prepared according to **General Procedure J** with silylated naphthol **211** (258 mg, 0.551 mmol) and potassium fluoride (64 mg, 1.10 mmol) in methanol (5.0 mL). Purification by trituration with ethyl acetate and washing with hexane yielded title compound **223** as a white solid (158 mg, 98%).

m.p. 210 °C

^1H NMR (500 MHz, CDCl_3) δ_{H} : 8.44 (d, $J = 8.4$ Hz, 1H, H16), 7.86 (d, $J = 7.9$ Hz, 1H, H19), 7.79 (d, $J = 8.6$ Hz, 1H, H10), 7.66 (d, $J = 8.7$ Hz, 1H, H6), 7.62 (d, $J = 8.7$ Hz, 1H, H1), 7.57 (dd, $J = 8.0, 6.9$ Hz, 1H, H18), 7.51–7.45 (1H, m, 1H, H17), 7.28 (d, $J = 8.6$ Hz, 1H, H9), 3.98 (dq, $J = 14.2, 7.1$ Hz, 1H, H12a), 3.43 (dq, $J = 13.4, 7.2$ Hz, 1H, H12b),

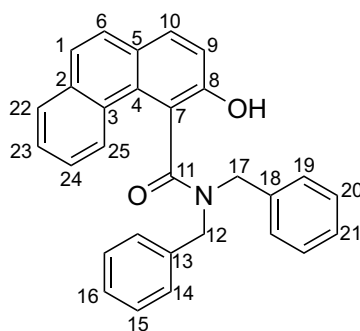
2.81 (dq, $J = 14.5, 7.2$ Hz, 1H, H14a), 2.62 (dq, $J = 14.2, 7.1$ Hz, 1H, H14b), 1.37 (t, $J = 7.1$ Hz, 3H, H13), 0.57 (t, $J = 7.2$ Hz, 3H, H15).

$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ_{C} : 171.3 (C11), 154.0 (C8), 133.4 (C2), 131.4 (C10), 128.9 (C3), 128.6 (C19), 128.1 (C4), 127.2 (C6 and 18), 126.9 (C5), 126.4 (C16), 125.8 (C17), 125.3 (C1), 117.9 (C9), 116.9 (C7), 43.2 (C14), 39.9 (C12), 13.1 (C15), 12.2 (C13).

FTIR (neat) $\nu/\text{cm}^{-1} = 2980, 1697, 1597, 1572, 1524, 1508, 1452, 1399, 1309, 1085, 837, 731$.

HRMS (m/z , EI^+): calculated for $\text{C}_{19}\text{H}_{19}\text{NO}_2$ ($[\text{M}]^+$) = 293.1416, found = 293.1412.

***N,N*-Dibenzyl-3-hydroxyphenanthrene-4-carboxamide (**224**)**



Prepared according to **General Procedure J** with silylated naphthol **212** (944 mg, 1.78 mmol) and potassium fluoride (206 mg, 3.55 mmol) in methanol (10 mL). Purification by trituration with ethyl acetate and washing with hexane yielded title compound **224** as a white solid (593 mg, 80%).

m.p. 215–217 °C

^1H NMR (500 MHz, CDCl_3) δ_{H} : 8.21 (d, $J = 8.4$ Hz, 1H, H25), 7.83 (s, 1H, OH), 7.81 (d, $J = 7.9$ Hz, 1H, H22), 7.69 (d, $J = 8.6$ Hz, 1H, H10), 7.59 (d, $J = 8.7$ Hz, 1H, H6), 7.58

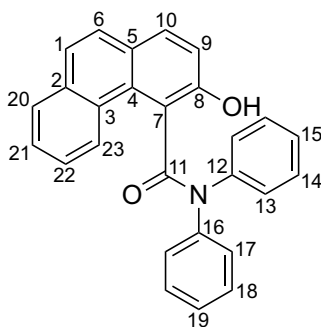
(d, J = 8.8 Hz, 1H, H1), 7.55–7.47 (m, 2H, H14), 7.49–7.45 (m, 1H, H23), 7.45–7.40 (m, 3H, H15 and H16), 7.24 (d, J = 8.6 Hz, 1H, H9), 7.21–7.09 (m, H20 and 3H, H21), 6.93 (dd, J = 8.4, 6.9 Hz, 1H, H24), 6.88–6.79 (m, 2H, H19), 5.51 (d, J = 13.9 Hz, 1H, H12a), 4.11 (d, J = 15.5 Hz, 1H, H17a), 4.01 (d, J = 13.9 Hz, 1H, H12b), 3.65 (d, J = 15.5 Hz, 1H, H17b).

$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ_{C} : 172.3 (C11), 154.2 (C8), 135.6 (C13), 135.5 (C18), 133.3 (C2), 131.8 (C10), 130.3 (C14), 129.0 (C15), 128.8 (C20), 128.8 (C3), 128.6 (C22), 128.3 (C4), 128.1 (C16), 128.0 (C19), 127.8 (C21), 127.2 (C6), 127.0 (C23), 127.0 (C5), 126.1 (C24), 125.9 (C25), 125.4 (C1), 118.2 (C9), 116.7 (C7), 51.3 (C17), 47.4 (C12).

FTIR (neat) ν/cm^{-1} = 3063, 2980, 1707, 1676, 1628, 1593, 1492, 1350, 1298, 1266, 1178, 1156, 1037, 823, 756, 728, 695.

HRMS (m/z , ESI^+): calculated for $\text{C}_{29}\text{H}_{24}\text{NO}_2$ ($[\text{M}+\text{H}]^+$) = 418.1802, found = 418.1801.

3-Hydroxy-*N,N*-diphenylphenanthrene-4-carboxamide (**225**)



Prepared according to **General Procedure J** with silylated naphthol **213** (600 mg, 1.18 mmol) and potassium fluoride (137 mg, 2.36 mmol) in methanol (10 mL). Purification

by trituration with ethyl acetate and washing with hexane yielded title compound **225** as a white solid (355 mg, 77%).

m.p. 215 °C

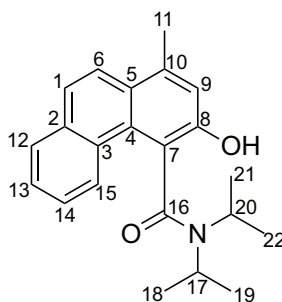
^1H NMR (500 MHz, CDCl_3) δ_{H} : 8.73 (d, J = 8.4 Hz, 1H, H23), 8.40 (s, 1H, OH), 7.73 (d, J = 7.9 Hz, 1H, H20), 7.71–7.63 (m, 1H, H22), 7.66 (d, J = 8.6 Hz, 1H, H10), 7.58 (dd, J = 8.0, 7.0 Hz, 1H, H21), 7.43 (d, J = 4.3 Hz, 4H, H17 and H18), 7.33 (s, 2H, H1 and H6), 7.31–7.26 (m, 1H, H19), 7.24 (d, J = 8.6 Hz, 1H, H9), 6.64–6.55 (m, 1H, H15), 6.51–6.44 (m, 2H, H14), 6.05–5.93 (m, 2H, H13).

$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ_{C} : 172.2 (C11), 156.3 (C8), 142.4 (C16), 141.6 (C12), 133.0 (C2), 132.4 (C10), 129.2 (C3), 129.2 (C17), 128.9 (C4), 128.1 (C20), 127.4 (C14), 127.1 (C23), 127.0 (C21), 126.7 (C19), 126.6 (C13), 126.3 (C5), 126.2 (C15), 126.0 (C6), 126.0 (C18), 125.3 (C22), 124.6 (C1), 117.1 (C9), 114.9 (C7).

FTIR (neat) ν/cm^{-1} = 3126, 2981, 1624, 1591, 1491, 1452, 1401, 1281, 1087, 944, 916, 833, 751, 699.

HRMS (m/z , ESI^+): calculated for $\text{C}_{27}\text{H}_{20}\text{NO}_2$ ($[\text{M}+\text{H}]^+$) = 390.1489, found = 390.1491.

3-Hydroxy-*N,N*-diisopropyl-1-methylphenanthrene-4-carboxamide (**226**)



Prepared according to **General Procedure J** with silylated naphthol **214** (213 mg, 0.490 mmol) and potassium fluoride (57 mg, 0.979 mmol) in methanol (5.0 mL). Purification by trituration with ethyl acetate and washing with hexane yielded title compound **226** as a white solid (57 mg, 36%).

m.p. > 200 °C

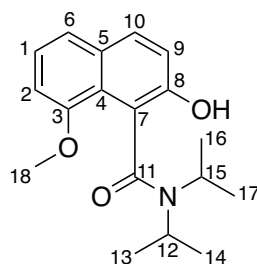
^1H NMR (500 MHz, CDCl_3) δ_{H} : 8.67–8.61 (m, 1H, H15), 7.86 (d, J = 7.9 Hz, 1H, H12), 7.84 (d, J = 9.0 Hz, 1H, H6), 7.64 (d, J = 9.0 Hz, 1H, H1), 7.56 (dd, J = 8.0, 6.9 Hz, 1H, H13), 7.52–7.44 (m, 1H, H14), 7.41 (s, 1H, OH), 7.05 (s, 1H, H9), 3.49 (hept, J = 6.8 Hz, 1H, H17), 3.30 (hept, J = 6.6 Hz, 1H, H20), 2.60 (s, 3H, H11), 1.77 (d, J = 6.8 Hz, 3H, H18), 1.68 (d, J = 6.8 Hz, 3H, H19), 0.82 (d, J = 6.7 Hz, 3H, H22), 0.39 (d, J = 6.7 Hz, 3H, H21).

$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ_{C} : 171.8 (C16), 153.0 (C8), 137.4 (C10), 133.1 (C2), 129.3 (C3), 128.4 (C4), 128.3 (C12), 127.7 (C15), 127.0 (C13), 125.6 (C5), 125.4 (C14), 124.8 (C1), 123.0 (C6), 119.4 (C9), 117.1 (C7), 51.4 (C20), 46.7 (C17), 21.3 (C19), 21.1 (C22), 20.2 (C11), 19.1 (C21), 19.0 (C18).

FTIR (neat) ν/cm^{-1} = 2973, 1581, 1525, 1506, 1461, 1369, 1340, 1311, 1287, 1208, 1160, 1107, 1062, 1031, 908, 863, 816, 744.

HRMS (m/z , ESI^+): calculated for $\text{C}_{22}\text{H}_{26}\text{NO}_2$ ($[\text{M}+\text{H}]^+$) = 336.1958, found = 336.1956.

2-Hydroxy-*N,N*-diisopropyl-8-methoxy-1-naphthamide (227)



Prepared according to **General Procedure J** with silylated naphthol **215** (380 mg, 0.916 mmol) and potassium fluoride (100 mg, 1.83 mmol) in methanol (5.0 mL). Purification by trituration with ethyl acetate and washing with hexane yielded title compound **227** as a white solid (120 mg, 44%).

m.p. > 230 °C

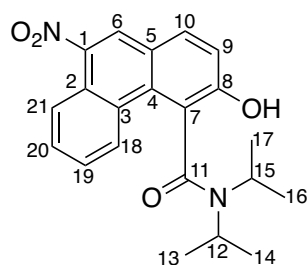
^1H NMR (700 MHz, CDCl_3) δ_{H} : 7.51 (s, 1H, OH), 7.39 (d, J = 8.7 Hz, 1H, H10), 7.30 (d, J = 8.1 Hz, 1H, H6), 7.21 (t, J = 7.9 Hz, 1H, H1), 6.89 (d, J = 8.8 Hz, 1H, H9), 6.79 (d, J = 7.5 Hz, 1H, H2), 3.90 (s, 3H, H18), 3.65 (hept, J = 6.7 Hz, 1H, H12), 3.53 (hept, J = 6.9 Hz, 1H, H15), 1.66 (d, J = 6.8 Hz, 3H, H17), 1.60 (d, J = 6.8 Hz, 3H, H16), 0.99 (d, J = 6.8 Hz, 6H, H13 and H14).

$^{13}\text{C}\{^1\text{H}\}$ NMR (176 MHz, CDCl_3) δ_{C} : 170.7 (C11), 154.6 (C3), 151.6 (C8), 130.0 (C5), 129.5 (C10), 123.5 (C1), 122.6 (C4), 121.0 (C6), 119.6 (C9), 116.9 (C7), 105.8 (C2), 55.3 (C18), 51.4 (C12), 46.1 (C15), 20.8 (C16), 20.7 (C14), 20.6 (C17), 19.6 (C13).

FTIR (neat) ν/cm^{-1} = 2977, 1575, 1516, 1430, 1366, 1340, 1215, 1215, 1115, 1050, 1030, 821, 738.

HRMS (m/z , ESI⁺): calculated for C₁₈H₂₄NO₃ ([M+H]⁺) = 302.1751, found = 302.1751.

3-Hydroxy-*N,N*-diisopropyl-9-nitrophenanthrene-4-carboxamide (**228**)



Phenanthrol **148** (200 mg, 0.622 mmol) and TBAB (20 mg, 0.0622 mmol) were dissolved in 1,2-dichloroethane (1.25 mL). 1 M Nitric acid (1.3 mL, 1.3 mmol) was added and the reaction was stirred vigorously at room temperature for 4 h. Saturated aqueous ammonium chloride was added and the organic layer was extracted with dichloromethane, dried with anhydrous sodium sulfate, filtered and concentrated under a stream of nitrogen. The crude was purified by column chromatography, eluting with 40% ethyl acetate in petrol, followed by trituration with ethyl acetate and washing with hexane to give title compound **228** as a yellow solid (110 mg, 44%).

m.p. > 225 °C

¹H NMR (500 MHz, CDCl₃) δ_H : 9.49 (s, 1H, OH), 8.80 (d, J = 8.8 Hz, 1H, H18), 8.56 (d, J = 8.5 Hz, 1H, H21), 8.43 (s, 1H, H6), 7.80–7.67 (m, 2H, H10 and H20), 7.60 (dd, J = 8.5, 7.0 Hz, 1H, H19), 7.21 (d, J = 8.6 Hz, 1H, H9), 3.52 (hept, J = 6.8 Hz, 1H, H12), 3.38

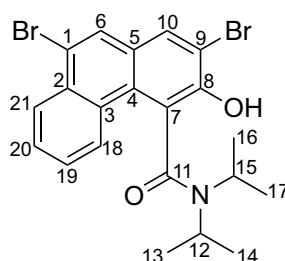
(hept, $J = 6.7$ Hz, 1H, H15), 1.78 (d, $J = 6.8$ Hz, 3H, H13), 1.52 (d, $J = 6.8$ Hz, 3H, H14), 0.75 (d, $J = 6.6$ Hz, 3H, H17), 0.60 (d, $J = 6.6$ Hz, 3H, H16).

$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ_{C} : 171.2 (C11), 157.5 (C8), 143.6 (C1), 132.8 (C10), 130.4 (C4), 129.8 (C3), 128.8 (C20), 127.2 (C18), 126.9 (C6), 126.8 (C19), 124.5 (C2), 123.9 (C21), 123.0 (C7), 119.6 (C9), 119.4 (C5), 52.0 (C15), 46.9 (C12), 20.7 (C14), 20.4 (C17), 19.8 (C16), 19.3 (C13).

FTIR (neat) $\nu/\text{cm}^{-1} = 2934, 1594, 1568, 1530, 1501, 1447, 1318, 1292, 1243, 900, 767$.

HRMS (m/z , ESI^+): calculated for $\text{C}_{21}\text{H}_{23}\text{N}_2\text{O}_4$ ($[\text{M}+\text{H}]^+$) = 367.1652, found = 367.1654.

2,9-Dibromo-3-hydroxy-*N,N*-diisopropylphenanthrene-4-carboxamide (**229**)



Bromine in acetic acid (650 μL , 1 M, 0.654 mmol) was added to a solution of **148** (100 mg, 0.311 mmol) in acetic acid (2.0 mL) and stirred for 1 h at reflux. The reaction was cooled to room temperature and ammonium chloride was added and the organic layer extracted with chloroform, dried with anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude was purified by column chromatography, eluting with 10–20% ethyl acetate in petrol, to afford title compound **229** as a white solid (95 mg, 64%)

m.p. 208–210 $^{\circ}\text{C}$

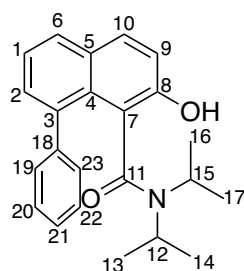
^1H NMR (500 MHz, CDCl_3) δ_{H} : 8.81 (dd, J = 8.5, 1.0 Hz, 1H, H18), 8.35 (dd, J = 8.3, 1.4 Hz, 1H, H21), 7.92 (s, 1H, H6), 7.87 (s, 1H, H10), 7.69 (ddd, J = 8.2, 7.0, 1.1 Hz, 1H, H20), 7.58 (ddd, J = 8.5, 7.0, 1.4 Hz, 1H, H19), 7.17–7.07 (s, 1H, OH), 3.60 (hept, J = 6.8 Hz, 1H, H12), 3.42 (hept, J = 6.7 Hz, 1H, H15), 1.80 (d, J = 6.9 Hz, 3H, H13), 1.71 (d, J = 6.8 Hz, 3H, H14), 1.00 (d, J = 6.6 Hz, 3H, H17), 0.65 (d, J = 6.6 Hz, 3H, H16).

$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ_{C} : 169.1 (C11), 148.8 (C8), 131.4 (C10), 131.2 (C2), 129.9 (C3), 129.5 (C6), 128.2 (C20), 128.1 (C5 and C21), 127.0 (C18), 126.9 (C4 and C19), 121.7 (C7), 120.8 (C1), 112.9 (C9), 51.6 (C15), 46.7 (C12), 20.6 (C14), 20.5 (C17), 19.9 (C16), 19.2 (C13).

FTIR (neat) ν/cm^{-1} = 2974, 1598, 1477, 1477, 1445, 1370, 1342, 1315, 1288, 1234, 1205, 932, 888, 754, 670, 624.

HRMS (m/z , ESI^+): calculated for $\text{C}_{21}\text{H}_{22}\text{Br}_2\text{NO}_2$ ($[\text{M}+\text{H}]^+$) = 478.0015, found = 478.0012.

2-Hydroxy-*N,N*-diisopropyl-8-phenyl-1-naphthamide (ASL-232)



This compound was prepared by Dr Antti Lahdenperä.

Prepared according to **General Procedure L** with **ASL-233** (163 mg, 0.430 mmol), LiHMDS (0.9 mL, 0.902 mmol) and $\text{Ir}(\text{fppy})_3$ (3.3 mg, 0.00430 mmol) in THF (4.9 mL).

Purification by trituration with ethyl acetate yielded title compound **ASL-232** as a white solid (100 mg, 67%).

m.p. 214–217 °C

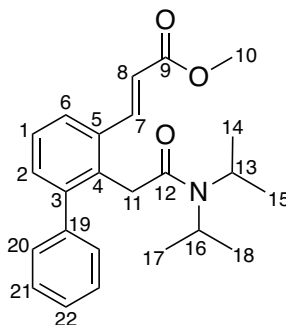
^1H NMR (500 MHz, CDCl_3) δ_{H} : 7.80 (d, J = 8.8 Hz, 1H, H10), 7.78–7.72 (m, 1H, H6), 7.63–7.57 (m, 2H, H23 and OH), 7.51 (brs, 1H, H19), 7.43–7.34 (m, 3H, H1, H2 and H20), 7.35–7.28 (m, 2H, H21 and H22), 7.25 (d, J = 8.9 Hz, 1H, H9), 3.23 (hept, J = 6.7 Hz, 1H, H12), 3.07 (hept, J = 6.8 Hz, 1H, H15), 1.39 (d, J = 6.7 Hz, 3H, H17), 0.86 (d, J = 6.6 Hz, 3H, H13), 0.62 (d, J = 6.7 Hz, 3H, H14), 0.58 (d, J = 6.9 Hz, 3H, H16).

$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ_{C} : 170.0 (C11), 154.0 (C8), 140.9 (C18), 138.2 (C3), 132.3 (br, C19), 131.9 (C2), 131.5 (C10), 129.5 (C5), 128.9 (br, C23), 128.4 (C6), 128.4 (C4), 128.3 (br, C20), 127.9 (br, C22), 127.7 (C21), 123.6 (C1), 118.8 (C9), 117.2 (C7), 50.7 (C12), 45.9 (C15), 21.3 (C14), 21.0 (C17), 19.5 (C16), 18.9 (C13).

FTIR (neat) ν/cm^{-1} = 3100, 3051, 2929, 2850, 1575, 1511, 1443, 1365, 1336, 1292, 833, 760, 700.

HRMS (m/z , ESI^+): calculated for $\text{C}_{23}\text{H}_{26}\text{NO}_2$ ($[\text{M}+\text{H}]^+$) = 348.1958, found = 348.1959.

Methyl (*E*)-3-(2-(2-(diisopropylamino)-2-oxoethyl)-[1,1'-biphenyl]-3-yl)acrylate
(ASL-233)



This compound was prepared by Dr Antti Lahdenperä.

Prepared according to **General Procedure K** with **105** (80 mg, 0.209 mmol), phenylboronic acid (28 mg, 0.230 mmol), sodium carbonate (67 mg, 0.627 mmol), palladium acetate (2.4 mg, 0.0100 mmol), and TBAB (51 mg, 0.209 mmol). Purification by column chromatography, eluting with 10–15% ethyl acetate in petrol, yielded title compound **ASL-233** as a white solid (61 mg, 77%).

m.p. 120–123 °C

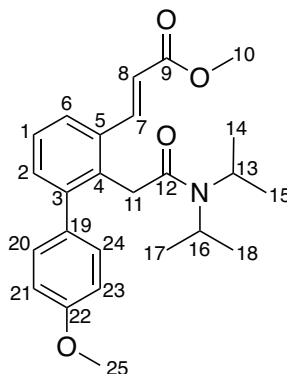
^1H NMR (400 MHz, CDCl_3) δ_{H} : 7.87 (d, J = 15.7 Hz, 1H, H7), 7.59 (dd, J = 7.6, 1.6 Hz, 1H, H6), 7.41–7.33 (m, 3H, H21 and H22), 7.32–7.29 (m, 3H, H1 and H20), 7.28 (dd, J = 7.6, 1.7 Hz, 1H, H2), 6.38 (d, J = 15.8 Hz, 1H, H8), 3.84 (hept, J = 6.7 Hz, 1H, H16), 3.78 (s, 3H, H10), 3.61 (s, 2H, H11), 3.39 (hept, J = 6.2 Hz, 1H, H13), 1.39 (d, J = 6.7 Hz, 6H, H14 and H15), 1.07 (d, J = 6.6 Hz, 6H, H17 and H18).

$^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ_{C} : 168.8 (C12), 167.5 (C9), 143.6 (C3 and C7), 141.7 (C19), 135.3 (C5), 133.8 (C4), 131.6 (C2), 129.3 (C20), 128.3 (C21), 127.3 (C22), 126.9 (C1), 126.1 (C6), 120.1 (C10), 51.7 (C10), 48.6 (C16), 46.1 (C13), 37.1 (C11), 20.8 (C17 and C18), 20.6 (C14 and C15).

FTIR (neat) ν/cm^{-1} = 3059, 2999, 2066, 1719, 1637, 1440, 1334, 1274, 1166, 1042, 763, 705.

HRMS (m/z , ESI^+): calculated for $\text{C}_{24}\text{H}_{29}\text{NNaO}_3$ ($[\text{M}+\text{Na}]^+$) = 402.2040, found = 402.2041.

Methyl (*E*)-3-(2-(2-(diisopropylamino)-2-oxoethyl)-4'-methoxy-[1,1'-biphenyl]-3-yl)acrylate (ASL-234)



This compound was prepared by Dr Antti Lahdenperä.

Prepared according to **General Procedure K** with **105** (150 mg, 0.392 mmol), *p*-methoxyphenylboronic acid (66 mg, 0.432 mmol), sodium carbonate (124 mg, 1.18 mmol), palladium acetate (4.4 mg, 0.0196 mmol), and TBAB (95 mg, 0.392 mmol). Purification by column chromatography, eluting with 10–15% ethyl acetate in petrol, yielded title compound **ASL-234** as a white solid (151 mg, 94%).

m.p. 119–121 °C

¹H NMR (400 MHz, CDCl₃) δ_H : 7.89 (d, J = 15.8 Hz, 1H, H7), 7.58 (dd, J = 7.1, 2.1 Hz, 1H, H6), 7.37–7.21 (m, 4H, H1, H2, H20 and H24), 6.94 (d, J = 8.7 Hz, 2H, H21 and H23), 6.40 (d, J = 15.8 Hz, 1H, H8), 3.97–3.86 (m, 1H, H16), 3.86 (s, 3H, H25), 3.80 (s, 3H, H10), 3.65 (s, 2H, H11), 3.52–3.33 (m, 1H, H13), 1.43 (d, J = 6.7 Hz, 6H, H14 and H15), 1.13 (d, J = 6.6 Hz, 6H, H17 and H18).

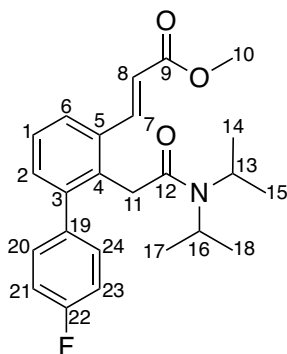
$^{13}\text{C}\{\text{H}\}$ NMR (101 MHz, CDCl_3) δ_{C} : 168.8 (C12), 167.3 (C9), 158.9 (C22), 143.5 (C7), 143.1 (C3), 135.1 (C5), 133.9 (C4 or C19), 133.9 (C4 or C19), 131.6 (C2), 130.3 (C20 and

C24), 126.7 (C1), 125.7 (C6), 119.9 (C8), 113.6 (C21 and 23), 55.3 (C25), 51.6 (C10), 48.5 (C16), 45.9 (C13), 37.0 (C11), 20.7 (C17 and C18), 20.5 (C14 and C15).

FTIR (neat) ν/cm^{-1} = 2998, 2965, 2933, 2837, 1717, 1634, 1610, 1513, 1442, 1244, 1213, 1166, 1038, 837, 729.

HRMS (m/z , ESI⁺): calculated for C₂₅H₃₂NO₄ ([M+H]⁺) = 410.2326, found = 410.2326.

Methyl (*E*)-3-(2-(2-(diisopropylamino)-2-oxoethyl)-4'-fluoro-[1,1'-biphenyl]-3-yl)acrylate (ASL-235)



This compound was prepared by Dr Antti Lahdenperä.

Prepared according to **General Procedure K** with **105** (100 mg, 0.262 mmol), *p*-fluorophenylboronic acid (41 mg, 0.288 mmol), sodium carbonate (83 mg, 0.785 mmol), palladium acetate (2.9 mg, 0.0130 mmol), and TBAB (63 mg, 0.262 mmol). Purification by column chromatography, eluting with 10–15% ethyl acetate in petrol, yielded title compound **ASL-235** as a white solid (96 mg, 93%).

m.p. 136–138 °C

¹H NMR (500 MHz, CDCl₃) δ_H : 7.85 (d, J = 15.8 Hz, 1H, H7), 7.58 (dd, J = 7.7, 1.4 Hz,

1H, H6), 7.34–7.27 (m, 3H, H1, H20 and H24), 7.25 (dd, J = 7.7, 1.4 Hz, 1H, H2), 7.07 (t, J = 8.7 Hz, 2H, H21 and H23), 6.38 (d, J = 15.7 Hz, 1H, H8), 3.87 (hept, J = 6.7 Hz, 1H, H16), 3.78 (s, 3H, H10), 3.58 (s, 2H, H11), 3.48–3.38 (m, 1H, H13), 1.39 (d, J = 6.8 Hz, 6H, H14 and H15), 1.11 (d, J = 6.7 Hz, 6H, H17 and H18).

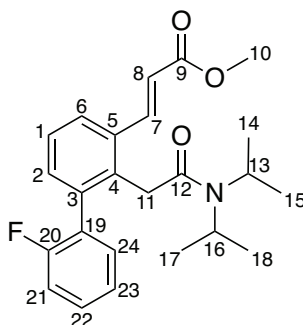
$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ_{C} : 168.7 (C12), 167.4 (C9), 162.4 (d, J = 246.2 Hz, C22), 143.3 (C7), 142.6 (C3), 137.6 (d, J = 3.3 Hz, C19), 135.3 (C5), 133.9 (C4), 131.6 (C2), 131.0 (d, J = 7.9 Hz, C20 and C24), 127.0 (C1), 126.3 (C6), 120.4 (C8), 115.1 (d, J = 21.1 Hz, C21 and C23), 51.8 (C10), 48.7 (C16), 46.1 (C13), 37.1 (C11), 20.9 (C17 and C18), 20.6 (C14 and C15).

^{19}F NMR (471 MHz, CDCl_3) δ_{F} : –115.4 (m, ArF)

FTIR (neat) ν/cm^{-1} = 2980, 2971, 2889, 1718, 1634, 1611, 1523, 1444, 1274, 1166, 823, 782, 728.

HRMS (m/z , ESI^+): calculated for $\text{C}_{24}\text{H}_{28}\text{FNNaO}_3$ ($[\text{M}+\text{Na}]^+$) = 420.1945, found = 420.1943.

Methyl (*E*)-3-(2-(2-(diisopropylamino)-2-oxoethyl)-2'-fluoro-[1,1'-biphenyl]-3-yl)acrylate (ASL-236)



This compound was prepared by Dr Antti Lahdenperä.

Prepared according to **General Procedure K** with **105** (150 mg, 0.392 mmol), *o*-fluorophenylboronic acid (60 mg, 0.432 mmol), sodium carbonate (125 mg, 1.18 mmol), palladium acetate (4.4 mg, 0.0200 mmol), and TBAB (95 mg, 0.392 mmol). Purification by column chromatography, eluting with 10–15% ethyl acetate in petrol, yielded title compound **ASL-236** as a white solid (116 mg, 74%).

m.p. 105–108 °C

^1H NMR (400 MHz, CDCl_3) δ_{H} : 7.87 (d, $J = 15.7$ Hz, 1H, H7), 7.58 (dd, $J = 7.6, 1.6$ Hz, 1H, H6), 7.36–7.20 (m, 4H, H1, H2, H22 and H24), 7.15–7.04 (m, 2H, H21 and H23), 6.35 (d, $J = 15.8$ Hz, 1H, H8), 3.87–3.75 (m, 1H, H13), 3.75 (s, 3H, H10), 3.67 (d, $J = 16.4$ Hz, 1H, H11a), 3.44 (d, $J = 16.5$ Hz, 1H, H11b), 3.31 (hept, $J = 6.4$ Hz, 1H, H16), 1.34–1.25 (m, 6H, H17 and H18), 1.17–1.05 (m, 3H, H14), 0.89 (d, $J = 6.6$ Hz, 3H, H15).

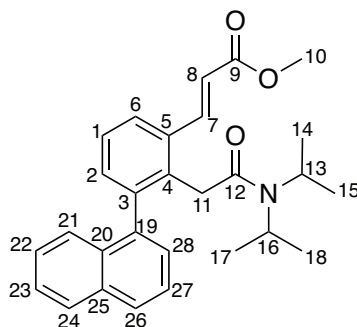
$^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ_{C} : 168.2 (C12), 167.3 (C9), 159.5 (d, $J = 245.7$ Hz, C20), 143.3 (C7), 136.9 (C3), 135.4 (C5), 134.6 (C4), 132.3 (d, $J = 3.2$ Hz, C22), 131.9 (C2), 129.5 (d, $J = 7.9$ Hz, C24), 128.6 (d, $J = 16.3$ Hz, C19), 126.8 (C1), 126.7 (C6), 124.1 (d, $J = 3.7$ Hz, C23), 120.2 (C8), 115.6 (d, $J = 22.2$ Hz, C21), 51.7 (C10), 48.5 (C13), 46.0 (C16), 36.8 (C11), 20.7 (C14), 20.5 (C15, C17 and C18).

^{19}F NMR (470 MHz, CDCl_3) δ_{F} : –114.8 (ddd, $J = 9.2, 7.7, 5.4$ Hz, *ArF*).

FTIR (neat) $\nu/\text{cm}^{-1} = 2999, 2965, 2929, 2873, 1718, 1635, 1440, 1370, 1276, 1166, 761, 729, 707$.

HRMS (m/z , ESI⁺): calculated for C₂₄H₂₈FNNaO₃ ([M+Na]⁺) = 420.1945, found = 420.1939.

Methyl (*E*)-3-(2-(2-(diisopropylamino)-2-oxoethyl)-3-(naphthalen-1-yl)phenyl)acrylate (ASL-237)



This compound was prepared by Dr Antti Lahdenperä.

Prepared according to **General Procedure K** with **105** (150 mg, 0.392 mmol), 1-naphthylboronic acid (74 mg, 0.432 mmol), sodium carbonate (125 mg, 1.18 mmol), palladium acetate (4.4 mg, 0.0200 mmol), and TBAB (95 mg, 0.392 mmol). Purification by column chromatography, eluting with 10–15% ethyl acetate in petrol, yielded title compound **ASL-237** as a white solid (128 mg, 76%).

m.p. 138 °C

¹H NMR (400 MHz, CDCl₃) δ_H : 7.93 (d, J = 15.8 Hz, 1H, H7), 7.87 (d, J = 8.4 Hz, 1H, H24), 7.85 (d, J = 8.0 Hz, 1H, H26), 7.70 (d, J = 7.7 Hz, 1H, H6), 7.55–7.43 (m, 3H, H21, H23 and H27), 7.40–7.33 (m, 3H, H1, H22 and H28), 7.29 (d, J = 7.5 Hz, 1H, H2), 6.46 (d, J = 15.8 Hz, 1H, H8), 3.79 (s, 3H, H10), 3.56 (d, J = 16.4 Hz, 1H, H11a), 3.54–3.47 (m, 1H, H16), 3.33 (d, J = 16.4 Hz, 1H, H11b), 3.26–3.19 (m, 1H, H13), 1.29 (d, J = 6.8 Hz,

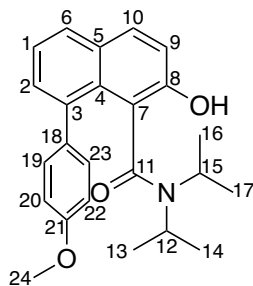
3H, H15), 1.20 (d, $J = 6.7$ Hz, 3H, H14), 0.82 (d, $J = 6.6$ Hz, 3H, H18), 0.72 (d, $J = 6.6$ Hz, 3H, H17).

$^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ_{C} : 168.2 (C12), 167.5 (C9), 143.6 (C7), 141.4 (C3), 138.8 (C19), 135.5 (C5), 135.2 (C4), 133.6 (C25), 132.2 (C2 and C20), 128.1 (C24), 127.8 (C22), 127.4 (C28), 126.8 (C1), 126.4 (C26 or C21), 126.4 (C26 or C21), 126.3 (C6), 125.9 (C23), 125.4 (C27), 119.8 (C8), 51.7 (C10), 48.2 (C16), 45.8 (C13), 36.5 (C11), 20.5 (C^iPr), 20.5 (C^iPr), 20.4 (C^iPr), 20.3 (C^iPr).

FTIR (neat) $\nu/\text{cm}^{-1} = 3057, 2999, 2965, 1716, 1635, 1442, 1333, 1314, 1275, 1165, 1165, 979, 799, 780, 728$.

HRMS (m/z , ESI^+): calculated for $\text{C}_{28}\text{H}_{31}\text{NNaO}_3$ ($[\text{M}+\text{Na}]^+$) = 452.2196, found = 452.2189.

2-Hydroxy-*N,N*-diisopropyl-8-(4-methoxyphenyl)-1-naphthamide (ASL-238)



This compound was prepared by Dr Antti Lahdenperä.

Prepared according to **General Procedure L** with **ASL-234** (59 mg, 0.144 mmol) and LiHMDS (0.3 mL, 0.300 mmol) in THF (4.9 mL). Purification by column chromatography, eluting with 10% diethyl ether in dichloromethane, yielded title compound **ASL-238** as a white solid (29 mg, 54%).

m.p. 230–233 °C

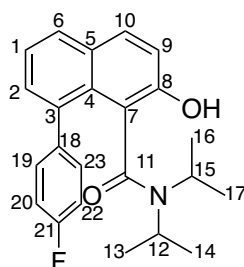
^1H NMR (500 MHz, CDCl_3) δ_{H} : 7.78 (d, J = 8.8 Hz, 1H, H10), 7.73 (dd, J = 7.0, 2.4 Hz, 1H, H6), 7.59 (s, 1H, OH), 7.49 (brs, 1H, H19), 7.44 (brs, 1H, H23), 7.40–7.32 (m, 2H, H1 and H2), 7.23 (d, J = 8.8 Hz, 1H, H9), 6.96 (brs, 1H, H20), 6.92–6.87 (brs, 1H, H22), 3.82 (s, 3H, H24), 3.22 (hept, J = 6.6 Hz, 1H, H12), 3.09 (hept, J = 6.5, 6.0 Hz, 1H, H15), 1.41 (d, J = 6.7 Hz, 3H, H16), 0.86 (d, J = 6.7 Hz, 3H, H13), 0.68 (d, J = 6.8 Hz, 3H, H17), 0.62 (d, J = 6.7 Hz, 3H, H14).

$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ_{C} : 170.2 (C11), 159.7 (C21), 153.8 (C8), 137.9 (C3), 133.4 (C18), 133.4 (br, C23), 131.4 (C2 and C10), 130.0 (br, C19), 129.6 (C5), 128.6 (C4), 128.0 (C6), 123.6 (C1), 118.8 (C9), 117.3 (C7), 114.8 (br, C20), 112.3 (br, C22), 55.6 (C24), 50.6 (C12), 45.9 (C15), 21.2 (C14), 21.0 (C16), 19.7 (C17), 18.9 (C13).

FTIR (neat) ν/cm^{-1} = 2957, 2921, 2851, 1589, 1504, 1463, 1442, 1337, 1296, 1171, 1035, 828, 718, 640.

HRMS (m/z , ESI^+): calculated for $\text{C}_{24}\text{H}_{28}\text{NO}_3$ ($[\text{M}+\text{H}]^+$) = 378.2064, found = 378.2070.

8-(4-Fluorophenyl)-2-hydroxy-*N,N*-diisopropyl-1-naphthamide (ASL-239)



This compound was prepared by Dr Antti Lahdenperä.

Prepared according to **General Procedure L** with **ASL-235** (95 mg, 0.239 mmol), LiHMDS (0.502 mL, 0.502 mmol), and Ir(fppy)₃ (1.8 mg, 0.0024 mmol) in THF (4.8 mL). Purification by column chromatography, eluting with 10% diethyl ether in dichloromethane, yielded title compound **ASL-239** as a white solid (52 mg, 59%).

m.p. 224–226 °C

¹H NMR (500 MHz, CDCl₃) δ_H : 7.80 (d, J = 8.8 Hz, 1H, H10), 7.76 (dd, J = 7.9, 1.6 Hz, 1H, H6), 7.55 (brs, 1H, H19), 7.48 (brs, 1H, H23), 7.44 (s, 1H, OH), 7.37 (t, J = 7.5 Hz, 1H, H1), 7.34 (dd, J = 7.1, 1.5 Hz, 1H, H2), 7.26 (d, J = 8.8 Hz, 1H, H9), 7.11 (brs, 1H, H20), 7.04 (brs, 1H, H22), 3.20 (hept, J = 6.7 Hz, 1H, H12), 3.11 (hept, J = 6.9 Hz, 1H, H15), 1.41 (d, J = 6.7 Hz, 3H, H16), 0.85 (d, J = 6.7 Hz, 3H, H13), 0.70 (d, J = 6.9 Hz, 3H, H17), 0.64 (d, J = 6.7 Hz, 3H, H14).

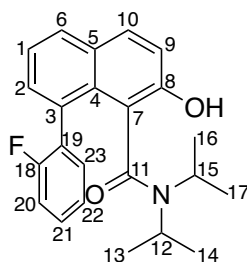
¹³C{¹H} NMR (126 MHz, CDCl₃) δ_C : 170.0 (C11), 162.9 (d, J = 246.6 Hz, C21), 153.9 (C10), 137.1 (C3), 136.9 (d, J = 3.3 Hz, C18), 134.0 (br, C23), 131.8 (C2), 131.5 (C10), 130.3 (br, C19), 129.5 (C5), 128.6 (C6), 128.3 (C4), 123.6 (C1), 118.9 (C9), 117.2 (C7), 115.1 (br, C20), 114.8 (br, C22), 50.7 (C12), 46.0 (C15), 21.2 (C14), 21.0 (C16), 19.5 (C17), 19.0 (C13).

¹⁹F NMR (470 MHz, CDCl₃) δ_F : -115.6 (tt, J = 8.7, 5.4 Hz, *ArF*).

FTIR (neat) ν/cm^{-1} = 3052, 2973, 2930, 1602, 1575, 1506, 1382, 1338, 1157, 828, 726.

HRMS (m/z , ESI⁺): calculated for C₂₃H₂₅FNO₂ ([M+H]⁺) = 366.1863, found = 366.1865.

8-(2-Fluorophenyl)-2-hydroxy-*N,N*-diisopropyl-1-naphthamide (ASL-240)



This compound was prepared by Dr Antti Lahdenperä.

Prepared according to **General Procedure L** with **ASL-236** (116 mg, 0.292 mmol) and LiHMDS (0.610 mL, 0.610 mmol) in THF (5.8 mL). Purification by column chromatography, eluting with 10% diethyl ether in dichloromethane, yielded title compound **ASL-240** as a 3:2 mixture of diastereomers (67 mg, 62%).

m.p. 238–240 °C

^1H NMR (500 MHz, CDCl_3) δ_{H} : 8.07 (s, 0.4H, OH min.), 7.92 (s, 1H, OH maj.), 7.74 (t, $J = 8.8$ Hz, 1H, *ArH*), 7.60 (d, $J = 8.8$ Hz, 0.6H, *ArH*), 7.50–7.40 (m, 1H, *ArH*), 7.43–7.31 (m, 2H, *ArH*), 7.34–7.22 (m, 1H, *ArH*), 7.19–7.04 (m, 2.6H, *ArH*), 6.92 (d, $J = 8.8$ Hz, 0.4H, *ArH*), 3.40–3.24 (m, 1H, H₁₂), 3.19–3.05 (m, 1H, H₁₅), 1.38–1.29 (m, 3H, H^{*i*}Pr), 0.93–0.81 (m, 3H, H^{*i*}Pr), 0.77 (d, $J = 6.6$ Hz, 1.2H, H^{*i*}Pr), 0.74–0.66 (m, 4.8H, H^{*i*}Pr).

$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ_{C} : 170.2 (C₁₁ maj.), 169.9 (C₁₁ min.), 161.5 (d, $J = 248.9$ Hz, C₁₈ min.), 159.7 (d, $J = 244.3$ Hz, C₁₈ maj.), 153.6 (C₈ maj.), 153.4 (C₈ min.), 153.4 (C₈ min.) 135.3 (*C_{Ar}*), 135.3 (*C_{Ar}*), 132.1 (*C_{Ar}*), 132.1 (*C_{Ar}*), 132.0 (*C_{Ar}*), 131.9 (*C_{Ar}*), 131.8 (*C_{Ar}*), 131.4 (*C_{Ar}*), 131.3 (*C_{Ar}*), 130.7 (*C_{Ar}*), 130.7 (*C_{Ar}*), 130.1 (*C_{Ar}*), 130.0 (*C_{Ar}*), 129.7 (*C_{Ar}*), 129.6 (*C_{Ar}*), 129.5 (*C_{Ar}*), 129.4 (*C_{Ar}*), 129.3 (*C_{Ar}*), 129.3 (*C_{Ar}*), 129.2 (*C_{Ar}*), 129.1 (*C_{Ar}*), 129.0 (*C_{Ar}*), 128.8 (*C_{Ar}*), 128.4 (*C_{Ar}*), 128.3 (*C_{Ar}*),

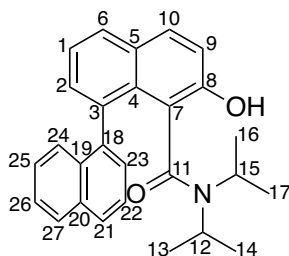
123.6 (CAr), 123.5 (CAr), 123.5 (CAr), 123.5 (CAr), 122.8 (CAr), 122.7 (CAr), 119.5 (CAr), 119.1 (CAr), 118.6 (CAr), 117.8 (CAr), 115.9 (CAr), 115.7 (CAr), 115.7 (CAr), 115.5 (CAr), 50.9 (C12 maj.), 50.8 (C12 min.), 46.0 (C15 min.), 46.0 (C15 maj.), 20.8 (CⁱPr maj.), 20.5 (CⁱPr maj.), 20.5 (CⁱPr maj.), 20.4 (CⁱPr maj.), 20.0 (CⁱPr min.), 19.7 (CⁱPr min.), 19.6 (CⁱPr min.), 19.6 (CⁱPr min.).

¹⁹F NMR (470 MHz, CDCl₃) δ_F : -108.1—108.3 (m, ArF min.), -114.5—114.7 (m, ArF maj.).

FTIR (neat) ν/cm^{-1} = 3054, 2971, 2924, 2753, 2657, 1600, 1573, 1512, 1445, 1365, 1337, 1297, 1209, 908, 831, 757, 728.

HRMS (m/z , ESI⁺): calculated for C₂₃H₂₅FNO₂ ([M+H]⁺) = 366.1864, found = 366.1865.

7-Hydroxy-*N,N*-diisopropyl-[1,1'-binaphthalene]-8-carboxamide (**ASL-241**)



This compound was prepared by Dr Antti Lahdenperä.

Prepared according to **General Procedure L** with **ASL-237** (110 mg, 0.151 mmol), LiHMDS (0.540 mL, 0.540 mmol) in THF (5.1 mL). Purification by column chromatography, eluting with 10% diethyl ether in dichloromethane, yielded title compound **ASL-241** as a 2:1 mixture of diastereomers (61 mg, 59%).

m.p. 225 °C

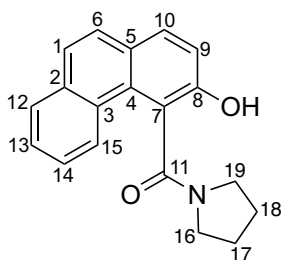
^1H NMR (500 MHz, CDCl_3) δ_{H} : 7.94–7.76 (m, 4H, *ArH*), 7.74 (d, J = 8.9 Hz, 0.33H, *ArH*), 7.64 (t, J = 8.5 Hz, 1.33H, *ArH*), 7.56–7.46 (m, 1H, *ArH*), 7.49–7.41 (m, 1H, *ArH*), 7.44–7.37 (m, 2H, *ArH*), 7.39–7.31 (m, 1H, *ArH*), 7.23 (t, J = 8.7 Hz, 0.33H, *ArH*), 7.12 (d, J = 9.0 Hz, 0.33H, *ArH*), 7.06 (d, J = 8.8 Hz, 0.67H, *ArH*), 3.41 (hept, J = 5.4 Hz, 0.33H, H^iPr min.), 3.23 (hept, J = 6.7 Hz, 0.67H, H^iPr maj.), 2.98 (hept, J = 6.6 Hz, 0.33H, H^iPr min.), 2.81 (hept, J = 6.1 Hz, 0.67H, H^iPr maj.), 1.26 (d, J = 6.7 Hz, 2H, H^iPr maj.), 1.13 (d, J = 6.7 Hz, 1H, H^iPr min.), 0.99 (d, J = 6.6 Hz, 1H, H^iPr min.), 0.72 (d, J = 6.6 Hz, 1H, H^iPr min.), 0.65 (d, J = 6.6 Hz, 2H, H^iPr maj.), 0.38 (d, J = 6.9 Hz, 1H H^iPr min.), 0.32 (d, J = 6.9 Hz, 2H H^iPr maj.), 0.01 (d, J = 6.6 Hz, 2H H^iPr maj.).

$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ_{C} : 170.2 (C11 maj.), 168.7 (C11 min.), 153.1 (C8 min.), 153.0 (C8 maj.), 139.9 (*C**Ar*), 137.0 (*C**Ar*), 136.6 (*C**Ar*), 135.3 (*C**Ar*), 134.2 (*C**Ar*), 133.7 (*C**Ar*), 133.4 (*C**Ar*), 132.8 (*C**Ar*), 132.7 (*C**Ar*), 132.2 (*C**Ar*), 131.5 (*C**Ar*), 131.2 (*C**Ar*), 131.1 (*C**Ar*), 130.2 (*C**Ar*), 129.9 (*C**Ar*), 129.7 (*C**Ar*), 129.1 (*C**Ar*), 129.0 (*C**Ar*), 128.8 (*C**Ar*), 128.7 (*C**Ar*), 128.5 (*C**Ar*), 128.0 (*C**Ar*), 127.9 (*C**Ar*), 127.7 (*C**Ar*), 126.8 (*C**Ar*), 126.0 (*C**Ar*), 125.9 (*C**Ar*), 125.6 (*C**Ar*), 125.5 (*C**Ar*), 125.4 (*C**Ar*), 124.9 (*C**Ar*), 123.3 (*C**Ar*), 122.7 (*C**Ar*), 119.2 (*C**Ar*), 119.1 (*C**Ar*), 119.1 (*C**Ar*), 119.0 (*C**Ar*), 50.7 (C14 maj.), 50.5 (C14 min.), 45.7 (C15 min.), 45.6 (C15 maj.), 20.7 (C^iPr min.), 20.6 (C^iPr maj.), 20.4 (C^iPr maj.), 20.4 (C^iPr maj.), 20.2 (C^iPr min.), 20.1 (C^iPr min.), 19.7 (C^iPr maj.), 19.6 (C^iPr min.).

FTIR (neat) ν/cm^{-1} = 3044, 2996, 2972, 2932, 1591, 1566, 1510, 1397, 1362, 1333, 1275, 833, 779.

HRMS (m/z , ESI^+): calculated for $\text{C}_{27}\text{H}_{28}\text{NO}_2$ ($[\text{M}+\text{H}]^+$) = 398.2115, found = 398.2115.

(3-Hydroxyphenanthren-4-yl)(pyrrolidin-1-yl)methanone (AM-242)



This compound was prepared by Dr Aroonroj Mekareeya.

Prepared according to **General Procedure L** with **AM-200** (101 mg, 0.151 mmol) and LiHMDS (0.320 mL, 0.320 mmol) in THF (3.0 mL). Purification by column chromatography, eluting with 50–100% ethyl acetate in petrol, yielded title compound **AM-242** as a white solid (60 mg, 69%).

m.p. 185–188 °C

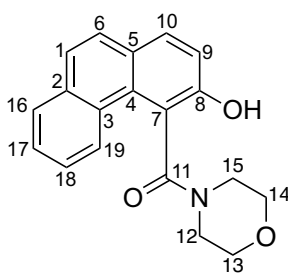
^1H NMR (500 MHz, CDCl_3) δ_{H} : 8.97 (s, 1H, OH), 8.41 (d, J = 8.4 Hz, 1H, H15), 7.86 (dd, J = 7.9, 1.4 Hz, 1H, H12), 7.63–7.58 (m, 3H, H1, H6, and H10), 7.57–7.53 (m, 1H, H13), 7.49 (ddd, J = 8.4, 6.9, 1.5 Hz, 1H, H14), 7.14 (d, J = 8.6 Hz, 1H, H9), 3.89–3.79 (m, 1H, H19a), 3.78–3.69 (m, 1H, H19b), 2.78–2.69 (m, 1H, H16a), 2.54–2.43 (m, 1H, H16b), 1.93–1.82 (m, 1H, H18a), 1.82–1.69 (m, 1H, H18b), 1.64–1.44 (m, 2H, H17).

$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ_{C} : 170.7 (C11), 154.6 (C8), 133.3 (C2), 131.5 (C10), 129.0 (C3), 128.7 (C12), 127.8 (C4), 127.3 (C6), 127.0 (C13), 126.6 (C5), 126.1 (C14), 125.1 (C15), 124.9 (C1), 117.9 (C9), 116.9 (C7), 47.7 (C16), 46.2 (C19), 25.7 (C17), 24.4 (C18).

FTIR (neat) ν/cm^{-1} = 3068, 2970, 2876, 2160, 2031, 1977, 1587, 1572, 1525, 1508, 1471, 1451, 1400.

HRMS (m/z , ESI⁺): calculated for C₁₉H₁₇NNaO₂ ([M+Na]⁺) = 314.1153, found = 314.1151.

(3-Hydroxyphenanthren-4-yl)(morpholino)methanone (AM-243)



This compound was prepared by Dr Aroonroj Mekareeya.

Prepared according to **General Procedure L** with **AM-201** (106 mg, 0.300 mmol) and LiHMDS (0.630 mL, 0.630 mmol) in THF (6.0 mL). Purification by column chromatography, eluting with 50–100% ethyl acetate in petrol, yielded title compound **AM-243** as a white solid (92 mg, 99%).

m.p. 215 °C (dec.)

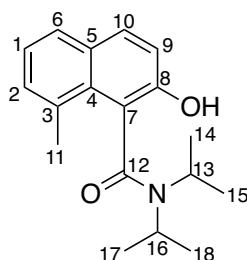
¹H NMR (400 MHz, CDCl₃) δ_H : 8.51 (s, 1H, OH), 8.42 (dd, J = 8.3, 1.2 Hz, 1H, H19), 7.86 (dd, J = 7.7, 1.6 Hz, 1H, H16), 7.62–7.55 (m, 4H, H1, H6, H10, and H17), 7.53 (ddd, J = 8.5, 7.0, 1.6 Hz, 1H, H18), 7.06 (d, J = 8.6 Hz, 1H, H9), 4.19–4.07 (m, 1H, H15a), 3.89–3.67 (m, 3H, H14 and 15b), 3.29–3.18 (m, 1H, H13a), 3.14–3.04 (m, 1H, H13b), 2.97–2.84 (m, 1H, H12a), 2.80–2.69 (m, 1H, H12b).

$^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ_{C} : 171.3 (C11), 154.3 (C8), 133.6 (C2), 131.6 (C10), 128.9 (C16), 128.7 (C3), 128.2 (C4), 127.2 (C17), 127.1 (C1), 126.6 (C5), 126.2 (C18), 125.8 (C19), 125.2 (C6), 117.9 (C9), 115.3 (C7), 66.3 (C14), 66.1 (C13), 46.9 (C12), 42.3 (C15).

FTIR (neat) ν/cm^{-1} = 3098, 2756, 2161, 2034, 1979, 1588, 1573, 1479, 1453, 1437, 1403.

HRMS (m/z , ESI^+): calculated for $\text{C}_{19}\text{H}_{17}\text{NNaO}_2$ ($[\text{M}+\text{Na}]^+$) = 314.1155, found = 314.1151.

2-Hydroxy-*N,N*-diisopropyl-8-methyl-1-naphthamide (AM-244)



This compound was prepared by Dr Aroonroj Mekareeya.

Prepared according to **General Procedure L** with **AM-203** (99 mg, 0.300 mmol) and LiHMDS (0.630 mL, 0.630 mmol) in THF (6.0 mL). Purification by column chromatography, eluting with 30–50% ethyl acetate in petrol, yielded title compound **AM-244** as a white solid (58 mg, 68%).

m.p. 204–206 °C

^1H NMR (500 MHz, CDCl_3) δ_{H} : 8.63 (s, 1H, OH), 7.51 (dd, J = 8.0, 1.5 Hz, 1H, H6), 7.29 (d, J = 8.9 Hz, 1H, H10), 7.21 (dt, J = 7.0, 1.3 Hz, 1H, H2), 7.15 (dd, J = 8.0, 7.0 Hz, 1H, H1), 6.73 (d, J = 8.8 Hz, 1H, H9), 3.69 (hept, J = 6.6 Hz, 1H, H16), 3.50 (hept, J =

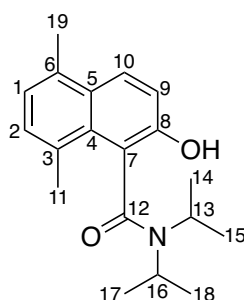
6.8 Hz, 1H, H13), 2.70 (s, 3H, H11), 1.61 (d, J = 6.8 Hz, 3H, H15), 1.49 (d, J = 6.8 Hz, 3H, H14), 1.01 (d, J = 6.6 Hz, 3H, H17), 0.93 (d, J = 6.5 Hz, 3H, H18).

$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ_{C} : 172.3 (C12), 152.8 (C8), 132.8 (C3), 130.7 (C10), 130.0 (C4), 129.4 (C5), 129.3 (C2), 127.2 (C6), 122.7 (C1), 118.8 (C9), 118.2 (C7), 51.7 (C16), 46.4 (C13), 22.1 (C11), 20.4 (C14 and C18), 19.7 (C15), 19.6 (C17).

FTIR (neat) ν/cm^{-1} = 3032, 2969, 2869, 2161, 2032, 1978, 1594, 1575, 1460, 1444, 1434.

HRMS (m/z , ESI^+): calculated for $\text{C}_{18}\text{H}_{23}\text{NNaO}_2$ ($[\text{M}+\text{Na}]^+$) = 308.1619, found = 308.1621.

2-Hydroxy-*N,N*-diisopropyl-5,8-dimethyl-1-naphthamide (AM-245)



This compound was prepared by Dr Aroonroj Mekareeya.

Prepared according to **General Procedure L** with **AM-204** (104 mg, 0.300 mmol) and LiHMDS (0.630 mL, 0.630 mmol) in THF (6.0 mL). Purification by column chromatography, eluting with 30–50% ethyl acetate in petrol, yielded title compound **AM-245** as an off-white solid (67 mg, 75%).

m.p. 224 °C (dec.)

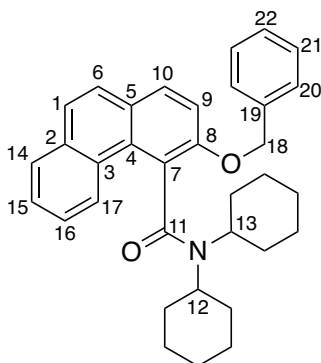
^1H NMR (500 MHz, CDCl_3) δ_{H} : 7.86 (s, 1H, OH), 7.51 (d, J = 9.1 Hz, 1H, H10), 7.13 (d, J = 7.1 Hz, 1H, H2), 7.04 (d, J = 7.1 Hz, 1H, H1), 6.80 (d, J = 9.1 Hz, 1H, H9), 3.61 (hept, J = 6.7 Hz, 1H, H16), 3.54 (hept, J = 6.8 Hz, 1H, H13), 2.69 (s, 3H, H11), 2.56 (s, 3H, H19), 1.62 (d, J = 6.9 Hz, 3H, H14), 1.57 (d, J = 6.7 Hz, 3H, H15), 1.02 (d, J = 6.7 Hz, 3H, H17), 0.98 (d, J = 6.6 Hz, 3H, H18).

$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ_{C} : 172.1 (C12), 152.1 (C8), 132.7 (C6), 131.1 (C3), 130.2 (C4), 129.3 (C2), 128.4 (C5), 126.6 (C10), 124.3 (C1), 119.3 (C7), 118.3 (C9), 51.6 (C16), 46.5 (C13), 22.1 (C11), 20.6 (C15 or C18), 20.6 (C15 or C18), 20.1 (C19), 19.7 (C14), 19.5 (C17).

FTIR (neat) ν/cm^{-1} = 3161, 2929, 2868, 2160, 2031, 1977, 1586, 1523, 1440, 1409.

HRMS (m/z , ESI^+): calculated for $\text{C}_{19}\text{H}_{25}\text{NNaO}_2$ ($[\text{M}+\text{Na}]^+$) = 322.1783, found = 322.1785.

3-(Benzyloxy)-*N,N*-dicyclohexylphenanthrene-4-carboxamide (**246**)



Asymmetric: Prepared according to **General Procedure N** with naphthol **221** (80 mg, 0.200 mmol), benzyl iodide (130 mg, 0.600 mmol), **186** (8.4 mg, 0.0100 mmol), and 50% w/w aqueous caesium carbonate (385 μL , 1.00 mmol) in benzene (20.0 mL). Purification

by column chromatography, eluting with 10–20% ethyl acetate in petrol, yielded title compound **246** as a white solid (85 mg, 87%, 98:2 e.r.).

Racemic: Prepared according to **General Procedure M** with naphthol **221** (30 mg, 0.0747 mmol), benzyl bromide (27 μ L, 0.224 mmol), TBAB (2.4 mg, 0.00747 mmol), and 50% w/w aqueous potassium hydroxide (28 μ L, 0.374 mmol) in toluene (750 μ L). Purification by column chromatography, eluting with 10–20% ethyl acetate in petrol, yielded title compound **246** as a white solid (35 mg, 95%).

m.p. 70–72 °C

^1H NMR (700 MHz, CDCl_3) δ_{H} : 9.01 (d, J = 8.5 Hz, 1H, H17), 7.83 (d, J = 8.1 Hz, 1H, H14), 7.82 (d, J = 8.4 Hz, 1H, H10), 7.65 (d, J = 8.7 Hz, 1H, H6), 7.60 (d, J = 8.7 Hz, 1H, H1), 7.59–7.52 (m, 1H, H15), 7.53–7.47 (m, 3H, H16 and H20), 7.37 (t, J = 7.5 Hz, 2H, H21), 7.35–7.29 (m, 2H, H9 and H22), 5.25 (d, J = 11.5 Hz, 1H, H18a), 5.16 (d, J = 11.5 Hz, 1H, H18b), 3.20–3.13 (m, 1H, H12), 3.11–3.05 (m, 1H, H13), 3.06–2.94 (m, 1H, H*Cy*), 2.82–2.73 (m, 1H, H*Cy*), 1.98–1.92 (m, 2H, H*Cy*), 1.80–1.74 (m, 1H, H*Cy*), 1.74–1.69 (m, 1H, H*Cy*), 1.70–1.63 (m, 1H, H*Cy*), 1.57–1.51 (m, 1H, H*Cy*), 1.48–1.41 (m, 1H, H*Cy*), 1.41–1.29 (m, 4H, H*Cy*), 1.30–1.18 (m, 4H, H*Cy*), 0.89–0.80 (m, 1H, H*Cy*), 0.81–0.71 (m, 1H, H*Cy*), 0.53–0.44 (m, 1H, H*Cy*).

$^{13}\text{C}\{^1\text{H}\}$ NMR (176 MHz, CDCl_3) δ_{C} : 170.0 (C11), 154.2 (C8), 137.0 (C19), 133.4 (C2), 130.2 (C10), 129.5 (C3), 128.6 (C14), 128.5 (C21), 128.2 (C5), 128.0 (C4), 128.0 (C22), 127.9 (C20), 127.3 (C6), 127.3 (C17), 126.9 (C15), 125.8 (C1), 125.7 (C16), 124.7 (C7), 114.0 (C9), 72.0 (C18), 60.5 (C12), 56.5 (C13), 31.0 ($2 \times \text{C*Cy*$), 29.9 (C*Cy*), 29.2 (C*Cy*), 27.0 (C*Cy*), 26.8 (C*Cy*), 25.8 (C*Cy*), 25.7 (C*Cy*), 25.6 (C*Cy*), 25.3 (C*Cy*).

FTIR (neat) ν/cm^{-1} = 2929, 2853, 1629, 1503, 1453, 1314, 1268, 1104, 997, 831, 733.

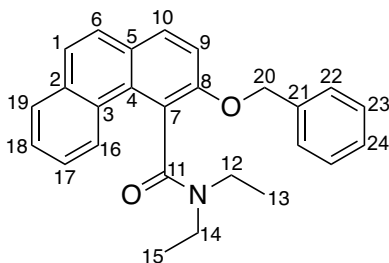
HRMS (m/z , ESI⁺): calculated for C₃₄H₃₈NO₂ ([M+H]⁺) = 492.2897, found = 492.2894.

$[\alpha]_D^{25}$ = -65.8° (98:2 e.r., c = 0.5, CHCl₃).

Chiral HPLC: (Chiralpak ADH, 30% isopropanol, 70% hexane, 1.0 mL/min, λ = 260 nm)

τ_R (major) = 6.8 min, τ_R (minor) = 10.9 min.

3-(Benzyloxy)-*N,N*-diethylphenanthrene-4-carboxamide (**247**)



Asymmetric: Prepared according to **General Procedure N** with naphthol **223** (59 mg, 0.200 mmol), benzyl iodide (130 mg, 0.600 mmol), **186** (8.4 mg, 0.0100 mmol), and 50% w/w aqueous caesium carbonate (385 μ L, 1.00 mmol) in benzene (20.0 mL). Purification by column chromatography, eluting with 10–20% ethyl acetate in petrol, yielded title compound **247** as a white solid (51 mg, 66%, 79:21 e.r.).

Racemic: Prepared according to **General Procedure M** with naphthol **223** (10 mg, 0.0340 mmol), benzyl bromide (12 μ L, 0.102 mmol), TBAB (1.1 mg, 0.00340 mmol), and 50% w/w aqueous potassium hydroxide (6 μ L, 0.170 mmol) in toluene (340 μ L). Purification by small-scale preparative TLC (30% ethyl acetate in petrol).

m.p. 112–115 °C

^1H NMR (500 MHz, CDCl_3) δ_{H} : 8.74 (d, $J = 8.4$ Hz, 1H, H16), 7.86 (d, $J = 8.5$ Hz, 1H, H10), 7.84 (d, $J = 8.6$ Hz, 1H, H19), 7.66 (d, $J = 8.8$ Hz, 1H, H6), 7.62 (d, $J = 8.8$ Hz, 1H, H1), 7.60–7.53 (m, 1H, H18), 7.52 (ddd, $J = 8.5, 6.8, 1.6$ Hz, 1H, H17), 7.49 (d, $J = 7.2$ Hz, 2H, H22), 7.42–7.34 (m, 3H, H9 and H23), 7.32 (t, $J = 7.3$ Hz, 1H, H24), 5.27 (d, $J = 11.7$ Hz, 1H, H20a), 5.21 (d, $J = 11.8$ Hz, 1H, H20b) 3.87–3.65 (m, 2H, H14), 3.15–3.01 (m, 2H, H12), 1.32 (t, $J = 7.1$ Hz, 3H, H15), 0.81 (t, $J = 7.2$ Hz, 3H, H13).

$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ_{C} : 170.3 (C11), 154.1 (C8), 137.0 (C21), 133.5 (C2), 130.8 (C10), 129.4 (C3), 128.8 (C19), 128.6 (C23), 128.2 (C4), 128.1 (C5), 128.0 (C24), 127.5 (C22), 127.2 (C6), 127.0 (C18), 126.2 (C17), 126.2 (C16), 126.0 (C1), 122.8 (C7), 113.7 (C9), 71.5 (C20), 43.1 (C12) 39.2 (C14), 13.6 (C13), 12.2 (C15).

FTIR (neat) $\nu/\text{cm}^{-1} = 2975, 1629, 1503, 1453, 1271, 1114, 834, 741$.

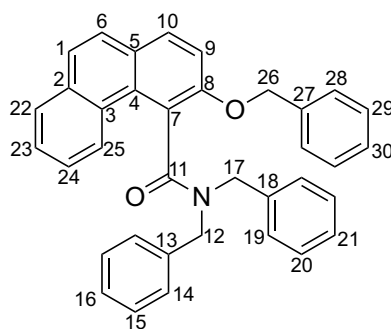
HRMS (m/z , ESI^+): calculated for $\text{C}_{26}\text{H}_{26}\text{NO}_2$ ($[\text{M}+\text{H}]^+$) = 384.1958, found = 384.1954.

$[\alpha]_D^{25} = -77.8^\circ$ (79:21 e.r., $c = 0.5$, CHCl_3).

Chiral HPLC: (Chiralpak ODH, 30% isopropanol, 70% hexane, 1.0 mL/min, $\lambda = 260$ nm)

τ_{R} (major) = 9.4 min, τ_{R} (minor) = 16.8 min.

***N,N*-Dibenzyl-3-(benzyloxy)phenanthrene-4-carboxamide (248)**



Asymmetric: Prepared according to **General Procedure N** with naphthol **224** (84 mg, 0.200 mmol), benzyl iodide (130 mg, 0.600 mmol), **186** (8.4 mg, 0.0100 mmol), and 50% w/w aqueous caesium carbonate (385 μ L, 1.00 mmol) in benzene (20.0 mL). Purification by column chromatography, eluting with 10–20% ethyl acetate in petrol, yielded title compound **248** as a white solid (23 mg, 27%, 74:26 e.r.).

Racemic: Prepared according to **General Procedure M** with naphthol **224** (84 mg, 0.200 mmol), benzyl bromide (71 μ L, 0.600 mmol), TBAB (6.5 mg, 0.0200 mmol), and 50% w/w aqueous potassium hydroxide (37 μ L, 1.00 mmol) in toluene (2.0 mL). Purification by column chromatography, eluting with 10–20% ethyl acetate in petrol, yielded title compound **248** as a white solid (92 mg, 91%).

m.p. 49–51 °C

^1H NMR (500 MHz, CDCl_3) δ_{H} : 8.64 (d, J = 8.5 Hz, 1H, H25), 7.85 (d, J = 7.8 Hz, 1H, H22), 7.84 (d, J = 8.8 Hz, 1H, H10), 7.64 (d, J = 8.7 Hz, 1H, H6), 7.62 (d, J = 8.8 Hz, 1H, H1), 7.60–7.55 (m, 3H, H21 and H28), 7.55–7.50 (m, 2H, H14), 7.46 (t, J = 7.5 Hz, 2H, H29), 7.42–7.38 (m, 1H, H30), 7.38–7.31 (m, 4H, H9, H15 and H16), 7.22 (dd, J = 8.5, 7.0 Hz, 1H, H24), 7.12 (t, J = 7.4 Hz, 1H, H23), 7.04 (t, J = 7.6 Hz, 2H, H20), 6.90 (d, J = 7.5 Hz, 2H, H19), 5.35 (d, J = 12.0 Hz, 1H, H26a), 5.24 (d, J = 12.0 Hz, 1H, H26b), 5.06 (d, J = 14.2 Hz, 1H, H12a), 4.74 (d, J = 14.1 Hz, 1H, H12b), 4.24 (d, J = 15.6 Hz, 1H, H17a), 4.18–4.12 (m, 1H, H17b).

$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ_{C} : 171.3 (C11), 154.2 (C8), 136.9 (C27), 136.0 (C13), 135.7 (C18), 133.5 (C2), 131.0 (C10), 130.0 (C14), 129.2 (C3), 128.8 (C22), 128.7 (C29), 128.6 (C15), 128.4 (C19), 128.3 (C20), 128.3 (C4), 128.1 (C30), 128.0 (C5), 127.6 (C16), 127.5 (C28), 127.4 (C21), 127.1 (C6), 127.0 (C23), 126.4 (C24), 126.0 (C1), 126.0 (C25),

121.9 (C7), 113.8 (C9), 71.5 (C26), 51.3 (C17), 46.9 (C12).

FTIR (neat) ν/cm^{-1} = 3030, 2918, 1631, 1502, 1452, 1267, 1216, 1103, 831, 736, 696.

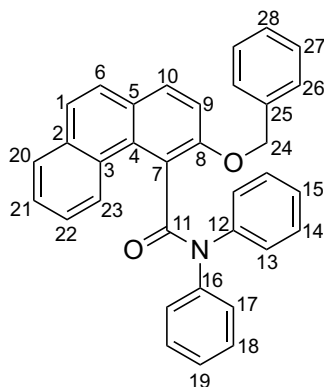
HRMS (m/z , ESI⁺): calculated for C₃₆H₃₀NO₂ ([M+H]⁺) = 508.2271, found = 508.2271.

$[\alpha]_D^{25}$ = -37.6° (74:26 e.r., c = 0.5, CHCl₃).

Chiral HPLC: (Chiralpak ODH, 30% isopropanol, 70% hexane, 1.0 mL/min, λ = 260 nm)

τ_R (major) = 13.7 min, τ_R (minor) = 24.1 min.

3-(Benzyloxy)-*N,N*-diphenylphenanthrene-4-carboxamide (**249**)



Asymmetric: Prepared according to **General Procedure N** with naphthol **225** (78 mg, 0.200 mmol), benzyl iodide (130 mg, 0.600 mmol), **186** (8.4 mg, 0.0100 mmol), and 50% w/w aqueous caesium carbonate (385 μ L, 1.00 mmol) in benzene (20.0 mL). Purification by column chromatography, eluting with 10–20% ethyl acetate in petrol, yielded title compound **249** as a white solid (30 mg, 31%, 55:45 e.r.).

Racemic: Prepared according to **General Procedure M** with naphthol **225** (78 mg, 0.200 mmol), benzyl bromide (71 μ L, 0.600 mmol), TBAB (6.5 mg, 0.0200 mmol), and 50% w/w aqueous potassium hydroxide (37 μ L, 1.00 mmol) in toluene (2.0 mL). Purification

by column chromatography, eluting with 10–20% ethyl acetate in petrol, yielded title compound **249** as a white solid (85 mg, 89%).

m.p. 172–174 °C

^1H NMR (500 MHz, CDCl_3) δ_{H} : 9.18 (d, J = 8.4 Hz, 1H, H23), 7.90 (d, J = 7.8 Hz, 1H, H20), 7.69 (d, J = 8.8 Hz, 1H, H10), 7.68 (d, J = 9.4 Hz, 1H, H22), 7.65 (t, J = 7.3 Hz, 1H, H21), 7.59 (d, J = 8.7 Hz, 1H, H1), 7.57 (d, J = 7.5 Hz, 2H, H26), 7.55 (d, J = 8.7 Hz, 1H, H6), 7.48–7.41 (m, 4H, H17 and H27), 7.42–7.39 (m, 1H, H28), 7.37 (t, J = 7.7 Hz, 2H, H18), 7.26 (t, J = 7.4 Hz, 1H, H19), 7.13 (d, J = 8.7 Hz, 1H, H9), 6.89–6.84 (m, 3H, H13 and H15), 6.77 (t, J = 7.8 Hz, 2H, H14), 5.28 (d, J = 11.2 Hz, 1H, H24a), 5.10 (d, J = 11.3 Hz, 1H, H24b).

$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ_{C} : 170.7 (C11), 153.8 (C8), 142.8 (C16), 142.7 (C12), 136.9 (C25), 133.7 (C2), 131.1 (C10), 129.4 (C3), 129.2 (C18), 129.1 (C20), 128.8 (C27), 128.7 (C4), 128.3 (C28), 128.2 (C14), 127.9 (C26), 127.7 (C5), 127.2 (C13 and C27), 127.1 (C6 and C17), 127.1 (C21), 126.8 (C19), 126.6 (C22), 126.5 (C23), 125.8 (C1), 122.7 (C7), 112.8 (C9), 71.5 (C24).

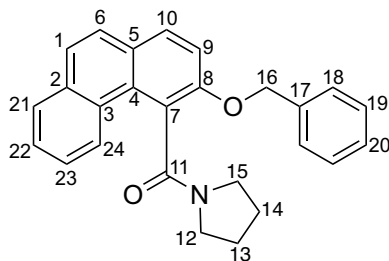
FTIR (neat) ν/cm^{-1} = 1620, 1502, 1453, 1269, 908, 831, 727, 700, 646.

HRMS (m/z , ESI^+): calculated for $\text{C}_{34}\text{H}_{26}\text{O}_2\text{N}$ ($[\text{M}+\text{H}]^+$) = 480.1958, found = 480.1957.

Chiral HPLC: (Chiralpak ODH, 30% isopropanol, 70% hexane, 1.0 mL/min, λ = 240 nm)

τ_{R} (major) = 11.1 min, τ_{R} (minor) = 17.8 min.

(3-(Benzyloxy)phenanthren-4-yl)(pyrrolidin-1-yl)methanone (250)



Asymmetric: Prepared according to **General Procedure N** with naphthol **AM-242** (58 mg, 0.200 mmol), benzyl iodide (130 mg, 0.600 mmol), **186** (8.4 mg, 0.0100 mmol), and 50% w/w aqueous caesium carbonate (385 μ L, 1.00 mmol) in benzene (20.0 mL). Purification by column chromatography, eluting with 20% ethyl acetate in petrol, yielded title compound **250** as a colourless semi-solid (37 mg, 48%, 55:45 e.r.).

Racemic: Prepared according to **General Procedure M** with naphthol **AM-242** (1 mg, 0.00343 mmol), benzyl bromide (1 μ L, 0.0756 mmol), TBAB (0.5 mg, 0.00144 mmol), and 50% w/w aqueous potassium hydroxide (1 μ L, 0.0270 mmol) in toluene (100 μ L). Purification by small-scale preparative TLC (30% ethyl acetate in petrol).

^1H NMR (500 MHz, CDCl_3) δ_{H} : 8.65 (d, J = 7.9 Hz, 1H, H24), 7.85 (d, J = 7.3 Hz, 1H, H21), 7.85 (d, J = 8.8 Hz, 1H, H10), 7.65 (d, J = 8.7 Hz, 1H, H6), 7.62 (d, J = 8.8 Hz, 1H, H1), 7.61–7.51 (m, 2H, H22 and H23), 7.48 (d, J = 7.1 Hz, 2H, H18), 7.42–7.33 (m, 3H, H9 and H19), 7.35–7.28 (m, 1H, H20), 5.32 (d, J = 12.2 Hz, 1H, H16a), 5.26 (d, J = 12.2 Hz, 1H, H16b), 3.93–3.79 (m, 2H, H15), 3.08–2.99 (m, 1H, H12a), 2.94–2.85 (m, 1H, H12b), 2.01–1.84 (m, 2H, H14), 1.79–1.61 (m, 2H, H13).

$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ_{C} : 169.3 (C11), 153.8 (C8), 137.2 (C17), 133.5 (C2), 130.9 (C10), 129.3 (C3), 128.9 (C21), 128.6 (C19), 128.2 (C5), 128.0 (C17), 127.7 (C4),

127.2 (C6), 127.2 (C18), 127.0 (C22), 126.7 (C23), 125.9 (C1), 125.2 (C24), 123.5 (C7), 114.0 (C9), 71.4 (C16), 47.4 (C12), 45.8 (C15), 25.8 (C13), 24.8 (C14).

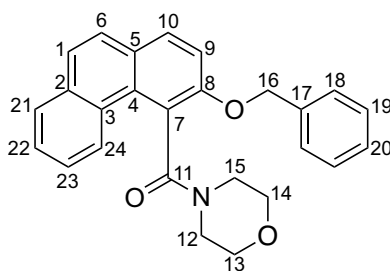
FTIR (neat) ν/cm^{-1} = 2872, 1629, 1453, 1425, 1269, 1225, 1106, 834, 748.

HRMS (m/z , ESI⁺): calculated for C₂₆H₂₄NO₂ ([M+H]⁺) = 382.1813, found = 382.1807.

Chiral HPLC: (Chiralpak IA, 30% isopropanol, 70% hexane, 1.0 mL/min, λ = 260 nm)

τ_R (major) = 12.3 min, τ_R (minor) = 16.9 min.

(3-(Benzyloxy)phenanthren-4-yl)(morpholino)methanone (251)



Asymmetric: Prepared according to **General Procedure N** with naphthol **AM-243** (61 mg, 0.200 mmol), benzyl iodide (130 mg, 0.600 mmol), **186** (8.4 mg, 0.0100 mmol), and 50% w/w aqueous caesium carbonate (385 μL , 1.00 mmol) in benzene (20.0 mL). Purification by column chromatography, eluting with 20% ethyl acetate in petrol, yielded title compound **251** as a colourless semi-solid (29 mg, 36%, 55:45 e.r.).

Racemic: Prepared according to **General Procedure M** with naphthol **AM-243** (1 mg, 0.00325 mmol), benzyl bromide (1 μL , 0.0756 mmol), TBAB (0.5 mg, 0.00144 mmol), and 50% w/w aqueous potassium hydroxide (1 μL , 0.0270 mmol) in toluene (100 μL). Purification by small-scale preparative TLC (30% ethyl acetate in petrol).

^1H NMR (500 MHz, CDCl_3) δ_{H} : 8.69 (d, $J = 7.5$ Hz, 1H, H24), 7.90–7.84 (m, 2H, H10 and H21), 7.66 (d, $J = 8.8$ Hz, 1H, H6), 7.63 (d, $J = 8.8$ Hz, 1H, H1), 7.62–7.55 (m, 2H, H22 and H23), 7.48 (d, $J = 7.3$ Hz, 2H, H18), 7.44–7.38 (m, 2H, H19), 7.38–7.31 (m, 2H, H9 and H20), 5.28 (d, $J = 11.9$ Hz, 1H, H16a), 5.26 (d, $J = 11.8$ Hz, 1H, H16b), 4.07–3.98 (m, 1H, H12a), 4.00–3.91 (m, 1H, H12b), 3.86–3.78 (m, 1H, H13a), 3.77–3.67 (m, 1H, H13b), 3.45–3.37 (m, 1H, H14a), 3.35–3.27 (m, 1H, H14b), 3.22–3.13 (m, 1H, H15a), 3.14–3.05 (m, 1H, H15b).

$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ_{C} : 169.8 (C11), 154.0 (C8), 136.8 (C17), 133.6 (C2), 131.2 (C10), 129.1 (C3), 129.1 (C21), 128.8 (C19), 128.2 (C20), 128.2 (C4 and C5), 127.4 (C18), 127.2 (C6 and C22), 126.7 (C23), 126.1 (C1), 125.6 (C24), 121.2 (C7), 113.7 (C9), 71.5 (C16), 66.5 (C14), 66.4 (C13), 46.7 (C15), 42.1 (C12).

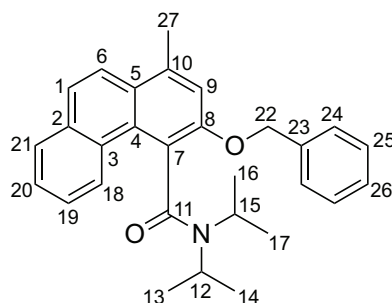
FTIR (neat) $\nu/\text{cm}^{-1} = 2980, 1633, 1503, 1453, 1272, 1228, 1113, 834, 737$.

HRMS (m/z , ESI^+): calculated for $\text{C}_{26}\text{H}_{24}\text{NO}_3$ ($[\text{M}+\text{H}]^+$) = 398.1751, found = 398.1754.

Chiral HPLC: (Chiralpak IA, 30% isopropanol, 70% hexane, 1.0 mL/min, $\lambda = 260$ nm)

τ_{R} (major) = 13.4 min, τ_{R} (minor) = 18.9 min.

3-(Benzyloxy)-*N,N*-diisopropyl-1-methylphenanthrene-4-carboxamide (**252**)



Asymmetric: Prepared according to **General Procedure N** with naphthol **226** (52 mg,

0.155 mmol), benzyl iodide (101 mg, 0.465 mmol), **186** (6.5 mg, 0.00775 mmol), and 50% w/w aqueous caesium carbonate (298 μ L, 0.776 mmol) in benzene (15.5 mL). Purification by column chromatography, eluting with 10–20% ethyl acetate in petrol, yielded title compound **252** as a white solid (55 mg, 83%, 97:3 e.r.).

Racemic: Prepared according to **General Procedure M** with naphthol **226** (1 mg, 0.00298 mmol), benzyl bromide (1 μ L, 0.0149 mmol), TBAB (1 mg, 0.000298 mmol), and 50% w/w aqueous potassium hydroxide (28 μ L, 0.374 mmol) in toluene (100 μ L). Purification by small-scale preparative TLC (20% ethyl acetate in petrol).

m.p. 133–135 °C

^1H NMR (400 MHz, CDCl_3) δ_{H} : 9.01 (d, J = 8.5 Hz, 1H, H18), 7.89 (d, J = 9.1 Hz, 1H, H6), 7.84 (d, J = 7.8 Hz, 1H, H21), 7.66 (d, J = 9.1 Hz, 1H, H1), 7.59–7.54 (m, 1H, H20), 7.54–7.46 (m, 3H, H19 and H24), 7.38 (t, J = 7.3 Hz, 2H, H25), 7.36–7.29 (m, 1H, H26), 7.25 (s, 1H, H9), 5.25 (d, J = 11.3 Hz, 1H, H22a), 5.16 (d, J = 11.3 Hz, 1H, H22b), 3.62 (hept, J = 6.7 Hz, 1H, H12), 3.50 (hept, J = 6.8 Hz, 1H, H15), 2.77 (s, 3H, H27), 1.79 (d, J = 6.8 Hz, 3H, H17), 1.48 (d, J = 6.8 Hz, 3H, H16), 0.94 (d, J = 6.7 Hz, 3H, H13), 0.73 (d, J = 6.7 Hz, 3H, H14).

$^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ_{C} : 170.0 (C11), 153.7 (C8), 137.0 (C23), 136.6 (C5), 133.1 (C2), 129.9 (C3), 128.5 (C21), 128.5 (C25), 128.3 (C4), 128.0 (C24), 128.0 (C26), 127.4 (C18), 126.8 (C20), 126.8 (C10), 125.7 (C19), 125.6 (C1), 122.9 (C6), 122.7 (C7), 115.7 (C9), 72.0 (C22), 51.3 (C12), 46.2 (C15), 21.1 (C27), 20.6 (C13), 20.5 (C14), 20.5 (C16), 19.5 (C17).

FTIR (neat) ν/cm^{-1} = 2972, 1624, 1588, 1504, 1368, 1326, 1272, 1114, 1065, 1036, 733.

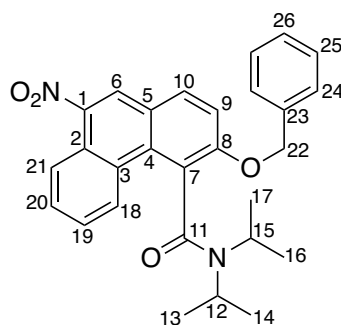
HRMS (m/z , ESI⁺): calculated for C₂₉H₃₂NO₂ ([M+H]⁺) = 426.2428, found = 426.2424.

$[\alpha]_D^{25} = -66.9^\circ$ (97:3 e.r., $c = 0.5$, CHCl₃).

Chiral HPLC: (Chiralpak ODH, 30% isopropanol, 70% hexane, 1.0 mL/min, $\lambda = 310$ nm)

τ_R (major) = 17.7 min, τ_R (minor) = 23.5 min.

3-(Benzyloxy)-*N,N*-diisopropyl-9-nitrophenanthrene-4-carboxamide (**253**)



Asymmetric: Prepared according to **General Procedure N** with naphthol **228** (73 mg, 0.200 mmol), benzyl iodide (130 mg, 0.600 mmol), **186** (8.4 mg, 0.0100 mmol), and 50% w/w aqueous caesium carbonate (385 μ L, 1.00 mmol) in benzene (20.0 mL). Purification by chromatography, eluting with 10–20% ethyl acetate in petrol, yielded title compound **253** as a yellow solid (57 mg, 62%, 91:9 e.r.).

Racemic: Prepared according to **General Procedure M** with naphthol **228** (5 mg, 0.0136 mmol), benzyl bromide (5 μ L, 0.0421 mmol), TBAB (0.4 mg, 0.00136 mmol), and 50% w/w aqueous potassium hydroxide (2.5 μ L, 0.0680 mmol) in toluene (136 μ L). Purification by small-scale preparative TLC (30% ethyl acetate in petrol).

m.p. 69–71 °C

¹H NMR (500 MHz, CDCl₃) δ_H : 9.10 (d, $J = 8.7$ Hz, 1H, H18), 8.50 (d, $J = 8.5$ Hz, 1H,

H21), 8.42 (s, 1H, H6), 7.98 (d, J = 8.8 Hz, 1H, H10), 7.73 (dd, J = 8.3, 6.9 Hz, 1H, H20), 7.63 (dd, J = 8.5, 6.9 Hz, 1H, H19), 7.53–7.48 (m, 2H, H24), 7.47 (d, J = 8.8 Hz, 1H, H9), 7.43–7.37 (m, 2H, H25), 7.37–7.32 (m, 1H, H26), 5.29 (d, J = 11.2 Hz, 1H, H22a), 5.21 (d, J = 11.2 Hz, 1H, H22b), 3.58–3.45 (m, 2H, H12 and H15), 1.78 (d, J = 6.9 Hz, 3H, H13), 1.46 (d, J = 6.8 Hz, 3H, H14), 0.95 (d, J = 6.6 Hz, 3H, H16), 0.74 (d, J = 6.7 Hz, 3H, H17).

$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ_{C} : 168.5 (C11), 157.2 (C8), 144.6 (C1), 135.9 (C23), 132.7 (C10), 130.4 (C3), 130.1 (C4), 128.8 (C20), 128.7 (C25), 128.4 (C26), 128.1 (C24), 127.5 (C18), 127.3 (C19), 126.4 (C6), 124.5 (C7), 124.5 (C5), 124.4 (C2), 123.7 (C21), 114.7 (C9), 71.7 (C22), 51.4 (C15), 46.4 (C12), 20.7 (C17), 20.6 (C16), 20.3 (C14), 19.5 (C13).

FTIR (neat) ν/cm^{-1} = 2978, 2160, 1565, 1473, 1428, 1306, 1271, 1117, 1059, 742.

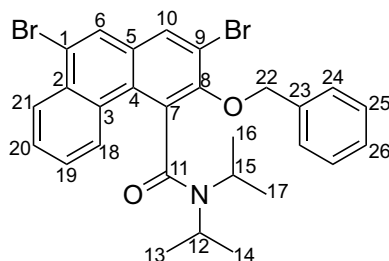
HRMS (m/z , ESI^+): calculated for $\text{C}_{28}\text{H}_{29}\text{N}_2\text{O}_4$ ($[\text{M}+\text{H}]^+$) = 457.2122, found = 457.2117.

$[\alpha]_D^{25} = -165.7^\circ$ (91:9 e.r., c = 0.5, CHCl_3).

Chiral HPLC: (Chiralpak ODH, 30% isopropanol, 70% hexane, 1.0 mL/min, λ = 260 nm)

τ_{R} (major) = 12.6 min, τ_{R} (minor) = 16.3 min.

3-(Benzyloxy)-2,9-dibromo-*N,N*-diisopropylphenanthrene-4-carboxamide
(254)



Asymmetric: Prepared according to **General Procedure N** with naphthol **229** (95 mg, 0.200 mmol), benzyl iodide (130 mg, 0.600 mmol), **186** (8.4 mg, 0.0100 mmol), and 50% w/w aqueous caesium carbonate (385 μ L, 1.00 mmol) in benzene (20.0 mL). Purification by column chromatography, eluting with 10–20% ethyl acetate in petrol, yielded title compound **254** as a white solid (81 mg, 71%, 88:12 e.r.).

Racemic: Prepared according to **General Procedure M** with naphthol **229** (5 mg, 0.0104 mmol), benzyl bromide (4 μ L, 0.0302 mmol), TBAB (0.3 mg, 0.00104 mmol), and 50% w/w aqueous potassium hydroxide (3 μ L, 0.0520 mmol) in toluene (104 μ L). Purification by small-scale preparative TLC (30% ethyl acetate in petrol).

m.p. 72–76 °C

¹H NMR (500 MHz, CDCl₃) δ_H : 8.97 (dd, J = 8.5, 1.0 Hz, 1H, H18), 8.38 (dd, J = 8.3, 1.4 Hz, 1H, H21), 8.05 (s, 1H, H10), 8.00 (s, 1H, H6), 7.71 (ddd, J = 8.2, 7.0, 1.1 Hz, 1H, H20), 7.65–7.58 (m, 3H, H19 and H24), 7.43–7.36 (m, 2H, H25), 7.40–7.30 (m, 1H, H26), 5.27 (d, J = 10.6 Hz, 1H, H22a), 5.25 (d, J = 10.6 Hz, 1H, H22b), 3.53 (hept, J = 6.9 Hz, 1H, H12), 3.37 (hept, J = 6.6 Hz, 1H, H15), 1.78 (d, J = 6.9 Hz, 3H, H13), 1.49 (d, J = 6.8 Hz, 3H, H14), 1.00 (d, J = 6.6 Hz, 3H, H16), 0.69 (d, J = 6.7 Hz, 3H, H17).

$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ_{C} : 168.3 (C11), 151.4 (C8), 137.3 (C23), 132.6 (C10), 131.6 (C7), 131.2 (C5), 131.1 (C2), 130.3 (C3), 129.8 (C6), 128.4 (C21), 128.3 (C20 and C24), 128.1 (C25), 128.0 (C26), 127.3 (C19), 126.9 (C19), 126.5 (C4), 122.8 (C1), 118.0 (C9), 77.0 (C22), 51.7 (C15), 46.5 (C12), 20.7 (C14), 20.5 (C16), 20.4 (C17), 19.3 (C13).

FTIR (neat) ν/cm^{-1} = 2972, 1622, 1412, 1369, 1333, 1227, 908, 753, 730.

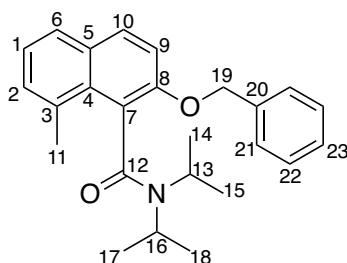
HRMS (m/z , ESI^+): calculated for $\text{C}_{28}\text{H}_{28}\text{Br}_2\text{NO}_2$ ($[\text{M}+\text{H}]^+$) = 568.0481, found = 568.0481.

$[\alpha]_D^{25} = -29.6^\circ$ (88:12 e.r., $c = 0.5$, CHCl_3).

Chiral HPLC: (Chiralpak ODH, 10% isopropanol, 90% hexane, 1.0 mL/min, $\lambda = 260$ nm)

τ_{R} (major) = 6.1 min, τ_{R} (minor) = 10.6 min.

2-(Benzyloxy)-*N,N*-diisopropyl-8-methyl-1-naphthamide (**255**)



Asymmetric: Prepared according to **General Procedure N** with naphthol **AM-244** (57 mg, 0.200 mmol), benzyl iodide (130 mg, 0.600 mmol), **186** (8.4 mg, 0.0100 mmol), and 50% w/w aqueous caesium carbonate (385 μL , 1.00 mmol) in benzene (20.0 mL). Purification by column chromatography, eluting with 10–20% ethyl acetate in petrol, yielded title compound **255** as a white solid (54 mg, 72%, 98:2 e.r.).

Racemic: Prepared according to **General Procedure M** with naphthol **AM-244** (1 mg,

0.00350 mmol), benzyl bromide (1 μ L, 0.0105 mmol), TBAB (0.5 mg, 0.00144 mmol), and 50% w/w aqueous potassium hydroxide (1 μ L, 0.0270 mmol) in toluene (100 μ L). Purification by small-scale preparative TLC (30% ethyl acetate in petrol).

m.p. 134 °C

^1H NMR (500 MHz, CDCl_3) δ_{H} : 7.79 (d, J = 9.0 Hz, 1H, H10), 7.64 (dd, J = 8.0, 1.6 Hz, 1H, H6), 7.47 (d, J = 6.9 Hz, 2H, H21), 7.36 (t, J = 7.6 Hz, 2H, H22), 7.35–7.29 (m, 1H, H23), 7.29–7.22 (m, 3H, H1, H2, and H9), 5.18 (d, J = 11.4 Hz, 1H, H19a), 5.13 (d, J = 11.4 Hz, 1H, H19b), 3.69 (hept, J = 6.6 Hz, 1H, H16), 3.46 (hept, J = 6.9 Hz, 1H, H13), 2.78 (s, 3H, H11), 1.59 (d, J = 6.8 Hz, 3H, H15), 1.40 (d, J = 6.8 Hz, 3H, H14), 1.05–1.00 (m, 6H, H17 and H18).

$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ_{C} : 169.4 (C12), 153.5 (C8), 137.0 (C20), 134.0 (C3), 130.9 (C10), 130.6 (C5), 130.1 (C4), 129.9 (C2), 128.5 (C22), 128.1 (C21), 128.1 (C23), 127.3 (C6), 124.0 (C1), 123.4 (C7), 114.8 (C9), 72.4 (C19), 51.2 (C16), 46.1 (C13), 22.3 (C11), 20.7 (C17), 20.2 (C14), 19.9 (C18), 19.8 (C15).

FTIR (neat) ν/cm^{-1} = 2972, 1626, 1511, 1433, 1368, 1310, 1247, 1040, 821, 735, 695.

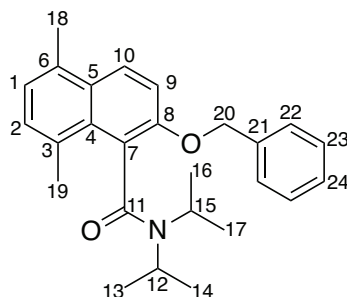
HRMS (m/z , ESI^+): calculated for $\text{C}_{25}\text{H}_{30}\text{NO}_2$ ($[\text{M}+\text{H}]^+$) = 376.2271, found = 376.2269.

$[\alpha]_D^{25} = -167.8^\circ$ (98:2 e.r., $c = 0.5$, CHCl_3).

Chiral HPLC: (Chiralpak ODH, 20% isopropanol, 80% hexane, 1.0 mL/min, $\lambda = 240$ nm)

τ_{R} (major) = 6.8 min, τ_{R} (minor) = 8.7 min.

2-(Benzyloxy)-*N,N*-diisopropyl-5,8-dimethyl-1-naphthamide (256)



Asymmetric: Prepared according to **General Procedure N** with naphthol **AM-245** (56 mg, 0.187 mmol), benzyl iodide (122 mg, 0.561 mmol), **186** (7.8 mg, 0.00935 mmol), and 50% aqueous caesium carbonate (360 μ L, 0.935 mmol) in benzene (18.7 mL). Purification by column chromatography, eluting with 10–20% ethyl acetate in petrol, yielded title compound **256** as a white solid (62 mg, 80%, 99:1 e.r.).

Racemic: Prepared according to **General Procedure M** with naphthol **AM-245** (1 mg, 0.00334 mmol), benzyl bromide (1.2 μ L, 0.0100 mmol), TBAB (0.1 mg, 0.000334 mmol), and 50% aqueous potassium hydroxide (1 μ L, 0.0269 mmol) in toluene (100 μ L). Purification by small-scale preparative TLC (30% ethyl acetate in petrol).

m.p. 127–128 °C

¹H NMR (500 MHz, CDCl₃) δ_H : 7.99 (d, J = 9.2 Hz, 1H, H10), 7.48 (d, J = 6.9 Hz, 2H, H22), 7.40–7.34 (m, 2H, H23), 7.34–7.28 (m, 2H, H9 and H24), 7.17 (d, J = 6.8 Hz, 1H, H2), 7.10 (d, J = 6.8 Hz, 1H, H1), 5.20 (d, J = 11.4 Hz, 1H, H20a), 5.14 (d, J = 11.4 Hz, 1H, H20b), 3.66 (hept, J = 6.7 Hz, 1H, H12), 3.46 (hept, J = 6.8 Hz, 1H, H15), 2.76 (s, 3H, H19), 2.64 (s, 3H, H18), 1.58 (d, J = 6.9 Hz, 3H, H16), 1.40 (d, J = 6.8 Hz, 3H, H17), 1.02 (d, J = 6.7 Hz, 3H, H13), 1.02 (d, J = 6.6 Hz, 3H, H14).

$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ_{C} : 169.6 (C11), 153.3 (C8), 137.0 (C21), 132.8 (C6), 132.3 (C3), 130.3 (C4), 129.8 (C2), 129.5 (C5), 128.5 (C23), 128.1 (C22), 128.0 (C24), 126.8 (C10), 125.1 (C1), 123.9 (C7), 114.3 (C9), 72.2 (C20), 51.2 (C12), 46.0 (C15), 22.4 (C19), 20.7 (C14), 20.2 (C17), 20.2 (C18), 19.9 (C13), 19.8 (C16).

FTIR (neat) ν/cm^{-1} = 2967, 1629, 1519, 1439, 1358, 1315, 1255, 1102, 1039, 827, 737.

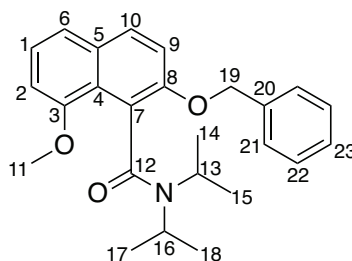
HRMS (m/z , ESI^+): calculated for $\text{C}_{26}\text{H}_{32}\text{NO}_2$ ($[\text{M}+\text{H}]^+$) = 390.2428, found = 390.2414.

$[\alpha]_D^{25} = -199.0^\circ$ (99:1 e.r., $c = 0.5$, CHCl_3).

Chiral HPLC: (Chiralpak ODH, 5% isopropanol, 95% hexane, 1.0 mL/min, $\lambda = 300$ nm)

τ_{R} (major) = 24.8 min, τ_{R} (minor) = 31.6 min.

2-(Benzyloxy)-*N,N*-diisopropyl-8-methoxy-1-naphthamide (**257**)



Asymmetric: Prepared according to **General Procedure N** with naphthol **227** (60 mg, 0.200 mmol), benzyl iodide (130 mg, 0.600 mmol), **186** (8.4 mg, 0.0100 mmol), and 50% w/w aqueous caesium carbonate (385 μL , 1.00 mmol) in benzene (20.0 mL). Purification by column chromatography, eluting with 10–20% ethyl acetate in petrol, yielded title compound **257** as a white solid (62 mg, 80%, 96:4 e.r.).

Racemic: Prepared according to **General Procedure M** with naphthol **227** (20 mg, 0.0664 mmol), benzyl bromide (32 μL , 0.332 mmol), TBAB (3.0 mg, 0.00664 mmol),

and 50% w/w aqueous potassium hydroxide (28 μ L, 0.374 mmol) in toluene (664 μ L).

Purification by small-scale preparative TLC (30% ethyl acetate in petrol).

m.p. 133–135 °C

^1H NMR (500 MHz, CDCl_3) δ_{H} : 7.73 (d, J = 8.9 Hz, 1H, H10), 7.53–7.44 (m, 2H, H21), 7.40–7.33 (m, 3H, H6 and H22), 7.32–7.27 (m, 2H, H9 and H23), 7.27–7.24 (m, 1H, H1), 6.82 (dd, J = 7.6, 1.0 Hz, 1H, H2), 5.21 (d, J = 11.5 Hz, 1H, H19a), 5.13 (d, J = 11.6 Hz, 1H, H19b), 3.91 (s, 3H, H11), 3.70 (hept, J = 6.7 Hz, 1H, H16), 3.45 (hept, J = 6.8 Hz, 1H, H13), 1.65 (d, J = 6.8 Hz, 3H, H15), 1.46 (d, J = 6.8 Hz, 3H, H14), 1.00 (d, J = 6.9 Hz, 3H, H18), 0.99 (d, J = 6.8 Hz, 3H, H17).

$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ_{C} : 168.2 (C12), 155.2 (C3), 152.6 (C8), 137.1 (C20), 130.9 (C5), 129.2 (C10), 128.3 (C22), 127.8 (C23), 127.8 (C21), 124.1 (C1), 123.0 (C4), 121.8 (C7), 120.7 (C6), 115.8 (C9), 106.0 (C2), 72.1 (C19), 55.3 (C11), 50.9 (C16), 45.5 (C13), 20.6 (C15 and C18), 20.4 (C14), 19.9 (C17).

FTIR (neat) ν/cm^{-1} = 2972, 1630, 1595, 1513, 1461, 1365, 1337, 1315, 1258, 1217, 1114, 1039, 821, 733, 696.

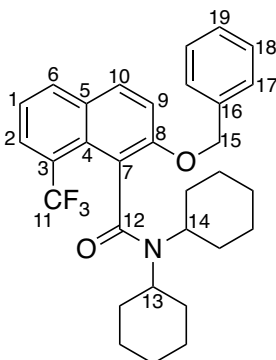
HRMS (m/z , ESI^+): calculated for $\text{C}_{25}\text{H}_{30}\text{NO}_3$ ($[\text{M}+\text{H}]^+$) = 392.2220, found = 392.2223.

$[\alpha]_D^{25} = -75.2^\circ$ (96:4 e.r., $c = 0.5$, CHCl_3).

Chiral HPLC: (Chiralpak IA, 40% isopropanol, 60% hexane, 1.0 mL/min, $\lambda = 240$ nm)

τ_{R} (major) = 6.5 min, τ_{R} (minor) = 11.5 min.

2-(Benzyloxy)-*N,N*-dicyclohexyl-8-(trifluoromethyl)-1-naphthamide (258)



Asymmetric: Prepared according to **General Procedure N** with naphthol **222** (73 mg, 0.200 mmol), benzyl iodide (130 mg, 0.600 mmol), **186** (8.4 mg, 0.00100 mmol), and 50% aqueous caesium carbonate (385 μ L, 1.00 mmol) in benzene (20.0 mL). Purification by column chromatography, eluting with 10–20% ethyl acetate in petrol, yielded title compound **258** as a white solid (62 mg, 63%, 91:9 e.r.).

Racemic: Prepared according to **General Procedure M** with naphthol **222** (5 mg, 0.0119 mmol), benzyl bromide (4 μ L, 0.0358 mmol), TBAB (0.5 mg, 0.00155 mmol), and 50% aqueous potassium hydroxide (2 μ L, 0.0596 mmol) in toluene (120 μ L). Purification by small-scale preparative TLC (30% ethyl acetate in petrol).

m.p. 77–79 °C

¹H NMR (500 MHz, CDCl₃) δ_H : 8.00 (d, J = 7.3 Hz, 1H, H2), 7.97 (d, J = 8.2 Hz, 1H, H6), 7.88 (d, J = 9.0 Hz, 1H, H10), 7.49–7.43 (m, 2H, H17), 7.43–7.32 (m, 4H, H1, H9, and H18), 7.33–7.27 (m, 1H, H19), 5.18 (d, J = 11.3 Hz, 1H, H15a), 5.12 (d, J = 11.4 Hz, 1H, H15b), 2.95–2.91 (m, 1H, H14), 2.94–2.84 (m, 1H, H13), 2.70–2.49 (m, 2H, H*Cy*), 1.86–1.73 (m, 2H, H*Cy*), 1.72–1.66 (m, 2H, H*Cy*), 1.63–1.49 (m, 3H, H*Cy*), 1.41–1.35 (m, 1H, H*Cy*), 1.36–1.02 (m, 7H, H*Cy*), 1.02–0.81 (m, 1H, H*Cy*), 0.79–0.66 (m, 2H, H*Cy*).

$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ_{C} : 166.6 (C12), 155.5 (C8), 136.4 (C16), 134.4 (C6), 131.8 (C10), 130.8 (C5), 128.5 (C18), 128.6–128.4 (m, C2), 128.4 (C17), 128.2 (C19), 126.8 (C4), 124.5 (q, $J = 30.9$ Hz, C3), 124.4 (q, $J = 273.5$ Hz, C11), 123.1 (C7), 122.3 (C1), 115.9 (C9), 72.5 (C15), 60.2 (C13), 56.4 (C14), 31.0 (CCy), 30.5 (CCy), 30.0 (CCy), 29.1 (CCy), 26.9 (CCy), 26.8 (CCy), 26.1 (CCy), 26.0 (CCy), 25.6 ($2 \times \text{CCy}$).

^{19}F NMR (377 MHz, CDCl_3) δ_{F} : -54.7 (CF_3).

FTIR (neat) $\nu/\text{cm}^{-1} = 2928, 2853, 1634, 1516, 1436, 1336, 1296, 1259, 1196, 1139$.

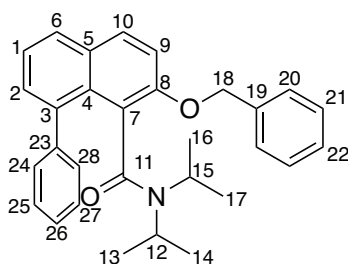
HRMS (m/z , ESI^+): calculated for $\text{C}_{31}\text{H}_{35}\text{F}_3\text{NO}_2$ ($[\text{M}+\text{H}]^+$) = 510.2614, found = 510.2610.

$[\alpha]_D^{25} = -136.6^\circ$ (91:9 e.r., $c = 0.5$, CHCl_3).

Chiral HPLC: (Chiralpak ODH, 30% isopropanol, 70% hexane, 1.0 mL/min, $\lambda = 240$ nm)

τ_{R} (major) = 8.4 min, τ_{R} (minor) = 14.8 min.

2-(Benzyloxy)-*N,N*-diisopropyl-8-phenyl-1-naphthamide (**259**)



Asymmetric: Prepared according to **General Procedure N** with naphthol **232** (80 mg, 0.200 mmol), benzyl iodide (130 mg, 0.600 mmol), **186** (8.4 mg, 0.0100 mmol), and 50% w/w aqueous caesium carbonate (385 μL , 1.00 mmol) in benzene (20.0 mL). Purification by column chromatography, eluting with 10–20% ethyl acetate in petrol, yielded title compound **259** as a white solid (67 mg, 79%, 98:2 e.r.).

Racemic: Prepared according to **General Procedure M** with naphthol **232** (5 mg, 0.0144 mmol), benzyl bromide (5 μ L, 0.0432 mmol), TBAB (0.5 mg, 0.00144 mmol), and 50% w/w aqueous potassium hydroxide (3 μ L, 0.0720 mmol) in toluene (100 μ L). Purification by small-scale preparative TLC (30% ethyl acetate in petrol).

m.p. 69–71 °C

^1H NMR (700 MHz, CDCl_3) δ_{H} : 7.88 (d, J = 9.0 Hz, 1H, H10), 7.80 (dd, J = 8.2, 1.4 Hz, 1H, H6), 7.63–7.56 (m, 1H, H24), 7.50–7.45 (m, 2H, H20), 7.45–7.42 (m, 1H, H28), 7.38–7.27 (m, 8H, H1, H9, H21, H22, H25, H26, and H27), 7.22 (dd, J = 7.1, 1.5 Hz, 1H, H2), 5.21 (d, J = 11.3 Hz, 1H, H18a), 5.09 (d, J = 11.3 Hz, 1H, H18b), 3.26 (hept, J = 6.7 Hz, 1H, H12), 2.98 (hept, J = 6.8 Hz, 1H, H15), 1.09 (d, J = 6.8 Hz, 3H, H17), 0.84 (d, J = 6.6 Hz, 3H, H13), 0.77 (d, J = 6.6 Hz, 3H, H14), 0.59 (d, J = 6.9 Hz, 3H, H16).

$^{13}\text{C}\{^1\text{H}\}$ NMR (176 MHz, CDCl_3) δ_{C} : 167.1 (C11), 154.1 (C8), 141.0 (C23), 139.5 (C3), 136.9 (C19), 133.9 (C24), 132.4 (C2), 130.8 (C10), 130.4 (C5), 129.8 (C28), 128.7 (C4), 128.6 (C6), 128.4 (C21), 128.1 (C20), 128.0 (C22), 127.4 (C26), 127.3 (C25), 126.9 (C27), 124.2 (C7), 123.4 (C1), 115.8 (C9), 72.5 (C18), 50.4 (C12), 45.4 (C15), 20.6 (C16), 20.5 (C14), 19.8 (C13), 19.8 (C17).

FTIR (neat) ν/cm^{-1} = 2973, 2929, 1633, 1510, 1448, 1367, 1304, 1255, 823, 761, 689.

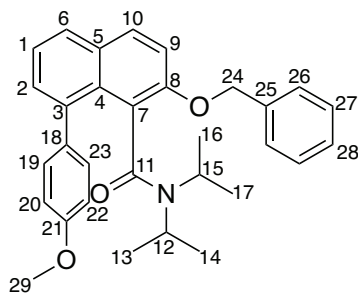
HRMS (m/z , ESI^+): calculated for $\text{C}_{30}\text{H}_{32}\text{NO}_2$ ($[\text{M}+\text{H}]^+$) = 438.2428, found = 438.2420.

$[\alpha]_D^{25} = -10.1^\circ$ (98:2 e.r., c = 0.5, CHCl_3).

Chiral HPLC: (Chiralpak IC, 10% isopropanol, 90% hexane, 1.0 mL/min, λ = 240 nm)

τ_{R} (minor) = 11.8 min, τ_{R} (major) = 24.3 min.

2-(Benzyloxy)-*N,N*-diisopropyl-8-(4-methoxyphenyl)-1-naphthamide (260)



Asymmetric: Prepared according to **General Procedure N** with naphthol **ASL-238** (68 mg, 0.180 mmol), benzyl iodide (118 mg, 0.540 mmol), **186** (7.6 mg, 0.00901 mmol), and 50% w/w aqueous caesium carbonate (347 μ L, 0.901 mmol) in benzene (18.0 mL). Purification by column chromatography, eluting with 10–20% ethyl acetate in petrol, yielded title compound **260** as a white solid (45 mg, 53%, 98:2 e.r.).

Racemic: Prepared according to **General Procedure M** with naphthol **ASL-238** (1 mg, 0.00265 mmol), benzyl bromide (1 μ L, 0.00825 mmol), TBAB (0.5 mg, 0.00155 mmol), and 50% w/w aqueous potassium hydroxide (1 μ L, 0.0269 mmol) in toluene (100 μ L). Purification by small-scale preparative TLC (30% ethyl acetate in petrol).

m.p. 66–68 °C

^1H NMR (500 MHz, CDCl_3) δ_{H} : 7.87 (d, J = 9.0 Hz, 1H, H10), 7.78 (dd, J = 8.2, 1.4 Hz, 1H, H6), 7.55–7.48 (m, 1H, H19), 7.51–7.43 (m, 2H, H26), 7.38–7.31 (m, 5H, H1, H9, H23, and H27), 7.31–7.27 (m, 1H, H28), 7.22 (dd, J = 7.1, 1.4 Hz, 1H, H2), 6.87 (ddd, J = 8.8, 3.5, 2.3 Hz, 2H, H20 and H22), 5.21 (d, J = 11.3 Hz, 1H, H24a), 5.09 (d, J = 11.3 Hz, 1H, H24b), 3.82 (s, 3H, H29), 3.24 (hept, J = 6.7 Hz, 1H, H12), 3.01 (hept, J = 6.9 Hz, 1H, H15), 1.11 (d, J = 6.7 Hz, 3H, H16), 0.84 (d, J = 6.7 Hz, 3H, H13), 0.76 (d, J = 6.6 Hz, 3H, H14), 0.69 (d, J = 6.9 Hz, 3H, H17).

$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ_{C} : 167.3 (C11), 159.5 (C21), 154.1 (C8), 139.2 (C3), 137.0 (C25), 135.0 (C19), 133.3 (C18), 132.3 (C2), 130.8 (C23), 130.8 (C10), 130.5 (C5), 129.0 (C4), 128.4 (C27), 128.4 (C6), 128.1 (C26), 128.0 (C28), 124.3 (C7), 123.5 (C1), 115.8 (C9), 113.7 (C22), 111.6 (C20), 72.5 (C24), 55.5 (C29), 50.4 (C12), 45.4 (C15), 20.7 (C17), 20.5 (C14), 19.8 (C13 and C16).

FTIR (neat) ν/cm^{-1} = 2972, 1631, 1507, 1434, 1306, 1246, 1037, 825, 732, 697.

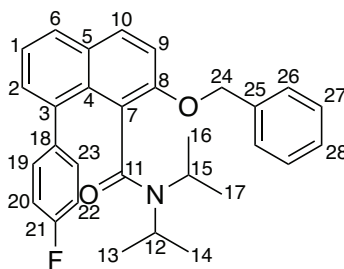
HRMS (m/z , ESI^+): calculated for $\text{C}_{31}\text{H}_{34}\text{NO}_3$ ($[\text{M}+\text{H}]^+$) = 468.2533, found = 468.2527.

$[\alpha]_D^{25} = -11.5^\circ$ (98:2 e.r., $c = 0.5$, CHCl_3).

Chiral HPLC: (Chiralpak ODH, 30% isopropanol, 70% hexane, 1.0 mL/min, $\lambda = 260$ nm)

τ_{R} (minor) = 7.8 min, τ_{R} (major) = 12.6 min.

2-(Benzyloxy)-8-(4-fluorophenyl)-*N,N*-diisopropyl-1-naphthamide (**261**)



Asymmetric: Prepared according to **General Procedure N** with naphthol **ASL-239** (73 mg, 0.200 mmol), benzyl iodide (130 mg, 0.600 mmol), **186** (8.4 mg, 0.00100 mmol), and 50% w/w aqueous caesium carbonate (385 μL , 1.00 mmol) in benzene (20.0 mL). Purification by column chromatography, eluting with 20% ethyl acetate in petrol, yielded title compound **261** as a white solid (63 mg, 69%, 98:2 e.r.).

Racemic: Prepared according to **General Procedure M** with naphthol **ASL-239** (1 mg, 0.00298 mmol), benzyl bromide (1 μ L, 0.0149 mmol), TBAB (1 mg, 0.000298 mmol), and 50% w/w aqueous potassium hydroxide (28 μ L, 0.374 mmol) in toluene (100 μ L). Purification by small-scale preparative TLC (20% ethyl acetate in petrol).

m.p. 126–128 °C

^1H NMR (500 MHz, CDCl_3) δ_{H} : 7.89 (d, J = 9.0 Hz, 1H, H10), 7.80 (dd, J = 8.2, 1.4 Hz, 1H, H6), 7.60–7.54 (m, 1H, H23), 7.46 (d, J = 6.9 Hz, 2H, H26), 7.41–7.37 (m, 1H, H19), 7.37–7.31 (m, 4H, H1, H9 and H27), 7.31–7.27 (m, 1H, H28), 7.19 (dd, J = 7.1, 1.5 Hz, 1H, H2), 7.06–6.97 (m, 2H, H20 and H22), 5.20 (d, J = 11.3 Hz, 1H, H24a), 5.09 (d, J = 11.3 Hz, 1H, H24b), 3.25 (hept, J = 6.7 Hz, 1H, H12), 3.02 (hept, J = 6.9 Hz, 1H, H15), 1.10 (d, J = 6.8 Hz, 3H, H17), 0.83 (d, J = 6.7 Hz, 3H, H13), 0.78 (d, J = 6.6 Hz, 3H, H14), 0.71 (d, J = 6.8 Hz, 3H, H16).

$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ_{C} : 167.3 (C11), 162.9 (d, J = 245.5 Hz, C21), 154.1 (C8), 138.3 (C5), 136.9 (d, J = 3.3 Hz, C18), 136.8 (C25), 135.7 (d, J = 8.2 Hz, C23), 132.4 (C2), 131.1 (d, J = 7.9 Hz, C19), 130.8 (C10), 130.4 (C4), 128.8 (C6), 128.7 (C3), 128.4 (C27), 128.1 (C26), 128.0 (C28), 123.9 (C7), 123.4 (C1), 115.7 (C9), 114.0 (d, J = 21.5 Hz, C20), 113.8 (d, J = 21.3 Hz, C22), 72.4 (C24), 50.4 (C12), 45.5 (C15), 20.6 (C16), 20.5 (C14), 19.8 (C13), 19.7 (C17).

^{19}F NMR (377 MHz, CDCl_3) δ_{F} : –116.2 (*ArF*).

FTIR (neat) ν/cm^{-1} = 2974, 2931, 1628, 1505, 1434, 1306, 1253, 1220, 1158, 1048, 826, 729.

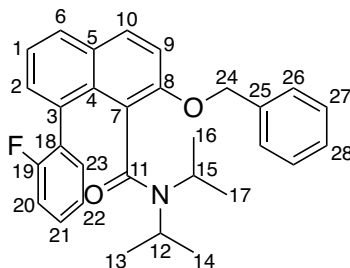
HRMS (m/z , ESI $^+$): calculated for $\text{C}_{30}\text{H}_{31}\text{FNO}_2$ ($[\text{M}+\text{H}]^+$) = 456.2333, found = 456.2327.

$[\alpha]_D^{25} = -16.3^\circ$ (98:2 e.r., $c = 0.5$, CHCl_3).

Chiral HPLC: (Chiralpak IC, 10% isopropanol, 90% hexane, 1.0 mL/min, $\lambda = 240$ nm)

τ_R (minor) = 9.8 min, τ_R (major) = 13.7 min.

2-(Benzyloxy)-8-(2-fluorophenyl)-*N,N*-diisopropyl-1-naphthamide (262)



Asymmetric: Prepared according to **General Procedure N** with naphthol **ASL-240** (72 mg, 0.200 mmol), benzyl iodide (130 mg, 0.600 mmol), **186** (8.4 mg, 0.0100 mmol), and 50% w/w aqueous caesium carbonate (385 μL , 1.00 mmol) in benzene (20.0 mL). Purification by column chromatography, eluting with 10–20% ethyl acetate in petrol, yielded title compound **262** as a 2:1 mixture of diastereomers (65 mg, 71%, maj. = 96:4 e.r., min. = 96:4 e.r.).

Racemic: Prepared according to **General Procedure M** with naphthol **ASL-240** (1 mg, 0.00270 mmol), benzyl bromide (1 μL , 0.0821 mmol), TBAB (0.5 mg, 0.00144 mmol), and 50% w/w aqueous potassium hydroxide (1 μL , 0.0270 mmol) in toluene (100 μL). Purification by small-scale preparative TLC (30% ethyl acetate in petrol).

^1H NMR (500 MHz, CDCl_3) δ_H : 7.92–7.86 (m, 1H, H10), 7.86–7.79 (m, 1H, H6), 7.54 (td, $J = 7.8, 1.8$ Hz, 0.67H, *ArH*), 7.44 (d, $J = 6.9$ Hz, 2H, H26), 7.40–7.27 (m, 7H, H9, H21, H27, H28, and *ArH*), 7.21 (dd, $J = 7.0, 1.4$ Hz, 0.33H, *ArH*), 7.16–7.08 (m, 1H, *ArH*) 7.08–7.00 (m, 1H, H20), 5.18 (d, $J = 11.3$ Hz, 1H, H24a), 5.08 (t, $J = 11.4$ Hz, 1H,

H24b), 3.35 (hept, $J = 6.6$ Hz, 0.67H, H12 maj.), 3.24 (hept, $J = 6.6$ Hz, 0.33H, H12 min.), 3.15–2.89 (m, 1H, H15), 1.11–1.02 (m, 3H, H17), 0.94–0.84 (m, 3H, H13), 0.84–0.78 (m, 3H, H14), 0.67–0.59 (m, 3H, H16).

$^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ_{C} : 167.2 (C11 maj.), 166.6 (C11 min.), 161.8 (d, $J = 248.8$ Hz, C19 min.), 160.0 (d, $J = 243.2$ Hz, 25, C19 maj.), 154.2 (C8 min.), 154.0 (C8 maj.), 136.8 (C25 maj.), 136.4 (C25 min.), 136.4 (*ArC*), 132.8 (*ArC*), 132.6 (*ArC*), 132.0 (*ArC*), 131.9 (*ArC*), 131.9 (*ArC*), 131.8 (*ArC*), 131.0 (C10 maj.), 130.8 (*ArC*), 130.7 (C10 min.), 130.1 (*ArC*), 130.0 (*ArC*), 130.0 (*ArC*), 129.7 (*ArC*), 129.5 (*ArC*), 129.4 (*ArC*), 129.3 (*ArC*), 129.3 (*ArC*), 129.3 (*ArC*), 129.1 (*ArC*), 128.5 (C27 maj.), 128.4 (C27 min.), 128.3 (*ArC*), 128.3, (C26 min.) 128.2 (C26 maj.), 128.0 (C28 maj.), 128.0 (C28 min.), 123.8 (C7 maj.), 123.6 (C7 min.), 123.4 (*ArC*), 123.3 (*ArC*), 123.2 (*ArC*), 123.1 (*ArC*), 123.0 (*ArC*), 123.0 (*ArC*), 115.8 (C9 min.), 115.6 (C9 maj.), 115.51 (d, $J = 22.3$ Hz, C20 min.), 115.02 (d, $J = 22.4$ Hz, C20 maj.), 72.4 (C24 min.), 72.4 (C24 maj.), 50.7 (C12 maj.), 50.3 (C12 min.), 45.6 (C15 min.), 45.5 (C15 maj.), 21.0 (C16 maj), 20.8 (C16 min.), 20.5 (C14 maj.), 20.4 (C^iPr), 20.3 (C^iPr), 20.2 (C^iPr), 19.6 (C17 maj.), 19.5 (C17 min.).

^{19}F NMR (377 MHz, CDCl_3) δ_{F} : -107.7 (ddd, $J = 9.8, 7.4, 5.0$ Hz, *ArF* min.) -113.8 (td, $J = 8.7, 5.4$ Hz, *ArF* maj.)

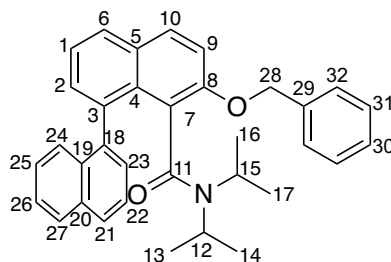
FTIR (neat) $\nu/\text{cm}^{-1} = 2973, 1632, 1510, 1492, 1451, 1533, 1368, 1306, 1254, 1213, 1035, 827, 756, 697$.

HRMS (m/z , ESI^+): calculated for $\text{C}_{30}\text{H}_{31}\text{FNO}_2$ ($[\text{M}+\text{H}]^+$) = 456.2333, found = 456.2328.

Chiral HPLC: (Chiralpak IC, 10% isopropanol, 90% hexane, 1.0 mL/min, $\lambda = 260$ nm)

major diastereomer: τ_R : (minor) = 9.9 min, τ_R (major) = 11.7 min, minor diastereomer:
 τ_R : (minor) = 21.7 min, τ_R (major) = 37.9 min.

7-(Benzyloxy)-*N,N*-diisopropyl-[1,1'-binaphthalene]-8-carboxamide (263)



Asymmetric: Prepared according to **General Procedure N** with naphthol **ASL-241** (80 mg, 0.200 mmol), benzyl iodide (130 mg, 0.600 mmol), **186** (8.4 mg, 0.0100 mmol), and 50% w/w aqueous caesium carbonate (385 μ L, 1.00 mmol) in benzene (20.0 mL). Purification by column chromatography, eluting with 10–20% ethyl acetate in petrol, yielded title compound **263** as a 3:2 mixture of diastereomers (74 mg, 76%, maj. = 98:2 e.r, min. = 96:4 e.r.).

Racemic: Prepared according to **General Procedure M** with naphthol **ASL-241** (1 mg, 0.00252 mmol), benzyl bromide (1 μ L, 0.0756 mmol), TBAB (0.5 mg, 0.00144 mmol), and 50% w/w aqueous potassium hydroxide (1 μ L, 0.0270 mmol) in toluene (100 μ L). Purification by small-scale preparative TLC (30% ethyl acetate in petrol).

^1H NMR (500 MHz, CDCl_3) δ_H : 7.93 (dd, J = 9.0, 5.6 Hz, 1H, *ArH*), 7.91–7.81 (m, 3H, *ArH*), 7.81–7.77 (m, 0.4H, *ArH*), 7.75 (dd, J = 7.2, 1.2 Hz, 0.6H, *ArH*), 7.61 (dd, J = 8.5, 1.0 Hz, 0.6H, *ArH*), 7.50 (dd, J = 8.2, 7.1 Hz, 0.6H, *ArH*), 7.46–7.26 (m, 10.4H, *ArH*), 7.20 (dd, J = 7.0, 1.5 Hz, 0.4H, *ArH*), 5.17 (d, J = 11.4 Hz, 0.6H, H28a maj.), 5.11 (d, J = 11.3 Hz, 0.4H, H28a min.), 5.07 (d, J = 11.4 Hz, 0.6H, H28b maj.), 5.01 (d, J = 11.3 Hz,

0.4H, H28b min.), 3.55 (hept, $J = 6.6$ Hz, 0.4H, H12 min.), 3.17 (hept, $J = 6.6$ Hz, 0.6H, H12 maj.), 2.88 (hept, $J = 6.8$ Hz, 0.4H, H15 min.), 2.70 (hept, $J = 6.8$ Hz, 0.6H, H15 maj.), 1.01 (d, $J = 6.6$ Hz, 1.2H, HⁱPr min.), 0.97 (d, $J = 6.8$ Hz, 1.8H, HⁱPr maj.), 0.87 (d, $J = 6.5$ Hz, 1.2H, HⁱPr min.), 0.83 (d, $J = 6.7$ Hz, 1.2H, HⁱPr min.), 0.71 (d, $J = 6.5$ Hz, 1.8H, HⁱPr maj.), 0.31 (d, $J = 6.9$ Hz, 1.8H, HⁱPr maj.), 0.27 (d, $J = 6.9$ Hz, 1.2H, HⁱPr min.), -0.14 (d, $J = 6.5$ Hz, 1.8H, HⁱPr maj.).

¹³C{¹H} NMR (126 MHz, CDCl₃) δ_C : 167.3 (C11, maj.), 166.2 (C11, min), 154.1 (C8), 140.4 (ArC), 137.4 (ArC), 136.9 (ArC), 136.7 (ArC), 136.5 (ArC), 134.7 (ArC), 133.9 (ArC), 133.7 (ArC), 133.3 (ArC), 133.2 (ArC), 132.5 (ArC), 132.2 (ArC), 131.0 (ArC), 131.0 (ArC), 130.9 (ArC), 130.4 (ArC), 130.3 (ArC), 129.9 (ArC), 129.0 (ArC), 128.9 (ArC), 128.5 (ArC), 128.4 (ArC), 128.4 (ArC), 128.4 (ArC), 128.3 (ArC), 128.2 (ArC), 128.1 (ArC), 128.1 (ArC), 128.0 (ArC), 127.8 (ArC), 127.7 (ArC), 127.4 (ArC), 126.9 (ArC), 125.8 (ArC), 125.7 (ArC), 125.6 (ArC), 125.3 (ArC), 125.1 (ArC), 124.5 (ArC), 124.4 (ArC), 123.9 (ArC), 123.4 (ArC), 123.2 (ArC), 115.8 (C9), 115.1 (C7), 72.5 (C28 maj.), 72.1 (C28 min.), 50.4 (C12, maj.), 50.3 (C12 min.), 45.4 (C15 min.), 45.2 (C15 maj.), 21.1 (CⁱPr maj.), 20.7 (CⁱPr min.), 20.4 (CⁱPr min.), 20.4 (CⁱPr min.), 20.3 (CⁱPr maj.), 19.8 (CⁱPr maj.), 19.5 (CⁱPr maj.), 19.3 (CⁱPr min.).

FTIR (neat) $\nu/\text{cm}^{-1} = 2980, 2857, 1633, 1502, 1452, 1272, 1228, 1113, 834, 737$.

HRMS (m/z , ESI⁺): calculated for C₃₄H₃₄NO₂ ([M+H]⁺) = 488.2584, found = 488.2580.

Chiral HPLC: (Chiralpak ADH, 5% isopropanol, 95% hexane, 1.0 mL/min, $\lambda = 240$ nm)
 minor diastereomer: τ_R : (minor) = 11.0 min, τ_R (major) = 12.3 min, major diastereomer:
 τ_R : (major) = 13.3 min, τ_R (minor) = 19.8 min.

6.4 Computational Calculations

6.4.1 Computational Methods

Density Functional Theory (DFT) calculations were performed with Gaussian09^[117] using Truhlar’s M06-2X hybrid meta GGA functional^[118] and Pople’s 6-31G(d) split valence basis set.^[119] M06-2X methods were found to give small errors for activation enthalpies when compared against G3B3,^[120] a standard method derived for predicting activation energies with high accuracies. Stationary points were optimized with default optimization criteria, tight SCF convergence and ultrafine grid for numerical integration of the exchange-correlation energy and potential. Solvation by dichloromethane (CH_2Cl_2) and toluene were described by a Solvent Model Based on Density Model (SMD).^[121] Additionally, high-precision harmonic frequencies for vibrational modes were computed from the Hessian. All transition structures (TSes) were verified by intrinsic reaction coordinate (IRC) calculations connecting them to relevant ground state structures. Reported energies are zero-point corrected electronic energies at 298.15K, using a quasi-RRHO treatment of vibrational entropies introduced by Grimme,^[122] unless otherwise stated. All molecular images are produced using Cylview.^[123]

6.4.2 Absolute Energies and Cartesian Coordinates

M06-2X/6-31g* in toluene (SMD)						
Cmpd.	E (au)	ZPE (au)	H (au)	T.qh-S (au)	qh-G(t) (au)	imag. ν
159 GS	−3318.5426	0.2556	−3318.2701	0.0591	−3318.3292	−72.26
159 TS	−3318.5948	0.2568	−3318.3201	0.0614	−3318.3815	
M06-2X/6-31g* in dichloromethane (SMD)						
160 GS	−3279.2895	0.2277	−3279.0466	0.0556	−3279.1023	−69.87
160 TS	−3279.3255	0.2288	−3279.0807	0.0570	−3279.1377	

Naphthamide 159 GS

				H	0.47393	−3.77936	0.14199
C	2.4828	2.9145	0.1278	H	−1.07645	−4.17995	0.93298
C	0.3171	1.0565	−0.0616	H	−1.03379	−3.75694	−0.80312
C	0.10281	2.46634	0.08587	C	−0.56231	−1.78992	1.88483
C	1.19406	3.36781	0.17215	H	−0.82329	−0.74492	2.05168
C	−1.22031	2.96411	0.14946	H	−1.17620	−2.41263	2.54168
H	−1.36363	4.03506	0.26308	H	0.49626	−1.93519	2.14137
C	−2.30522	2.13406	0.07837	C	2.72502	1.52870	0.01285
C	−2.09870	0.74444	−0.08521	H	3.74307	1.15606	−0.00119
C	−0.82279	0.20939	−0.16268	C	1.68630	0.63713	−0.07148
H	3.32114	3.59982	0.19055	Br	2.18870	−1.19543	−0.16201
H	0.97916	4.42772	0.27583	C	−4.44450	0.34382	−0.17095
H	−3.30663	2.54244	0.13683	H	−4.68578	0.85131	0.76996
O	−3.11756	−0.14677	−0.16521	H	−4.61248	1.02687	−1.01087
C	−0.76533	−1.26278	−0.52136	H	−5.08316	−0.53164	−0.28269
O	−0.74344	−1.59535	−1.69624	Naphthamide 159 TS			
N	−0.81303	−2.15633	0.50513				
C	−0.60189	−3.55193	0.17490	C	−3.19893	1.87356	1.00673

C	-0.76374	0.73127	0.05110	H	4.00793	2.21455	-1.34762
C	-0.91192	2.13889	0.26313	H	3.93743	1.31317	0.20772
C	-2.11894	2.68104	0.76679	H	4.65091	0.55903	-1.24434
C	0.15283	3.01660	-0.08225	Naphthamide 160 GS			
H	0.00164	4.08397	0.05465	C	-3.12664	1.55426	1.14596
C	1.30873	2.54972	-0.63673	C	-0.62388	0.70231	0.04840
C	1.51279	1.15014	-0.70790	C	-0.97813	2.08269	0.16934
C	0.56549	0.24532	-0.24151	C	-2.20434	2.48632	0.74466
H	-4.12504	2.27669	1.40200	C	-0.10346	3.07652	-0.36107
H	-2.17039	3.75159	0.94377	H	-0.41370	4.11630	-0.30778
H	2.07780	3.23090	-0.98231	C	1.06398	2.73520	-0.96497
O	2.63794	0.63958	-1.25425	C	1.52351	1.39168	-0.88329
C	1.08630	-1.06176	0.28411	C	0.75329	0.38786	-0.29268
O	0.44096	-2.06596	0.45922	H	-4.06287	1.84877	1.60741
N	2.44746	-0.97709	0.80090	H	-2.40083	3.54956	0.84866
C	2.39662	-1.18054	2.25021	H	1.72056	3.46769	-1.42098
H	2.02834	-2.17982	2.52536	O	2.76980	1.21869	-1.35976
H	3.40418	-1.04646	2.65416	H	3.07217	0.31502	-1.12022
H	1.74185	-0.42821	2.70068	C	1.42605	-0.86580	0.18759
C	3.29126	-1.98871	0.16654	O	0.87809	-1.93263	0.37581
H	3.31892	-1.80800	-0.91135	N	2.81774	-0.75602	0.41590
H	4.30661	-1.89239	0.56347	C	3.30352	0.29281	1.32808
H	2.93348	-3.01264	0.35237	H	3.28548	-0.07622	2.36083
C	-3.13224	0.51875	0.63208	H	4.33066	0.55704	1.06536
H	-4.02462	-0.09621	0.66782	H	2.68272	1.18529	1.26947
C	-1.97009	-0.02888	0.13514	C	3.47102	-2.03608	0.68075
Br	-2.18315	-1.71398	-0.71055	H	3.19702	-2.75578	-0.09020
C	3.87479	1.23357	-0.88127	H	4.55104	-1.87539	0.66276

H	3.18109	-2.44066	1.65794
C	-2.89456	0.20505	0.83125
H	-3.68462	-0.52449	0.97093
C	-1.71002	-0.20434	0.25300
Br	-1.82194	-1.92041	-0.56760

Naphthamide 159 TS

C	2.64764	-2.37819	0.41652
C	1.01114	-0.08502	-0.03365
C	2.41957	0.02348	0.18361
C	3.20852	-1.12683	0.42050
C	3.03475	1.30716	0.12790
H	4.10621	1.37206	0.29497
C	2.31587	2.42574	-0.16688
C	0.91165	2.32957	-0.34900
C	0.24992	1.11922	-0.18748
H	3.24864	-3.26167	0.60208
H	4.27256	-0.99554	0.59552

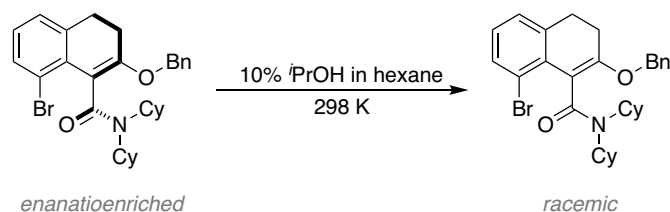
H	2.77772	3.40279	-0.25774
O	0.27034	3.48089	-0.62591
H	-0.63709	3.25210	-0.92238
C	-1.24559	1.23803	-0.13507
O	-1.83587	1.84755	-1.04054
N	-1.88633	0.80862	0.97505
C	-3.33773	0.73292	0.96136
H	-3.64746	-0.31683	0.87713
H	-3.73892	1.14917	1.88913
H	-3.71550	1.29513	0.11059
C	-1.24663	0.17229	2.11409
H	-0.21093	0.49643	2.20488
H	-1.78502	0.46982	3.01760
H	-1.28327	-0.92062	2.02625
C	1.27886	-2.51915	0.11764
H	0.83727	-3.50636	0.03818
C	0.49752	-1.41244	-0.11509
Br	-1.28482	-1.76243	-0.68848

7 Appendices

7.1 Barriers to Rotation

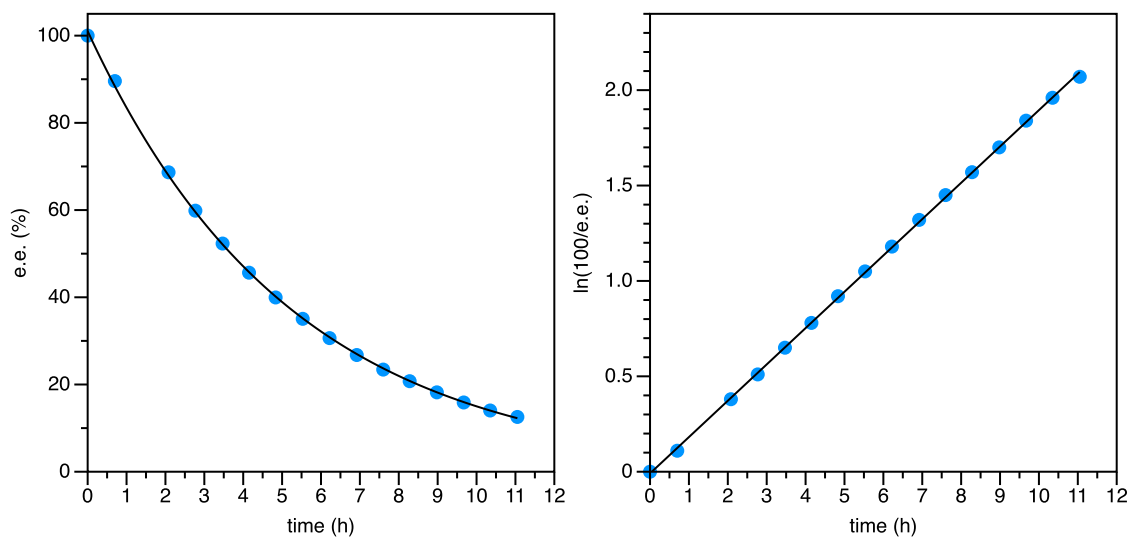
Barriers to rotation of benzylated naphthols were measured in *m*-xylene (10 mg/mL) and heated to the temperature stated by an oil bath. Samples were removed periodically and diluted with 50% isopropanol in hexane at room temperature. Barriers of enol ethers and naphthols were measured in solvent stated (concentration unknown) at room temperature (298 K) and samples were directly injected into HPLC.

7.1.1 Barrier to Rotation of 135



time (h)	time (s)	major ent. (%)	minor ent. (%)	e.e. (%)	$\ln(\frac{100}{\text{e.e.}})$
0.00	0	100.00	0.00	100.00	0.00
0.70	2520	94.79	5.21	89.58	0.11
2.08	7500	84.33	15.67	68.66	0.38
2.77	9960	79.93	20.07	59.86	0.51
3.47	12480	76.16	23.84	52.32	0.65
4.15	14940	72.82	27.18	45.64	0.78
4.83	17400	69.98	30.02	39.96	0.92
5.53	19920	67.53	32.47	35.06	1.05
6.22	22380	65.32	34.68	30.64	1.18

time (h)	time (s)	major ent. (%)	minor ent. (%)	e.e. (%)	$\ln(\frac{100}{\text{e.e.}})$
6.92	24900	63.38	36.62	26.76	1.32
7.60	27360	61.71	38.29	23.42	1.45
8.28	29820	60.38	39.62	20.76	1.57
8.98	32340	59.10	40.90	18.20	1.70
9.67	34800	57.94	42.06	15.88	1.84
10.35	37260	57.02	42.98	14.04	1.96
11.05	39780	56.28	43.72	12.56	2.07



$$\ln\left(\frac{100}{\text{e.e.}}\right) = k_{rac} \times t + \ln\left(\frac{100}{\text{e.e.}_{t=0}}\right)$$

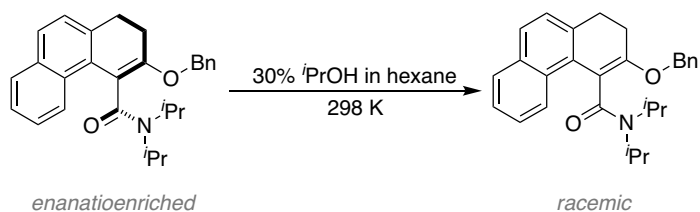
$$\text{and } k_{ent} = \frac{1}{2}k_{rac}$$

$$\text{Therefore } k_{ent} = \frac{1}{2} \text{slope} = 2.65 \times 10^{-5}$$

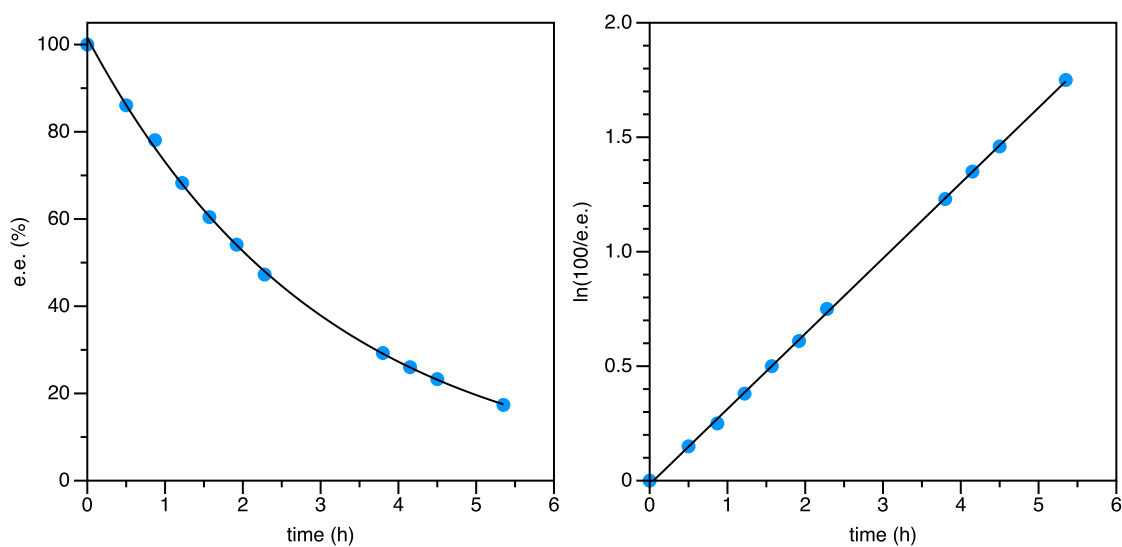
$$\Delta G_T^\ddagger = \ln\left(\frac{k_B T}{h \times k_{ent}}\right) RT = 23.7 \text{ kcal mol}^{-1}$$

$$t_{\frac{1}{2}}(rac) = \frac{\ln(2)}{k_{rac}} = 3.6 \text{ h}$$

7.1.2 Barrier to Rotation of 136



time (h)	time (s)	major ent. (%)	minor ent. (%)	e.e. (%)	$\ln(\frac{100}{\text{e.e.}})$
0.00	0	100.00	0.00	100.00	0.00
0.50	1800	93.04	6.96	86.08	0.15
0.87	3120	89.04	10.96	78.08	0.25
1.22	4380	84.13	15.87	68.26	0.38
1.57	5640	80.22	19.78	60.44	0.50
1.92	6900	77.06	22.94	54.12	0.61
2.28	8220	73.63	26.37	47.26	0.75
3.80	13680	64.63	35.37	29.26	1.23
4.15	14940	63.01	36.99	26.02	1.35
4.50	16200	61.64	38.36	23.28	1.46
5.35	19260	58.68	41.32	17.36	1.75



$$\ln\left(\frac{100}{\text{e.e.}}\right) = k_{rac} \times t + \ln\left(\frac{100}{\text{e.e.}_{t=0}}\right)$$

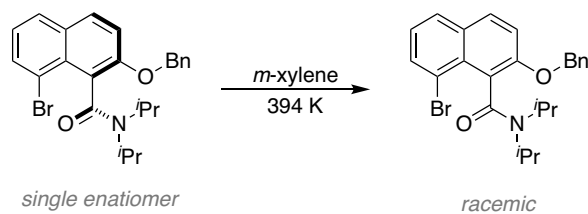
and $k_{ent} = \frac{1}{2}k_{rac}$

Therefore $k_{ent} = \frac{1}{2}slope = 4.56 \times 10^{-5}$

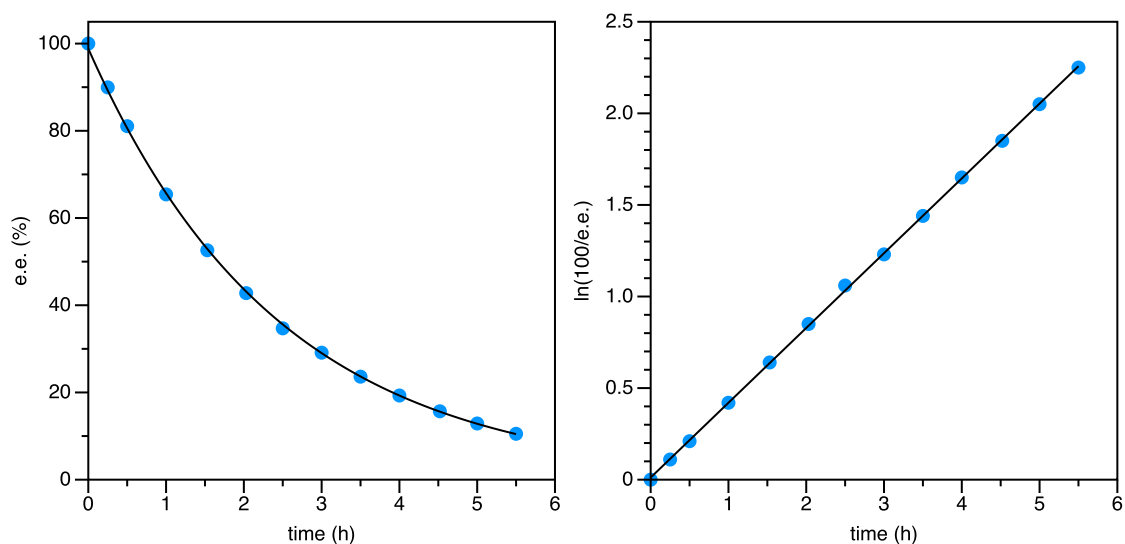
$$\Delta G_T^\ddagger = \ln\left(\frac{k_B T}{h \times k_{ent}}\right) RT = 23.4 \text{ kcal mol}^{-1}$$

$$t_{\frac{1}{2}}(rac) = \frac{\ln(2)}{k_{rac}} = 2.1 \text{ h}$$

7.1.3 Barrier to Rotation of 144



time (h)	time (s)	major ent. (%)	minor ent. (%)	e.e. (%)	$\ln(\frac{100}{\text{e.e.}})$
0.00	0	100.00	0.00	100.00	0.00
0.25	900	94.98	5.02	89.96	0.11
0.50	1800	90.53	9.47	81.06	0.21
1.00	3600	82.71	17.29	65.42	0.42
1.53	5520	76.30	23.70	52.60	0.64
2.03	7320	71.39	28.61	42.78	0.85
2.50	9000	67.35	32.65	34.70	1.06
3.00	10800	64.56	35.44	29.12	1.23
3.50	12600	61.81	38.19	23.62	1.44
4.00	14400	59.65	40.35	19.30	1.65
4.52	16260	57.84	42.16	15.68	1.85
5.00	18000	56.44	43.56	12.88	2.05
5.50	19800	55.26	44.74	10.52	2.25



$$\ln\left(\frac{100}{\text{e.e.}}\right) = k_{rac} \times t + \ln\left(\frac{100}{\text{e.e., } t=0}\right)$$

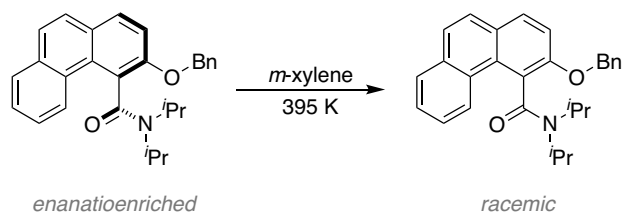
$$\text{and } k_{ent} = \frac{1}{2}k_{rac}$$

$$\text{Therefore } k_{ent} = \frac{1}{2}\text{slope} = 5.68 \times 10^{-5}$$

$$\Delta G_T^\ddagger = \ln\left(\frac{k_B T}{h \times k_{ent}}\right) RT = 30.9 \text{ kcal mol}^{-1}$$

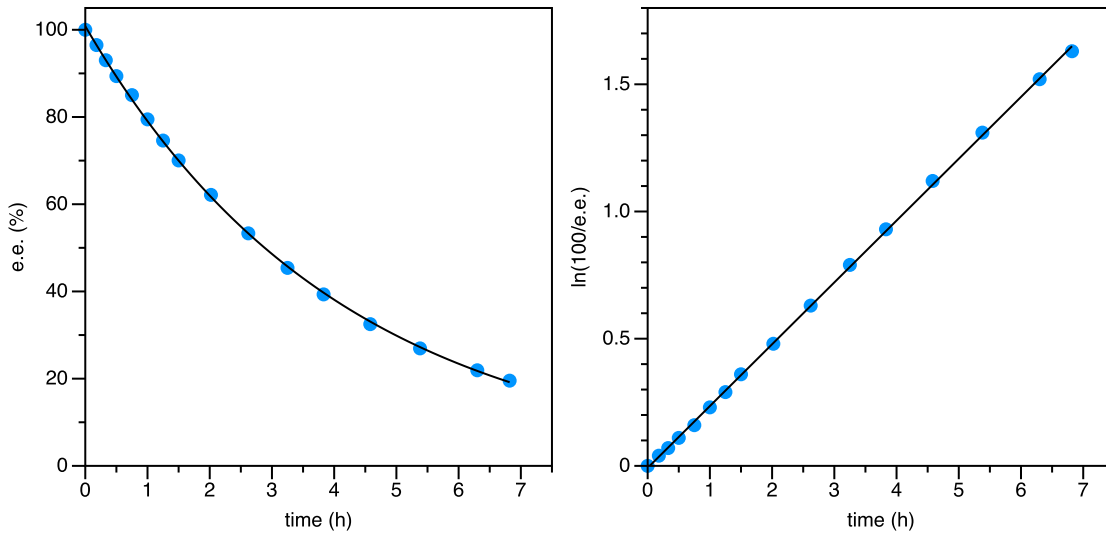
$$t_{\frac{1}{2}}(rac) = \frac{\ln(2)}{k_{rac}} = 102 \text{ min}$$

7.1.4 Barrier to Rotation of 145



time (h)	time (s)	major ent. (%)	minor ent. (%)	e.e. (%)	$\ln(\frac{100}{\text{e.e.}})$
0.00	0	100.00	0.00	100.00	0.00
0.18	660	98.25	1.75	96.5	0.04
0.33	1200	96.51	3.49	93.02	0.07

time (h)	time (s)	major ent. (%)	minor ent. (%)	e.e. (%)	$\ln(\frac{100}{e.e.})$
0.50	1800	94.69	5.31	89.38	0.11
0.75	2700	92.51	7.49	85.02	0.16
1.00	3600	89.73	10.27	79.46	0.23
1.25	4500	87.30	12.70	74.60	0.29
1.50	5400	85.02	14.98	70.04	0.36
2.02	7260	81.07	18.93	62.14	0.48
2.62	9420	76.66	23.34	53.32	0.63
3.25	11700	72.70	27.30	45.40	0.79
3.83	13800	69.66	30.34	39.32	0.93
4.58	16500	66.25	33.75	32.5	1.12
5.38	19380	63.47	36.53	26.94	1.31
6.30	22680	60.96	39.04	21.92	1.52
6.82	24540	59.77	40.23	19.54	1.63



$$\ln \left(\frac{100}{e.e.} \right) = k_{rac} \times t + \ln \left(\frac{100}{e.e., t=0} \right)$$

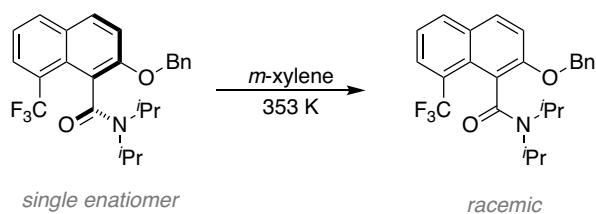
$$\text{and } k_{ent} = \frac{1}{2}k_{rac}$$

$$\text{Therefore } k_{ent} = \frac{1}{2}slope = 3.38 \times 10^{-5}$$

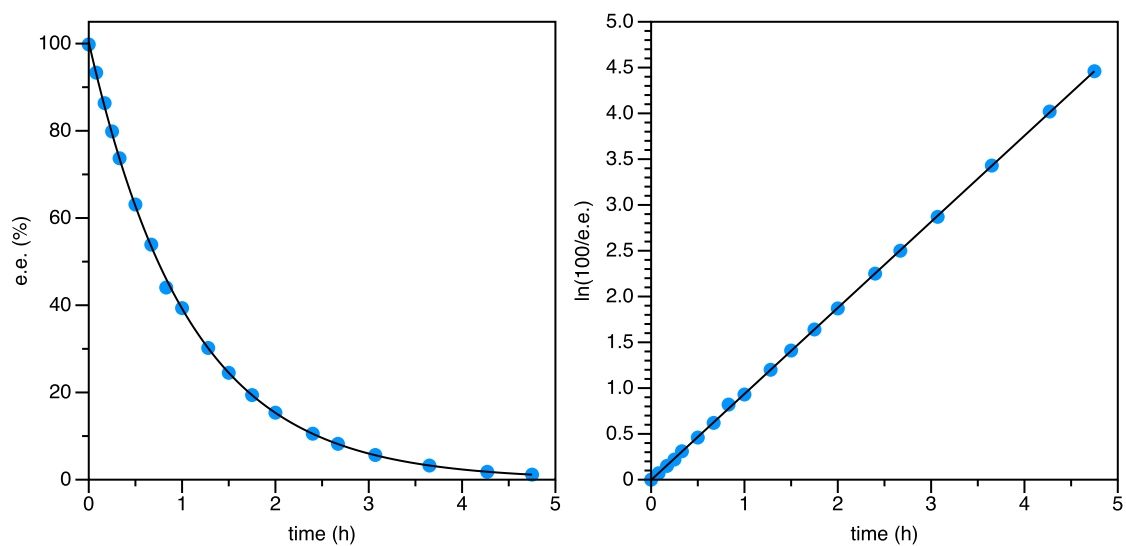
$$\Delta G_T^\ddagger = \ln \left(\frac{k_B T}{h \times k_{ent}} \right) RT = 31.4 \text{ kcal mol}^{-1}$$

$$t_{\frac{1}{2}}(rac) = \frac{\ln(2)}{k_{rac}} = 2.8 \text{ h}$$

7.1.5 Barrier to Rotation of 146



time (h)	time (s)	major ent. (%)	minor ent. (%)	e.e. (%)	$\ln(\frac{100}{\text{e.e.}})$
0.00	0	99.80	0.00	99.80	0.00
0.08	300	96.67	3.33	93.34	0.07
0.17	600	93.17	6.83	86.34	0.15
0.25	900	89.93	10.07	79.86	0.22
0.33	1200	86.85	13.15	73.70	0.31
0.50	1800	81.55	18.45	63.10	0.46
0.67	2400	76.95	23.05	53.90	0.62
0.83	3000	72.03	27.97	44.06	0.82
1.00	3600	69.67	30.33	39.34	0.93
1.28	4620	65.10	34.90	30.20	1.20
1.50	5400	62.25	37.75	24.50	1.41
1.75	6300	59.70	40.30	19.40	1.64
2.00	7200	57.68	42.32	15.36	1.87
2.40	8640	55.27	44.73	10.54	2.25
2.67	9600	54.11	45.89	8.22	2.50
3.07	11040	52.83	47.17	5.66	2.87
3.65	13140	51.62	48.38	3.24	3.43
4.27	15360	50.90	49.10	1.80	4.02
4.75	17100	50.58	49.42	1.16	4.46



$$\ln\left(\frac{100}{\text{e.e.}}\right) = k_{rac} \times t + \ln\left(\frac{100}{\text{e.e.}_{t=0}}\right)$$

$$\text{and } k_{ent} = \frac{1}{2}k_{rac}$$

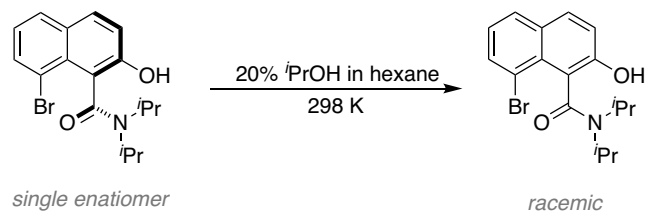
$$\text{Therefore } k_{ent} = \frac{1}{2} \text{slope} = 1.31 \times 10^{-4}$$

$$\Delta G_T^\ddagger = \ln\left(\frac{k_B T}{h \times k_{ent}}\right) RT = 27.1 \text{ kcal mol}^{-1}$$

$$t_{\frac{1}{2}}(rac) = \frac{\ln(2)}{k_{rac}} = 44 \text{ min}$$

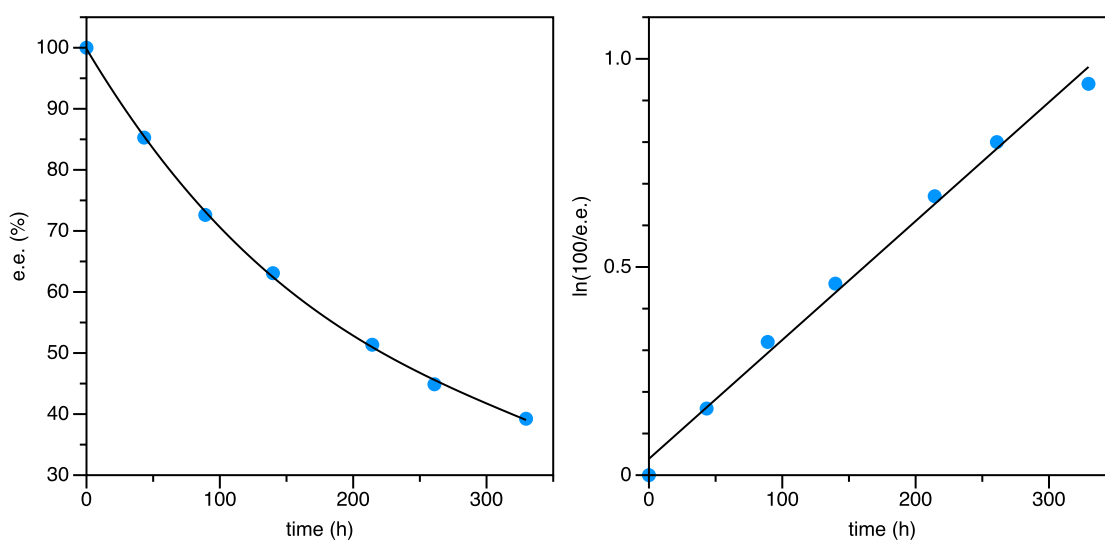
7.1.6 Barrier to Rotation of 147

20% Isopropanol in Hexane



time (h)	time (s)	major ent. (%)	minor ent. (%)	e.e. (%)	$\ln(\frac{100}{\text{e.e.}})$
0.00	0	100	0	100	0
43.27	155760	92.64	7.36	85.28	0.16

time (h)	time (s)	major ent. (%)	minor ent. (%)	e.e. (%)	$\ln(\frac{100}{e.e.})$
89.07	320640	86.31	13.69	72.62	0.32
139.80	503280	81.54	18.46	63.08	0.46
214.30	771480	75.68	24.32	51.36	0.67
260.93	939360	72.44	27.56	44.88	0.80
329.63	1186680	69.62	30.38	39.24	0.94



$$\ln \left(\frac{100}{e.e.} \right) = k_{rac} \times t + \ln \left(\frac{100}{e.e., t=0} \right)$$

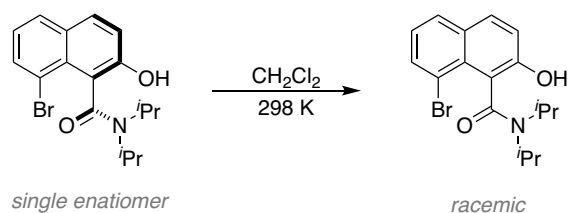
$$\text{and } k_{ent} = \frac{1}{2} k_{rac}$$

$$\text{Therefore } k_{ent} = \frac{1}{2} \text{slope} = 3.95 \times 10^{-7}$$

$$\Delta G_T^\ddagger = \ln \left(\frac{k_B T}{h \times k_{ent}} \right) RT = 26.2 \text{ kcal mol}^{-1}$$

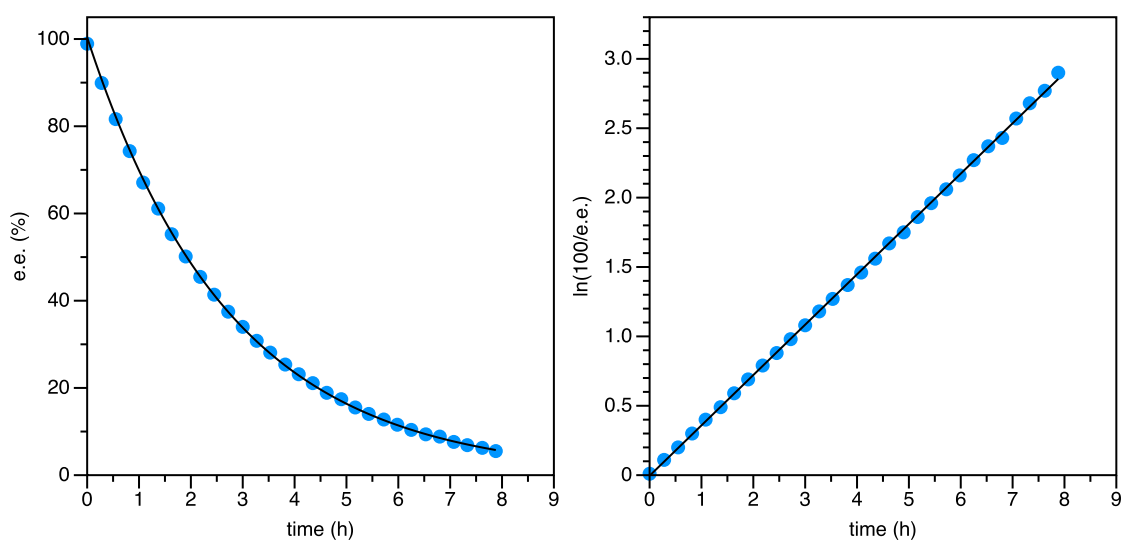
$$t_{\frac{1}{2}}(rac) = \frac{\ln(2)}{k_{rac}} = 10 \text{ days}$$

Dichloromethane



time (h)	time (s)	major ent. (%)	minor ent. (%)	e.e. (%)	$\ln(\frac{100}{e.e.})$
0.00	0	99.46	0.54	98.92	0.01
0.28	1020	94.96	5.04	89.92	0.11
0.55	1980	90.82	9.18	81.64	0.20
0.82	2940	87.15	12.85	74.30	0.30
1.08	3900	83.54	16.46	67.08	0.40
1.37	4920	80.56	19.44	61.12	0.49
1.63	5880	77.62	22.38	55.24	0.59
1.90	6840	75.07	24.93	50.14	0.69
2.18	7860	72.73	27.27	45.46	0.79
2.45	8820	70.69	29.31	41.38	0.88
2.72	9780	68.74	31.26	37.48	0.98
3.00	10800	67.00	33.00	34.00	1.08
3.27	11760	65.40	34.60	30.80	1.18
3.53	12720	64.05	35.95	28.10	1.27
3.82	13740	62.68	37.32	25.36	1.37
4.08	14700	61.57	38.43	23.14	1.46
4.35	15660	60.55	39.45	21.10	1.56
4.62	16620	59.44	40.56	18.88	1.67
4.90	17640	58.71	41.29	17.42	1.75
5.17	18600	57.76	42.24	15.52	1.86
5.43	19560	57.02	42.98	14.04	1.96
5.72	20580	56.38	43.62	12.76	2.06
5.98	21540	55.78	44.22	11.56	2.16
6.25	22500	55.19	44.81	10.38	2.27
6.53	23520	54.68	45.32	9.36	2.37

time (h)	time (s)	major ent. (%)	minor ent. (%)	e.e. (%)	$\ln(\frac{100}{e.e.})$
6.80	24480	54.42	45.58	8.84	2.43
7.07	25440	53.81	46.19	7.62	2.57
7.33	26400	53.44	46.56	6.88	2.68
7.62	27420	53.13	46.87	6.26	2.77
7.88	28380	52.76	47.24	5.52	2.90



$$\ln \left(\frac{100}{e.e.} \right) = k_{rac} \times t + \ln \left(\frac{100}{e.e., t=0} \right)$$

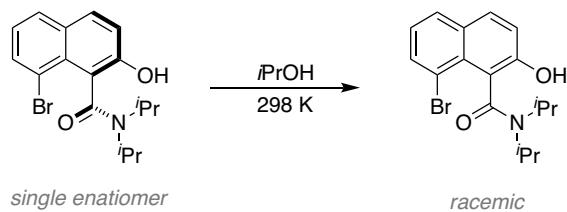
$$\text{and } k_{ent} = \frac{1}{2} k_{rac}$$

$$\text{Therefore } k_{ent} = \frac{1}{2} \text{slope} = 5.04 \times 10^{-5}$$

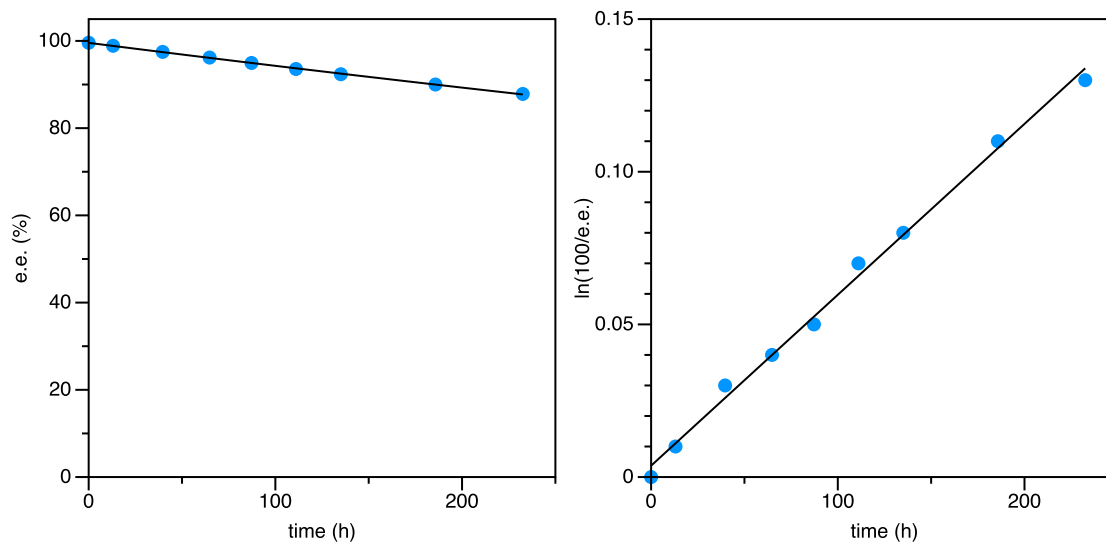
$$\Delta G_T^\ddagger = \ln \left(\frac{k_B T}{h \times k_{ent}} \right) RT = 23.3 \text{ kcal mol}^{-1}$$

$$t_{\frac{1}{2}}(rac) = \frac{\ln(2)}{k_{rac}} = 1.9 \text{ h}$$

Isopropanol



time (h)	time (s)	major ent. (%)	minor ent. (%)	e.e. (%)	$\ln(\frac{100}{\text{e.e.}})$
0.00	0	99.79	0.21	99.58	0.00
13.07	47040	99.44	0.56	98.88	0.01
39.65	142740	98.74	1.26	97.48	0.03
64.77	233160	98.09	1.91	96.18	0.04
87.23	314040	97.47	2.53	94.94	0.05
111.05	399780	96.78	3.22	93.56	0.07
135.08	486300	96.18	3.82	92.36	0.08
185.75	668700	95.00	5.00	90.00	0.11
232.53	837120	93.92	6.08	87.84	0.13



$$\ln\left(\frac{100}{\text{e.e.}}\right) = k_{\text{rac}} \times t + \ln\left(\frac{100}{\text{e.e.}_{t=0}}\right)$$

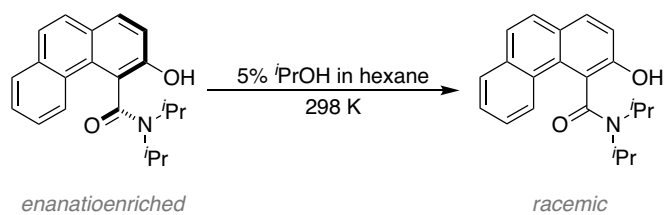
$$\text{and } k_{\text{ent}} = \frac{1}{2}k_{\text{rac}}$$

Therefore $k_{ent} = \frac{1}{2} \text{slope} = 7.55 \times 10^{-8}$

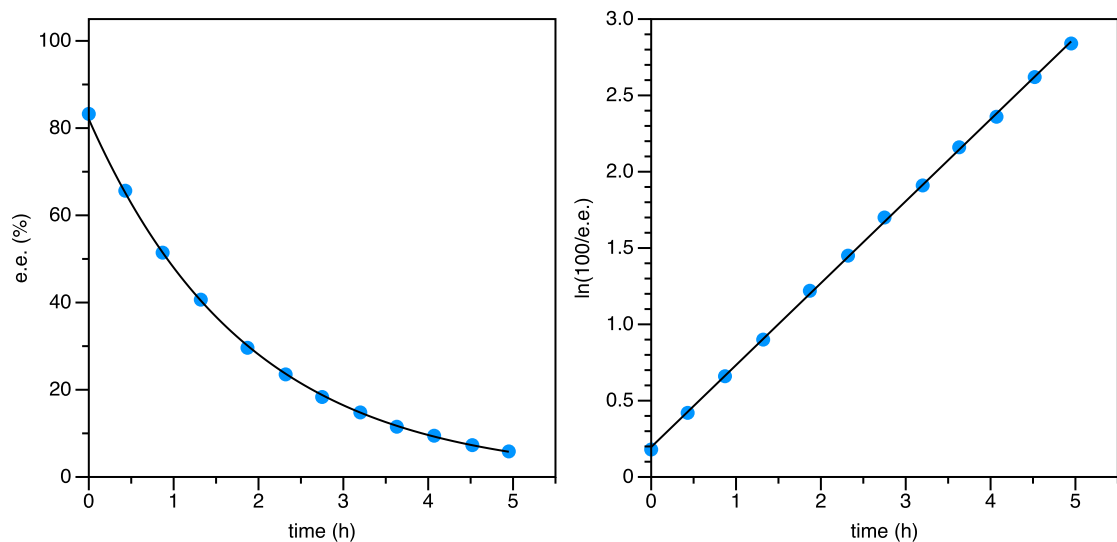
$$\Delta G_T^\ddagger = \ln \left(\frac{k_B T}{h \times k_{ent}} \right) RT = 27.2 \text{ kcal mol}^{-1}$$

$$t_{\frac{1}{2}}(rac) = \frac{\ln(2)}{k_{rac}} = 53 \text{ days}$$

7.1.7 Barrier to Rotation of 148



time (h)	time (s)	major ent. (%)	minor ent. (%)	e.e. (%)	$\ln(\frac{100}{\text{e.e.}})$
0.00	0	91.63	8.37	83.26	0.18
0.43	1560	82.82	17.18	65.64	0.42
0.87	3120	75.72	24.28	51.44	0.66
1.32	4740	70.33	29.67	40.66	0.90
1.87	6720	64.81	35.19	29.62	1.22
2.32	8340	61.76	38.24	23.52	1.45
2.75	9900	59.17	40.83	18.34	1.70
3.20	11520	57.40	42.60	14.80	1.91
3.63	13080	55.76	44.24	11.52	2.16
4.07	14640	54.73	45.27	9.46	2.36
4.52	16260	53.65	46.35	7.30	2.62
4.95	17820	52.93	47.07	5.86	2.84



$$\ln\left(\frac{100}{\text{e.e.}}\right) = k_{rac} \times t + \ln\left(\frac{100}{\text{e.e.}_{t=0}}\right)$$

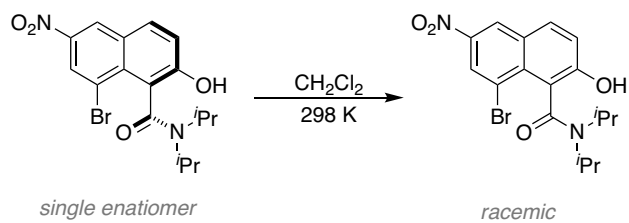
$$\text{and } k_{ent} = \frac{1}{2}k_{rac}$$

$$\text{Therefore } k_{ent} = \frac{1}{2}\text{slope} = 7.44 \times 10^{-5}$$

$$\Delta G_T^\ddagger = \ln\left(\frac{k_B T}{h \times k_{ent}}\right) RT = 23.1 \text{ kcal mol}^{-1}$$

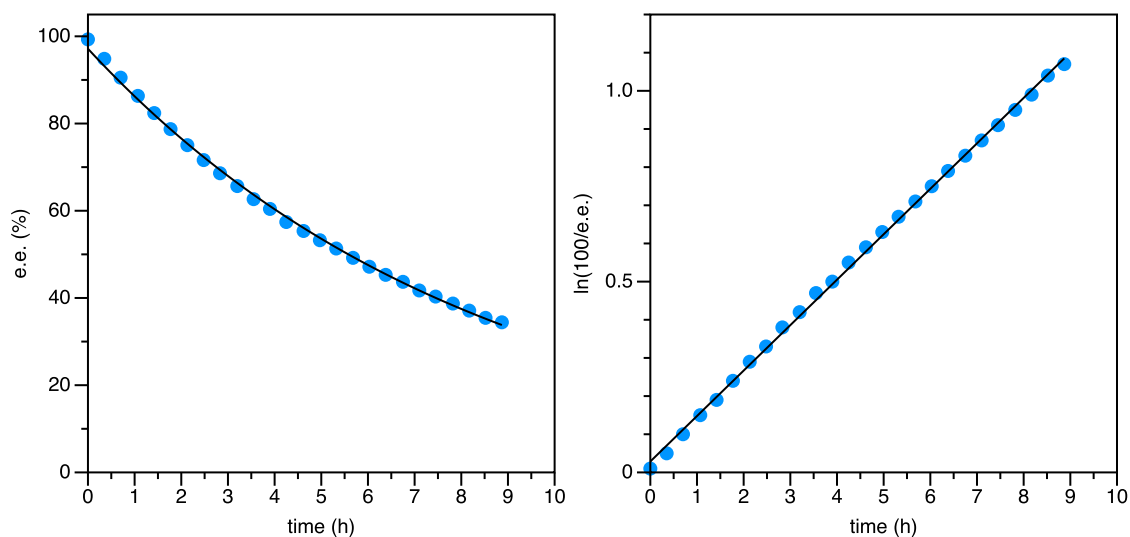
$$t_{\frac{1}{2}}(rac) = \frac{\ln(2)}{k_{rac}} = 78 \text{ min}$$

7.1.8 Barrier to Rotation of 161



time (h)	time (s)	major ent. (%)	minor ent. (%)	e.e. (%)	$\ln(\frac{100}{\text{e.e.}})$
0.00	0	99.65	0.35	99.30	0.01
0.35	1260	97.42	2.58	94.84	0.05
0.70	2520	95.26	4.74	90.52	0.10

time (h)	time (s)	major ent. (%)	minor ent. (%)	e.e. (%)	$\ln(\frac{100}{\text{e.e.}})$
1.07	3840	93.17	6.83	86.34	0.15
1.42	5100	91.20	8.80	82.40	0.19
1.77	6360	89.36	10.64	78.72	0.24
2.13	7680	87.52	12.48	75.04	0.29
2.48	8940	85.81	14.19	71.62	0.33
2.83	10200	84.30	15.70	68.60	0.38
3.20	11520	82.83	17.17	65.66	0.42
3.55	12780	81.33	18.67	62.66	0.47
3.90	14040	80.21	19.79	60.42	0.50
4.25	15300	78.71	21.29	57.42	0.55
4.62	16620	77.68	22.32	55.36	0.59
4.97	17880	76.62	23.38	53.24	0.63
5.32	19140	75.67	24.33	51.34	0.67
5.68	20460	74.60	25.40	49.20	0.71
6.03	21720	73.58	26.42	47.16	0.75
6.38	22980	72.65	27.35	45.30	0.79
6.75	24300	71.85	28.15	43.70	0.83
7.10	25560	70.86	29.14	41.72	0.87
7.45	26820	70.16	29.84	40.32	0.91
7.82	28140	69.36	30.64	38.72	0.95
8.17	29400	68.55	31.45	37.10	0.99
8.52	30660	67.72	32.28	35.44	1.04
8.87	31920	67.21	32.79	34.42	1.07



$$\ln\left(\frac{100}{\text{e.e.}}\right) = k_{rac} \times t + \ln\left(\frac{100}{\text{e.e.}_{t=0}}\right)$$

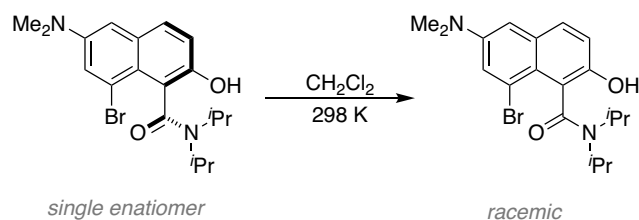
$$\text{and } k_{ent} = \frac{1}{2}k_{rac}$$

$$\text{Therefore } k_{ent} = \frac{1}{2} \text{slope} = 1.65 \times 10^{-5}$$

$$\Delta G_T^\ddagger = \ln\left(\frac{k_B T}{h \times k_{ent}}\right) RT = 24.0 \text{ kcal mol}^{-1}$$

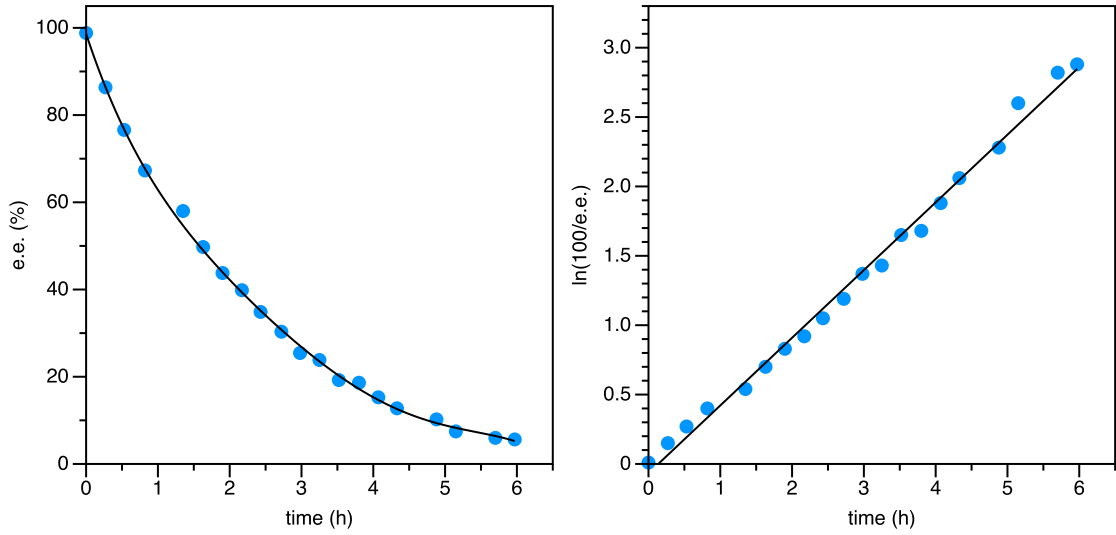
$$t_{\frac{1}{2}}(rac) = \frac{\ln(2)}{k_{rac}} = 5.8 \text{ h}$$

7.1.9 Barrier to Rotation of 163



time (h)	time (s)	major ent. (%)	minor ent. (%)	e.e. (%)	$\ln(\frac{100}{\text{e.e.}})$
0.00	0	99.41	0.59	98.82	0.01
0.27	960	93.18	6.82	86.36	0.15
0.53	1920	88.30	11.70	76.60	0.27
0.82	2940	83.65	16.35	67.30	0.40

time (h)	time (s)	major ent. (%)	minor ent. (%)	e.e. (%)	$\ln(\frac{100}{e.e.})$
1.35	4860	79.00	21.00	58.00	0.54
1.63	5880	74.87	25.13	49.74	0.70
1.90	6840	71.89	28.11	43.78	0.83
2.17	7800	69.92	30.08	39.84	0.92
2.43	8760	67.43	32.57	34.86	1.05
2.72	9780	65.16	34.84	30.32	1.19
2.98	10740	62.72	37.28	25.44	1.37
3.25	11700	61.92	38.08	23.84	1.43
3.52	12660	59.62	40.38	19.24	1.65
3.80	13680	59.31	40.69	18.62	1.68
4.07	14640	57.64	42.36	15.28	1.88
4.33	15600	56.38	43.62	12.76	2.06
4.88	17580	55.11	44.89	10.22	2.28
5.15	18540	53.73	46.27	7.46	2.60
5.70	20520	52.99	47.01	5.98	2.82
5.97	21480	52.81	47.19	5.62	2.88



$$\ln \left(\frac{100}{e.e.} \right) = k_{rac} \times t + \ln \left(\frac{100}{e.e., t=0} \right)$$

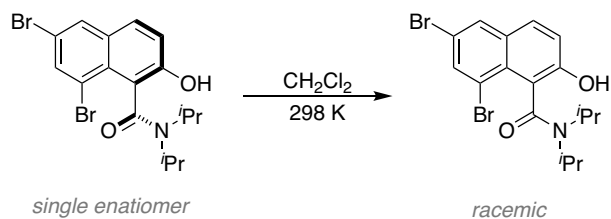
$$\text{and } k_{ent} = \frac{1}{2}k_{rac}$$

Therefore $k_{ent} = \frac{1}{2} slope = 7.06 \times 10^{-5}$

$$\Delta G_T^\ddagger = \ln \left(\frac{k_B T}{h \times k_{ent}} \right) RT = 23.1 \text{ kcal mol}^{-1}$$

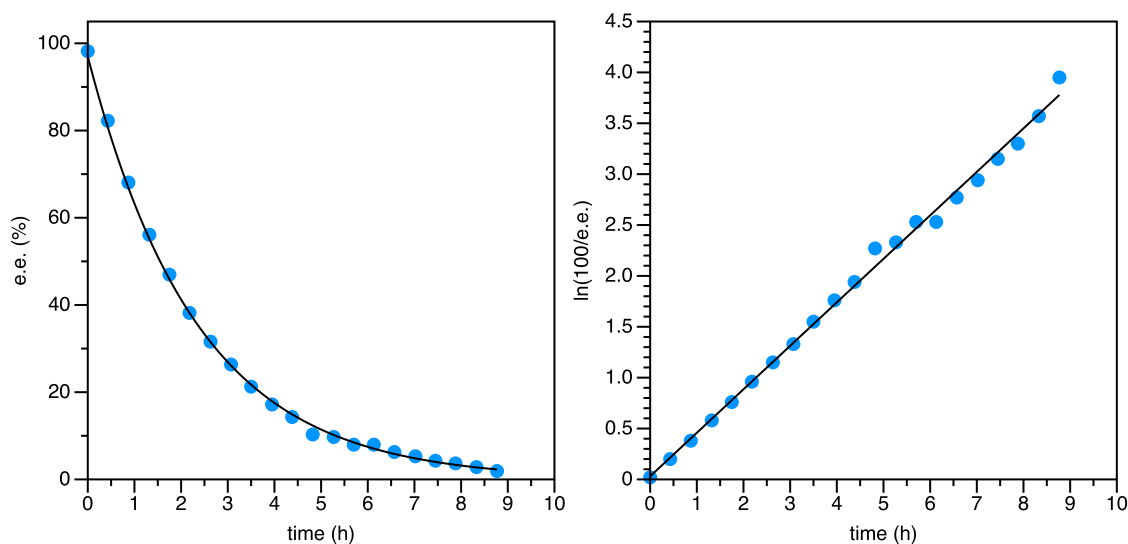
$$t_{\frac{1}{2}}(rac) = \frac{\ln(2)}{k_{rac}} = 82 \text{ min}$$

7.1.10 Barrier to Rotation of 164



time (h)	time (s)	major ent. (%)	minor ent. (%)	e.e. (%)	$\ln(\frac{100}{\text{e.e.}})$
0.00	0	99.10	0.90	98.20	0.02
0.43	1560	91.12	8.88	82.24	0.20
0.87	3120	84.04	15.96	68.08	0.38
1.32	4740	78.05	21.95	56.10	0.58
1.75	6300	73.48	26.52	46.96	0.76
2.18	7860	69.09	30.91	38.18	0.96
2.63	9480	65.79	34.21	31.58	1.15
3.07	11040	63.17	36.83	26.34	1.33
3.50	12600	60.63	39.37	21.26	1.55
3.95	14220	58.59	41.41	17.18	1.76
4.38	15780	57.15	42.85	14.30	1.94
4.82	17340	55.15	44.85	10.30	2.27
5.27	18960	54.86	45.14	9.72	2.33
5.70	20520	53.98	46.02	7.96	2.53
6.13	22080	53.98	46.02	7.96	2.53
6.57	23640	53.14	46.86	6.28	2.77
7.02	25260	52.65	47.35	5.30	2.94
7.45	26820	52.14	47.86	4.28	3.15
7.88	28380	51.84	48.16	3.68	3.30

time (h)	time (s)	major ent. (%)	minor ent. (%)	e.e. (%)	$\ln(\frac{100}{\text{e.e.}})$
8.33	30000	51.41	48.59	2.82	3.57
8.77	31560	50.96	49.04	1.92	3.95



$$\ln\left(\frac{100}{\text{e.e.}}\right) = k_{rac} \times t + \ln\left(\frac{100}{\text{e.e.}, t=0}\right)$$

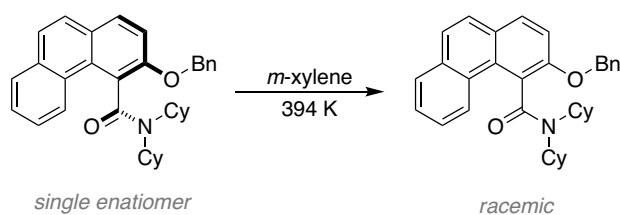
$$\text{and } k_{ent} = \frac{1}{2}k_{rac}$$

$$\text{Therefore } k_{ent} = \frac{1}{2}\text{slope} = 5.94 \times 10^{-5}$$

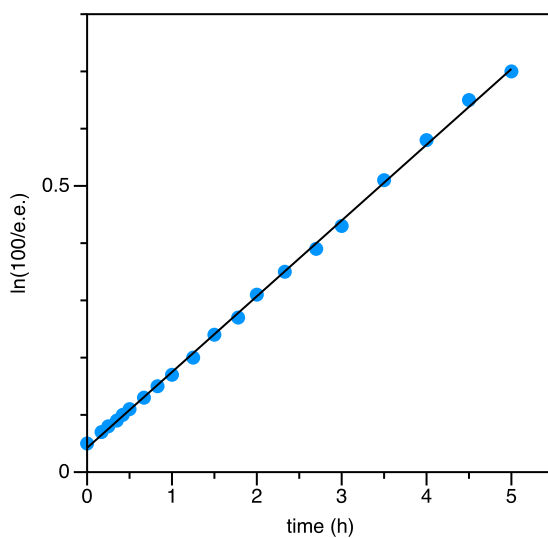
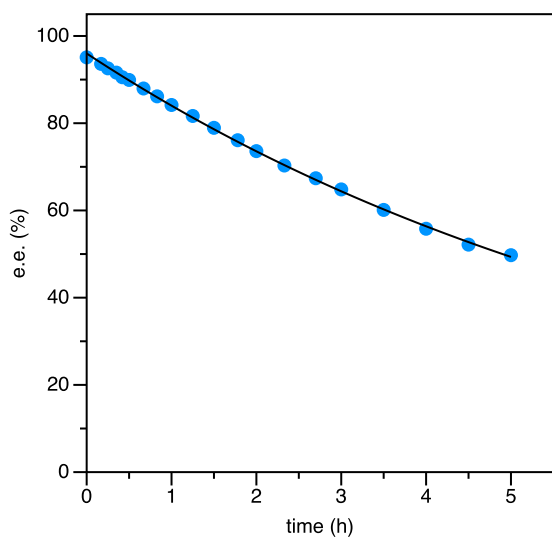
$$\Delta G_T^\ddagger = \ln\left(\frac{k_B T}{h \times k_{ent}}\right) RT = 23.2 \text{ kcal mol}^{-1}$$

$$t_{\frac{1}{2}}(rac) = \frac{\ln(2)}{k_{rac}} = 97 \text{ min}$$

7.1.11 Barrier to Rotation of 246



time (h)	time (s)	major ent. (%)	minor ent. (%)	e.e. (%)	$\ln(\frac{100}{e.e.})$
0.00	0	97.55	2.45	95.10	0.05
0.17	600	96.80	3.20	93.60	0.07
0.25	900	96.29	3.71	92.58	0.08
0.35	1260	95.80	4.20	91.60	0.09
0.42	1500	95.27	4.73	90.54	0.10
0.50	1800	94.96	5.04	89.92	0.11
0.67	2400	93.98	6.02	87.96	0.13
0.83	3000	93.08	6.92	86.16	0.15
1.00	3600	92.09	7.91	84.18	0.17
1.25	4500	90.83	9.17	81.66	0.20
1.50	5400	89.47	10.53	78.94	0.24
1.78	6420	88.05	11.95	76.10	0.27
2.00	7200	86.80	13.20	73.60	0.31
2.33	8400	85.15	14.85	70.30	0.35
2.70	9720	83.69	16.31	67.38	0.39
3.00	10800	82.41	17.59	64.82	0.43
3.50	12600	80.06	19.94	60.12	0.51
4.00	14400	77.90	22.10	55.80	0.58
4.50	16200	76.08	23.92	52.16	0.65
5.00	18000	74.87	25.13	49.74	0.70



$$\ln\left(\frac{100}{\text{e.e.}}\right) = k_{rac} \times t + \ln\left(\frac{100}{\text{e.e., } t=0}\right)$$

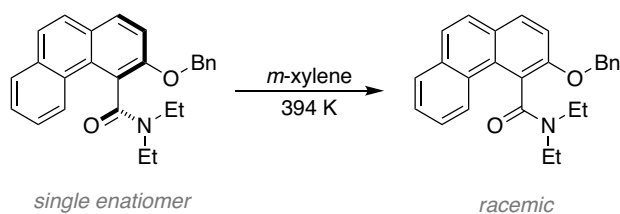
$$\text{and } k_{ent} = \frac{1}{2}k_{rac}$$

$$\text{Therefore } k_{ent} = \frac{1}{2}\text{slope} = 1.85 \times 10^{-5}$$

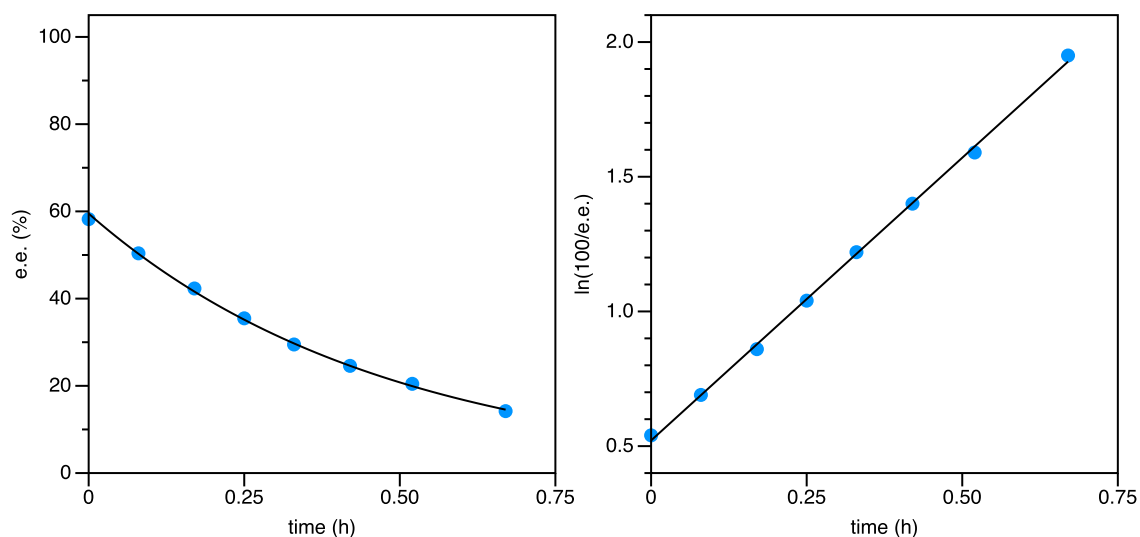
$$\Delta G_T^\ddagger = \ln\left(\frac{k_B T}{h \times k_{ent}}\right) RT = 31.8 \text{ kcal mol}^{-1}$$

$$t_{\frac{1}{2}}(rac) = \frac{\ln(2)}{k_{rac}} = 5.2 \text{ h}$$

7.1.12 Barrier to Rotation of 247



time (h)	time (s)	major ent. (%)	minor ent. (%)	e.e. (%)	$\ln\left(\frac{100}{\text{e.e.}}\right)$
0.00	0	79.11	20.89	58.22	0.54
0.08	300	75.19	24.81	50.38	0.69
0.17	600	71.16	28.84	42.32	0.86
0.25	900	67.74	32.26	35.48	1.04
0.33	1200	64.74	35.26	29.48	1.22
0.42	1500	62.29	37.71	24.58	1.40
0.52	1860	60.23	39.77	20.46	1.59
0.67	2400	57.10	42.90	14.20	1.95



$$\ln\left(\frac{100}{\text{e.e.}}\right) = k_{rac} \times t + \ln\left(\frac{100}{\text{e.e.}_{t=0}}\right)$$

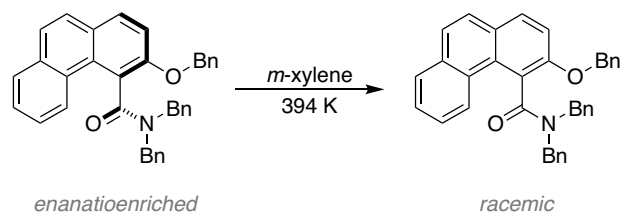
$$\text{and } k_{ent} = \frac{1}{2}k_{rac}$$

$$\text{Therefore } k_{ent} = \frac{1}{2} \text{slope} = 2.94 \times 10^{-4}$$

$$\Delta G_T^\ddagger = \ln\left(\frac{k_B T}{h \times k_{ent}}\right) RT = 29.6 \text{ kcal mol}^{-1}$$

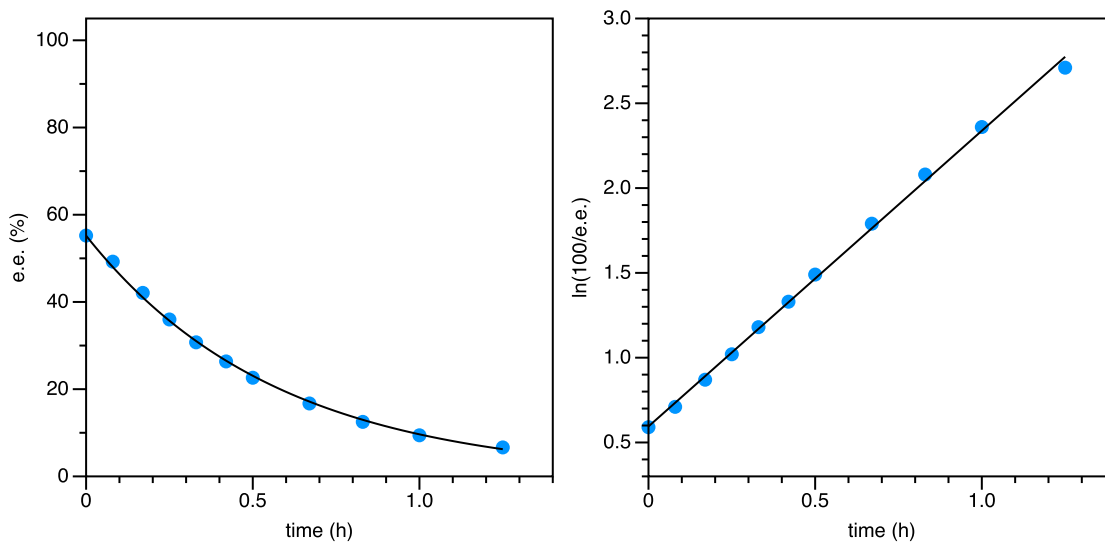
$$t_{\frac{1}{2}}(rac) = \frac{\ln(2)}{k_{rac}} = 20 \text{ min}$$

7.1.13 Barrier to Rotation of 248



time (h)	time (s)	major ent. (%)	minor ent. (%)	e.e. (%)	$\ln(\frac{100}{\text{e.e.}})$
0.00	0	77.61	22.39	55.22	0.59
0.08	300	74.62	25.38	49.24	0.71
0.17	600	71.04	28.96	42.08	0.87
0.25	900	67.99	32.01	35.98	1.02

time (h)	time (s)	major ent. (%)	minor ent. (%)	e.e. (%)	$\ln(\frac{100}{e.e.})$
0.33	1200	65.37	34.63	30.74	1.18
0.42	1500	63.18	36.82	26.36	1.33
0.50	1800	61.31	38.69	22.62	1.49
0.67	2400	58.36	41.64	16.72	1.79
0.83	3000	56.25	43.75	12.50	2.08
1.00	3600	54.71	45.29	9.42	2.36
1.25	4500	53.32	46.68	6.64	2.71



$$\ln \left(\frac{100}{e.e.} \right) = k_{rac} \times t + \ln \left(\frac{100}{e.e., t=0} \right)$$

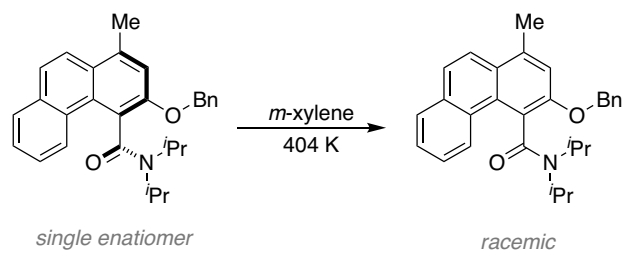
$$\text{and } k_{ent} = \frac{1}{2} k_{rac}$$

$$\text{Therefore } k_{ent} = \frac{1}{2} \text{slope} = 2.42 \times 10^{-4}$$

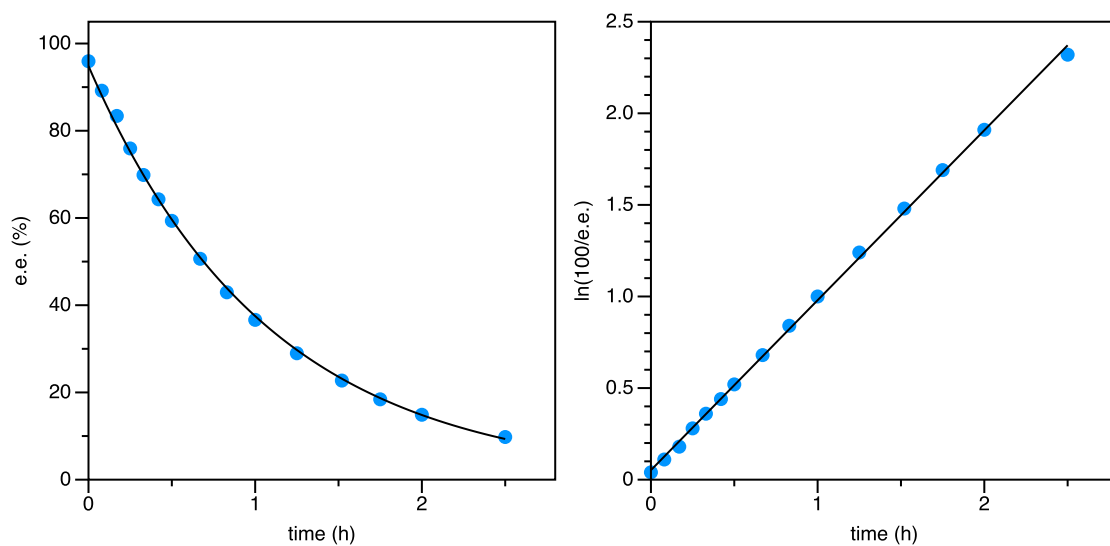
$$\Delta G_T^\ddagger = \ln \left(\frac{k_B T}{h \times k_{ent}} \right) RT = 29.8 \text{ kcal mol}^{-1}$$

$$t_{\frac{1}{2}}(rac) = \frac{\ln(2)}{k_{rac}} = 24 \text{ min}$$

7.1.14 Barrier to Rotation of 252



time (h)	time (s)	major ent. (%)	minor ent. (%)	e.e. (%)	$\ln(\frac{100}{\text{e.e.}})$
0.00	0	97.97	2.03	95.94	0.04
0.08	300	94.59	5.41	89.18	0.11
0.17	600	91.70	8.30	83.40	0.18
0.25	900	87.97	12.03	75.94	0.28
0.33	1200	84.93	15.07	69.86	0.36
0.42	1500	82.14	17.86	64.28	0.44
0.50	1800	79.67	20.33	59.34	0.52
0.67	2400	75.32	24.68	50.64	0.68
0.83	3000	71.48	28.52	42.96	0.84
1.00	3600	68.32	31.68	36.64	1.00
1.25	4500	64.49	35.51	28.98	1.24
1.52	5460	61.36	38.64	22.72	1.48
1.75	6300	59.21	40.79	18.42	1.69
2.00	7200	57.44	42.56	14.88	1.91
2.50	9000	54.89	45.11	9.78	2.32



$$\ln\left(\frac{100}{\text{e.e.}}\right) = k_{rac} \times t + \ln\left(\frac{100}{\text{e.e., } t=0}\right)$$

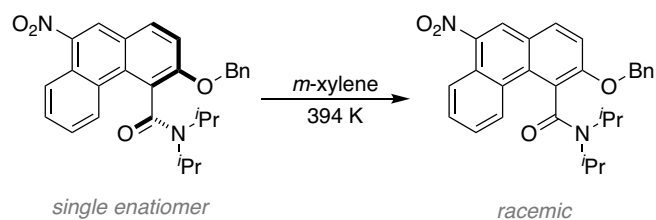
$$\text{and } k_{ent} = \frac{1}{2}k_{rac}$$

$$\text{Therefore } k_{ent} = \frac{1}{2}\text{slope} = 1.29 \times 10^{-4}$$

$$\Delta G_T^\ddagger = \ln\left(\frac{k_B T}{h \times k_{ent}}\right) RT = 31.1 \text{ kcal mol}^{-1}$$

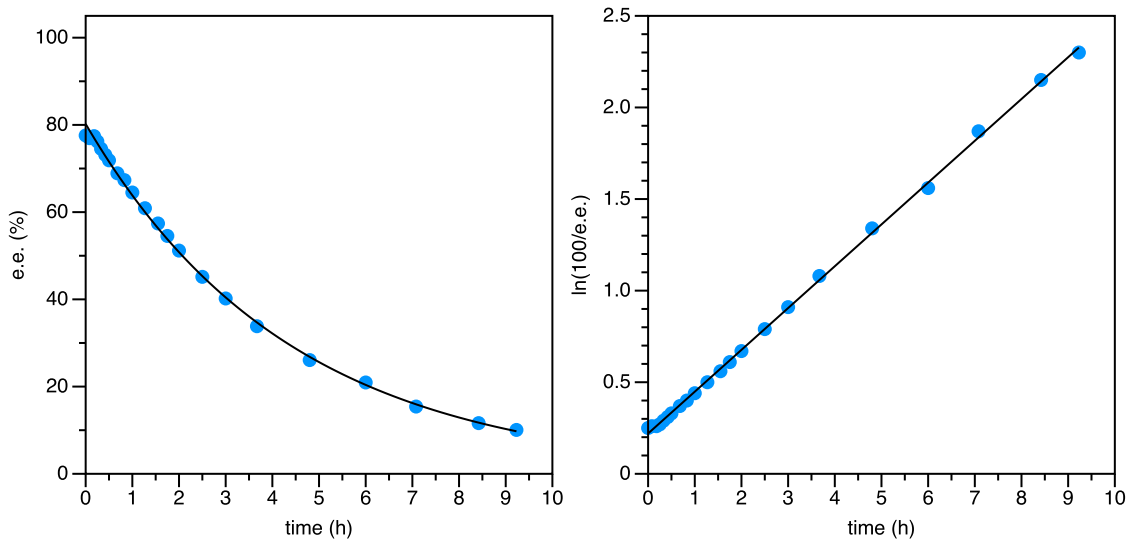
$$t_{\frac{1}{2}}(rac) = \frac{\ln(2)}{k_{rac}} = 45 \text{ min}$$

7.1.15 Barrier to Rotation of 253



time (h)	time (s)	major ent. (%)	minor ent. (%)	e.e. (%)	$\ln\left(\frac{100}{\text{e.e.}}\right)$
0.00	0	88.79	11.21	77.58	0.25
0.08	300	88.48	11.52	76.96	0.26
0.18	660	88.71	11.29	77.42	0.26

0.25	900	88.11	11.89	76.22	0.27
0.33	1200	87.26	12.74	74.52	0.29
0.42	1500	86.57	13.43	73.14	0.31
0.50	1800	85.94	14.06	71.88	0.33
0.68	2460	84.45	15.55	68.90	0.37
0.83	3000	83.67	16.33	67.34	0.40
1.00	3600	82.25	17.75	64.50	0.44
1.27	4560	80.45	19.55	60.90	0.50
1.55	5580	78.70	21.30	57.40	0.56
1.75	6300	77.27	22.73	54.54	0.61
2.00	7200	75.59	24.41	51.18	0.67
2.50	9000	72.58	27.42	45.16	0.79
3.00	10800	70.10	29.90	40.20	0.91
3.67	13200	66.92	33.08	33.84	1.08
4.80	17280	63.04	36.96	26.08	1.34
6.00	21600	60.47	39.53	20.94	1.56
7.08	25500	57.71	42.29	15.42	1.87
8.42	30300	55.81	44.19	11.62	2.15
9.23	33240	55.03	44.97	10.06	2.30



$$\ln \left(\frac{100}{\text{e.e.}} \right) = k_{rac} \times t + \ln \left(\frac{100}{\text{e.e.}_{t=0}} \right)$$

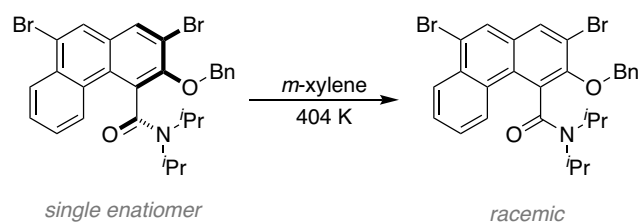
$$\text{and } k_{ent} = \frac{1}{2}k_{rac}$$

$$\text{Therefore } k_{ent} = \frac{1}{2}slope = 3.17 \times 10^{-5}$$

$$\Delta G_T^\ddagger = \ln\left(\frac{k_B T}{h \times k_{ent}}\right) RT = 31.4 \text{ kcal mol}^{-1}$$

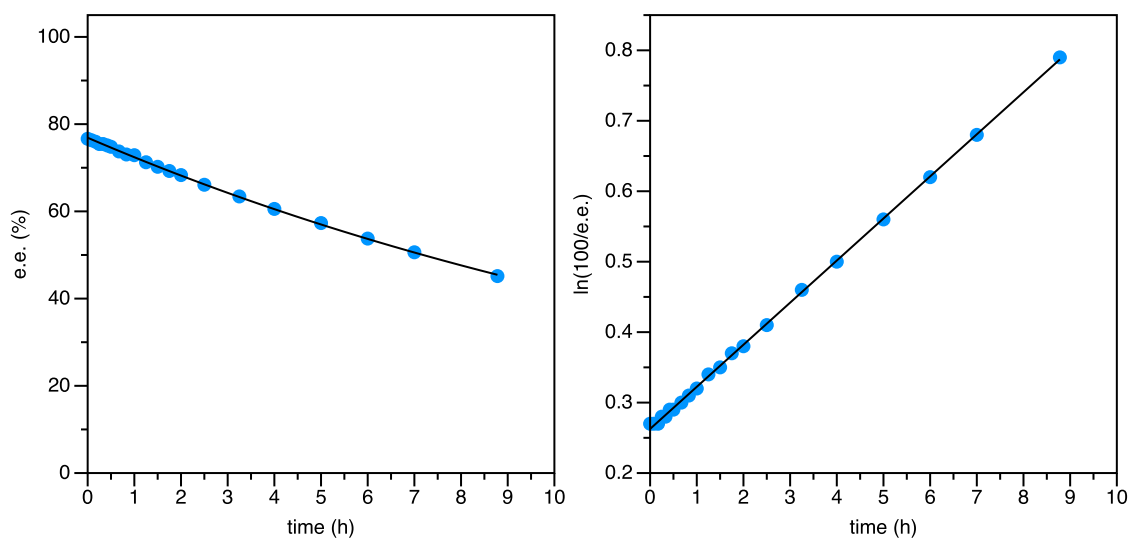
$$t_{\frac{1}{2}}(rac) = \frac{\ln(2)}{k_{rac}} = 3 \text{ h}$$

7.1.16 Barrier to Rotation of 254



time (h)	time (s)	major ent. (%)	minor ent. (%)	e.e. (%)	$\ln(\frac{100}{\text{e.e.}})$
0.00	0	88.32	11.68	76.64	0.27
0.08	300	88.16	11.84	76.32	0.27
0.17	600	87.98	12.02	75.96	0.27
0.25	900	87.72	12.28	75.44	0.28
0.33	1200	87.72	12.28	75.44	0.28
0.42	1500	87.56	12.44	75.12	0.29
0.50	1800	87.40	12.60	74.80	0.29
0.67	2400	86.87	13.13	73.74	0.30
0.83	3000	86.52	13.48	73.04	0.31
1.00	3600	86.44	13.56	72.88	0.32
1.25	4500	85.63	14.37	71.26	0.34
1.50	5400	85.11	14.89	70.22	0.35
1.75	6300	84.63	15.37	69.26	0.37
2.00	7200	84.16	15.84	68.32	0.38
2.50	9000	83.05	16.95	66.10	0.41
3.25	11700	81.71	18.29	63.42	0.46
4.00	14400	80.28	19.72	60.56	0.50

time (h)	time (s)	major ent. (%)	minor ent. (%)	e.e. (%)	$\ln(\frac{100}{e.e.})$
5.00	18000	78.66	21.34	57.32	0.56
6.00	21600	76.88	23.12	53.76	0.62
7.00	25200	75.31	24.69	50.62	0.68
8.78	31620	72.58	27.42	45.16	0.79



$$\ln\left(\frac{100}{e.e.}\right) = k_{rac} \times t + \ln\left(\frac{100}{e.e._{t=0}}\right)$$

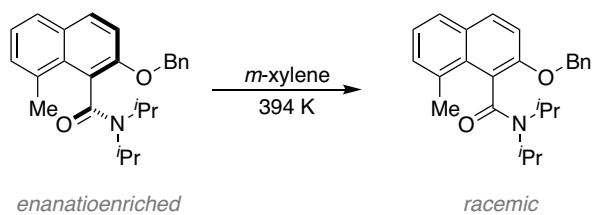
$$\text{and } k_{ent} = \frac{1}{2}k_{rac}$$

$$\text{Therefore } k_{ent} = \frac{1}{2}slope = 8.31 \times 10^{-6}$$

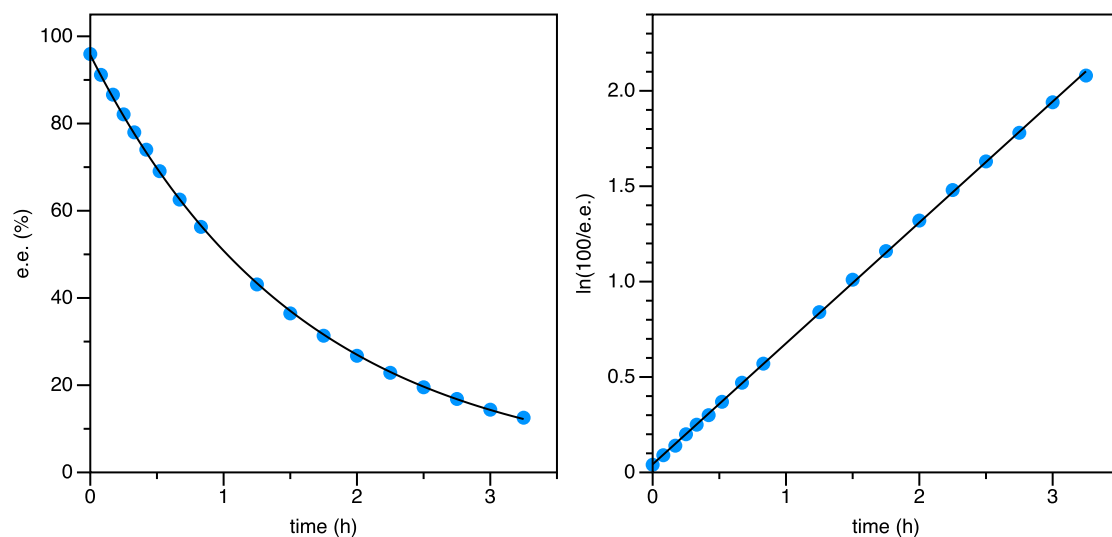
$$\Delta G_T^\ddagger = \ln\left(\frac{k_B T}{h \times k_{ent}}\right) RT = 33.3 \text{ kcal mol}^{-1}$$

$$t_{\frac{1}{2}}(rac) = \frac{\ln(2)}{k_{rac}} = 11.6 \text{ h}$$

7.1.17 Barrier to Rotation of 255



time (h)	time (s)	major ent. (%)	minor ent. (%)	e.e. (%)	$\ln(\frac{100}{\text{e.e.}})$
0.00	0	97.97	2.03	95.94	0.04
0.08	300	95.58	4.42	91.16	0.09
0.17	600	93.31	6.69	86.62	0.14
0.25	900	91.05	8.95	82.10	0.20
0.33	1200	88.99	11.01	77.98	0.25
0.42	1500	87.00	13.00	74.00	0.30
0.52	1860	84.54	15.46	69.08	0.37
0.67	2400	81.28	18.72	62.56	0.47
0.83	3000	78.15	21.85	56.30	0.57
1.25	4500	71.55	28.45	43.10	0.84
1.50	5400	68.23	31.77	36.46	1.01
1.75	6300	65.67	34.33	31.34	1.16
2.00	7200	63.37	36.63	26.74	1.32
2.25	8100	61.42	38.58	22.84	1.48
2.50	9000	59.76	40.24	19.52	1.63
2.75	9900	58.42	41.58	16.84	1.78
3.00	10800	57.19	42.81	14.38	1.94
3.25	11700	56.27	43.73	12.54	2.08



$$\ln\left(\frac{100}{\text{e.e.}}\right) = k_{rac} \times t + \ln\left(\frac{100}{\text{e.e.}_{t=0}}\right)$$

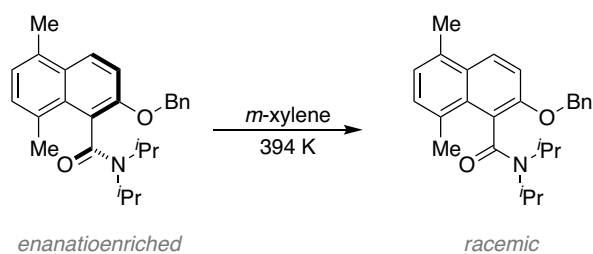
$$\text{and } k_{ent} = \frac{1}{2}k_{rac}$$

$$\text{Therefore } k_{ent} = \frac{1}{2} \text{slope} = 1.76 \times 10^{-4}$$

$$\Delta G_T^\ddagger = \ln\left(\frac{k_B T}{h \times k_{ent}}\right) RT = 30.6 \text{ kcal mol}^{-1}$$

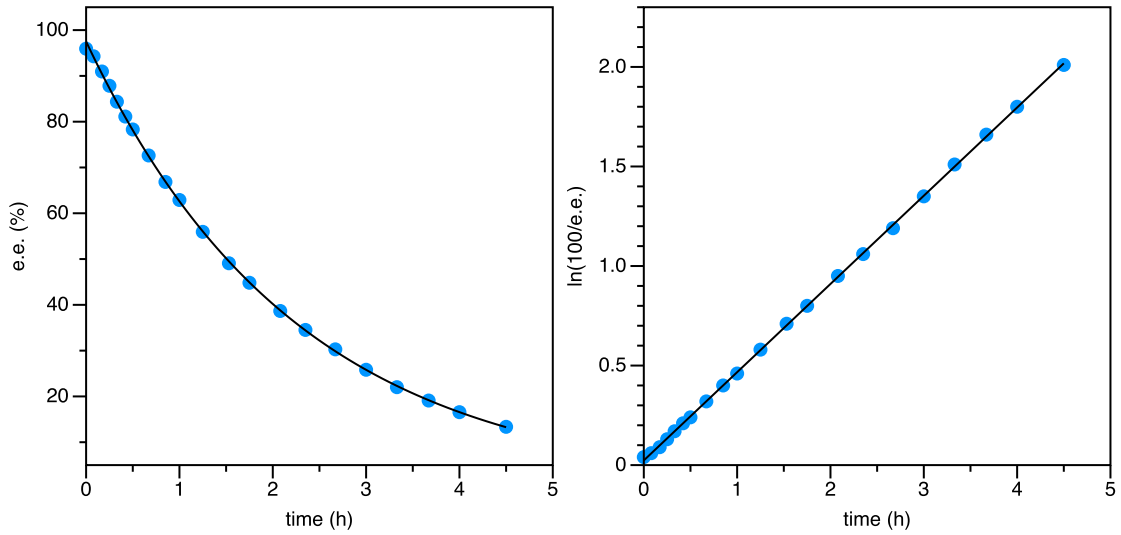
$$t_{\frac{1}{2}}(rac) = \frac{\ln(2)}{k_{rac}} = 66 \text{ min}$$

7.1.18 Barrier to Rotation of 256



time (h)	time (s)	major ent. (%)	minor ent. (%)	e.e. (%)	$\ln(\frac{100}{\text{e.e.}})$
0.00	0	97.97	2.03	95.94	0.04
0.08	300	97.14	2.86	94.28	0.06
0.17	600	95.48	4.52	90.96	0.09

time (h)	time (s)	major ent. (%)	minor ent. (%)	e.e. (%)	$\ln(\frac{100}{e.e.})$
0.25	900	93.92	6.08	87.84	0.13
0.33	1200	92.18	7.82	84.36	0.17
0.42	1500	90.56	9.44	81.12	0.21
0.50	1800	89.15	10.85	78.30	0.24
0.67	2400	86.31	13.69	72.62	0.32
0.85	3060	83.42	16.58	66.84	0.40
1.00	3600	81.45	18.55	62.90	0.46
1.25	4500	77.97	22.03	55.94	0.58
1.53	5520	74.54	25.46	49.08	0.71
1.75	6300	72.41	27.59	44.82	0.80
2.08	7500	69.33	30.67	38.66	0.95
2.35	8460	67.26	32.74	34.52	1.06
2.67	9600	65.14	34.86	30.28	1.19
3.00	10800	62.91	37.09	25.82	1.35
3.33	12000	61.01	38.99	22.02	1.51
3.67	13200	59.55	40.45	19.10	1.66
4.00	14400	58.28	41.72	16.56	1.80
4.50	16200	56.68	43.32	13.36	2.01



$$\ln \left(\frac{100}{e.e.} \right) = k_{rac} \times t + \ln \left(\frac{100}{e.e._{t=0}} \right)$$

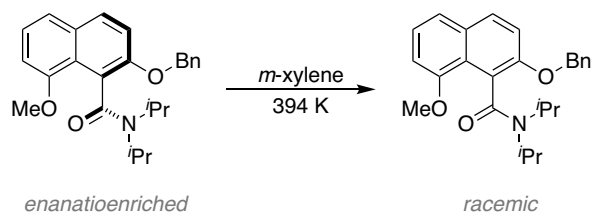
and $k_{ent} = \frac{1}{2}k_{rac}$

Therefore $k_{ent} = \frac{1}{2}slope = 6.16 \times 10^{-5}$

$$\Delta G_T^\ddagger = \ln\left(\frac{k_B T}{h \times k_{ent}}\right) RT = 30.9 \text{ kcal mol}^{-1}$$

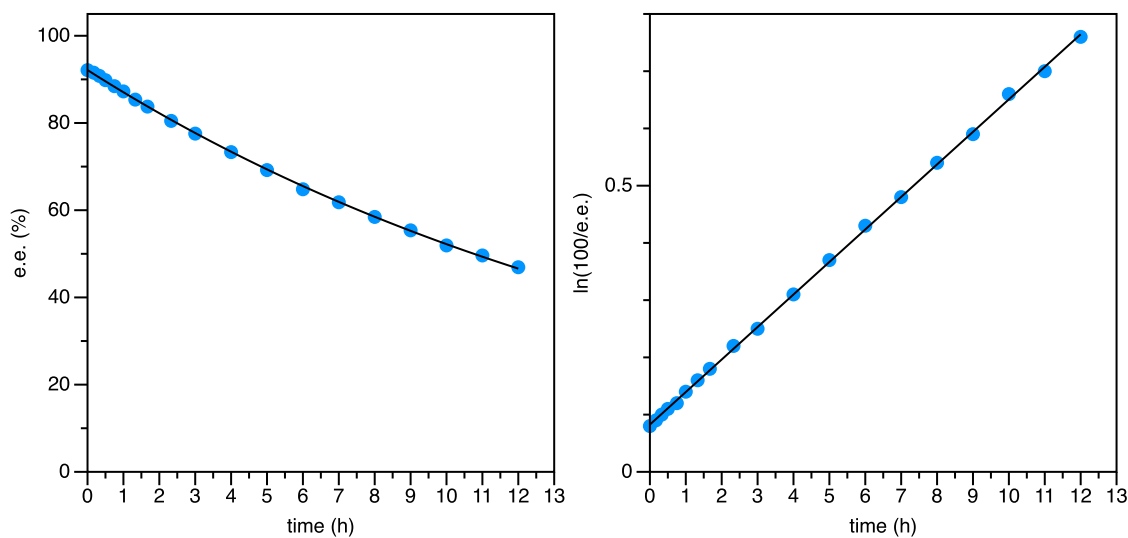
$$t_{\frac{1}{2}}(rac) = \frac{\ln(2)}{k_{rac}} = 94 \text{ min}$$

7.1.19 Barrier to Rotation of 257



time (h)	time (s)	major ent. (%)	minor ent. (%)	e.e. (%)	$\ln(\frac{100}{\text{e.e.}})$
0.00	0	96.06	3.94	92.12	0.08
0.17	600	95.77	4.23	91.54	0.09
0.33	1200	95.40	4.60	90.80	0.10
0.50	1800	94.91	5.09	89.82	0.11
0.75	2700	94.22	5.78	88.44	0.12
1.00	3600	93.62	6.38	87.24	0.14
1.33	4800	92.68	7.32	85.36	0.16
1.67	6000	91.88	8.12	83.76	0.18
2.33	8400	90.24	9.76	80.48	0.22
3.00	10800	88.78	11.22	77.56	0.25
4.00	14400	86.66	13.34	73.32	0.31
5.00	18000	84.60	15.40	69.20	0.37
6.00	21600	82.40	17.60	64.80	0.43
7.00	25200	80.91	19.09	61.82	0.48
8.00	28800	79.23	20.77	58.46	0.54
9.00	32400	77.69	22.31	55.38	0.59
10.00	36000	75.96	24.04	51.92	0.66

time (h)	time (s)	major ent. (%)	minor ent. (%)	e.e. (%)	$\ln(\frac{100}{\text{e.e.}})$
11.00	39600	74.81	25.19	49.62	0.70
12.00	43200	73.46	26.54	46.92	0.76



$$\ln\left(\frac{100}{\text{e.e.}}\right) = k_{rac} \times t + \ln\left(\frac{100}{\text{e.e.}_{t=0}}\right)$$

$$\text{and } k_{ent} = \frac{1}{2}k_{rac}$$

$$\text{Therefore } k_{ent} = \frac{1}{2}\text{slope} = 7.89 \times 10^{-6}$$

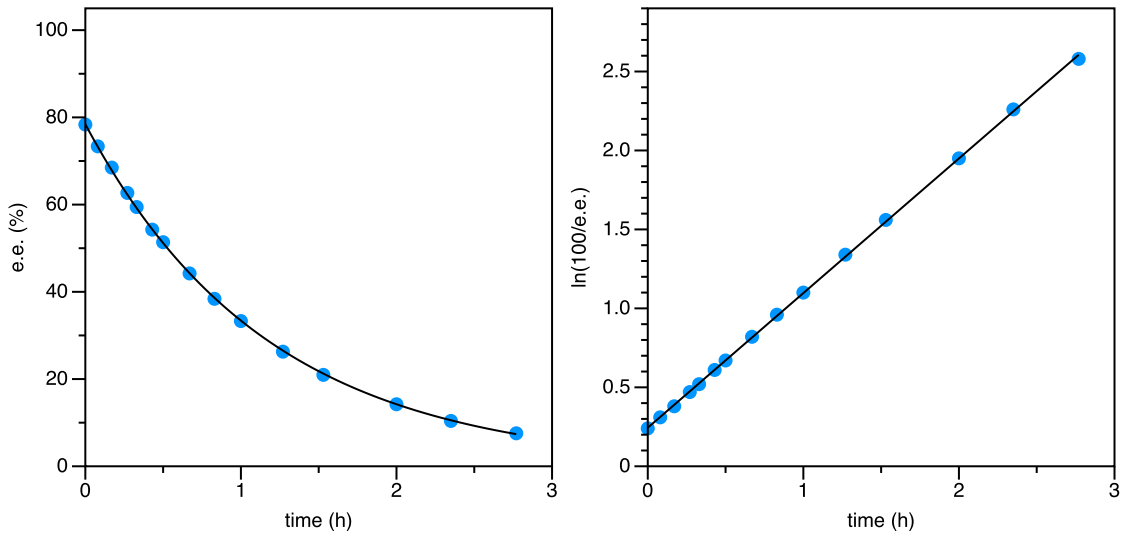
$$\Delta G_T^\ddagger = \ln\left(\frac{k_B T}{h \times k_{ent}}\right) RT = 32.5 \text{ kcal mol}^{-1}$$

$$t_{\frac{1}{2}}(rac) = \frac{\ln(2)}{k_{rac}} = 12.2 \text{ h}$$

7.1.20 Barrier to Rotation of 258



time (h)	time (s)	major ent. (%)	minor ent. (%)	e.e. (%)	$\ln(\frac{100}{e.e.})$
0.00	0	89.18	10.82	78.36	0.24
0.08	300	86.68	13.32	73.36	0.31
0.17	600	84.24	15.76	68.48	0.38
0.27	960	81.34	18.66	62.68	0.47
0.33	1200	79.72	20.28	59.44	0.52
0.43	1560	77.13	22.87	54.26	0.61
0.50	1800	75.69	24.31	51.38	0.67
0.67	2400	72.11	27.89	44.22	0.82
0.83	3000	69.20	30.80	38.40	0.96
1.00	3600	66.65	33.35	33.30	1.10
1.27	4560	63.14	36.86	26.28	1.34
1.53	5520	60.48	39.52	20.96	1.56
2.00	7200	57.11	42.89	14.22	1.95
2.35	8460	55.20	44.80	10.40	2.26
2.77	9960	53.78	46.22	7.56	2.58



$$\ln\left(\frac{100}{e.e.}\right) = k_{rac} \times t + \ln\left(\frac{100}{e.e., t=0}\right)$$

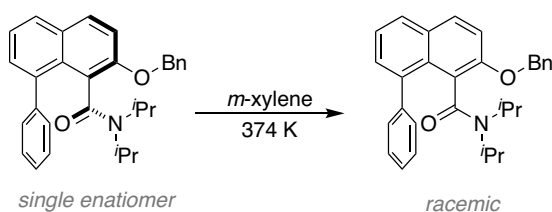
$$\text{and } k_{ent} = \frac{1}{2}k_{rac}$$

Therefore $k_{ent} = \frac{1}{2} slope = 1.19 \times 10^{-4}$

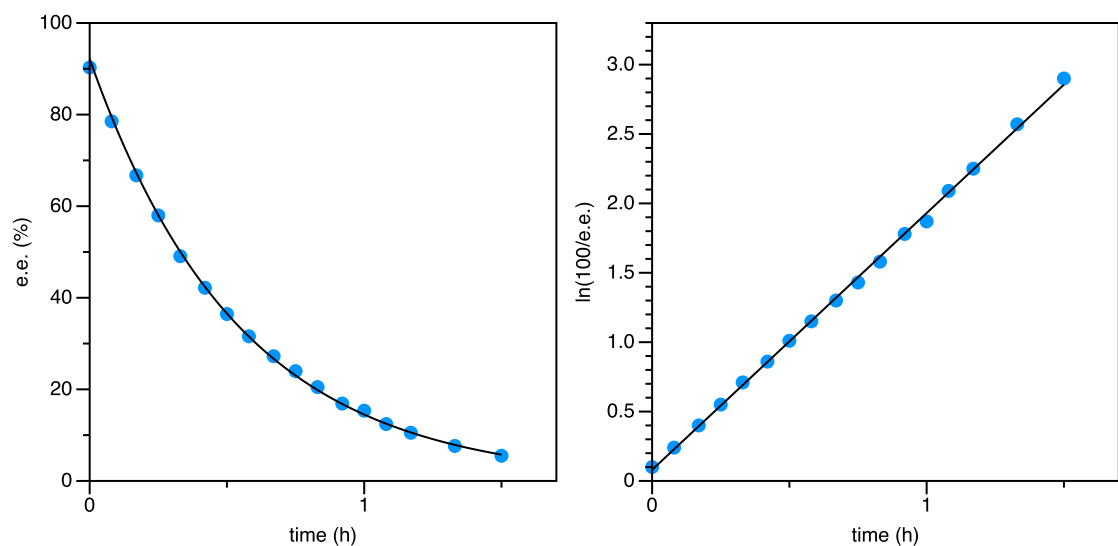
$$\Delta G_T^\ddagger = \ln \left(\frac{k_B T}{h \times k_{ent}} \right) RT = 27.2 \text{ kcal mol}^{-1}$$

$$t_{\frac{1}{2}}(rac) = \frac{\ln(2)}{k_{rac}} = 49 \text{ min}$$

7.1.21 Barrier to Rotation of 259



time (h)	time (s)	major ent. (%)	minor ent. (%)	e.e. (%)	$\ln(\frac{100}{\text{e.e.}})$
0.00	0	95.14	4.86	90.28	0.10
0.08	300	89.26	10.74	78.52	0.24
0.17	600	83.37	16.63	66.74	0.40
0.25	900	78.99	21.01	57.98	0.55
0.33	1200	74.54	25.46	49.08	0.71
0.42	1500	71.09	28.91	42.18	0.86
0.50	1800	68.22	31.78	36.44	1.01
0.58	2100	65.79	34.21	31.58	1.15
0.67	2400	63.62	36.38	27.24	1.30
0.75	2700	61.99	38.01	23.98	1.43
0.83	3000	60.25	39.75	20.50	1.58
0.92	3300	58.45	41.55	16.90	1.78
1.00	3600	57.67	42.33	15.34	1.87
1.08	3900	56.21	43.79	12.42	2.09
1.17	4200	55.26	44.74	10.52	2.25
1.33	4800	53.82	46.18	7.64	2.57
1.50	5400	52.75	47.25	5.50	2.90



$$\ln\left(\frac{100}{\text{e.e.}}\right) = k_{rac} \times t + \ln\left(\frac{100}{\text{e.e.}_{t=0}}\right)$$

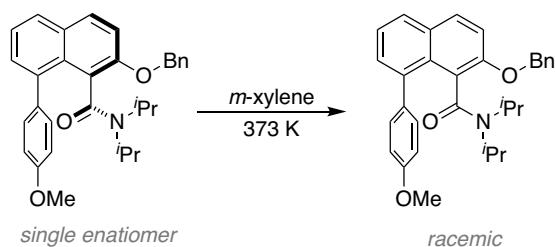
$$\text{and } k_{ent} = \frac{1}{2}k_{rac}$$

$$\text{Therefore } k_{ent} = \frac{1}{2} \text{slope} = 2.57 \times 10^{-4}$$

$$\Delta G_T^\ddagger = \ln\left(\frac{k_B T}{h \times k_{ent}}\right) RT = 28.2 \text{ kcal mol}^{-1}$$

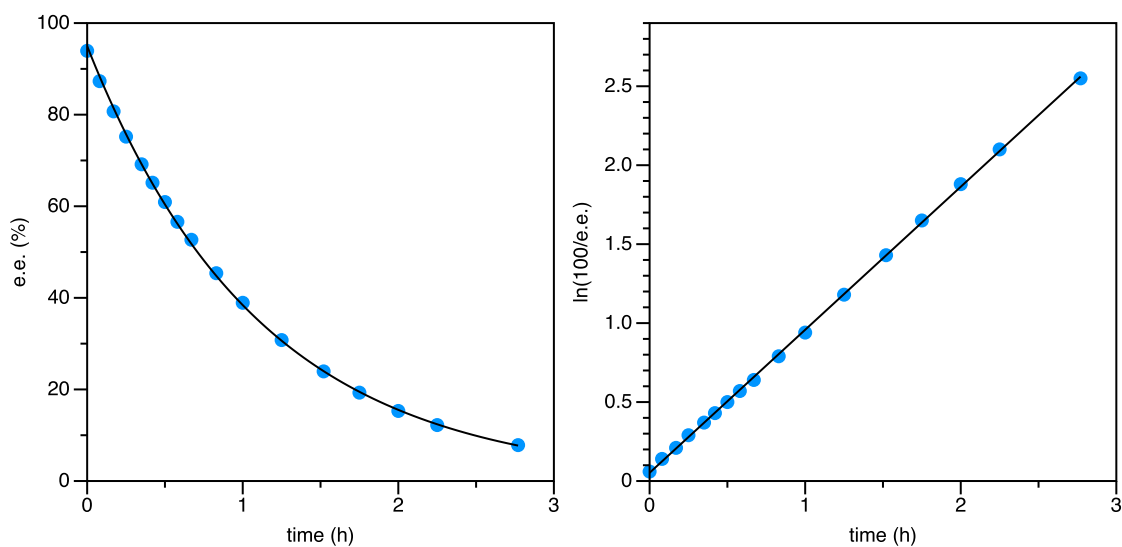
$$t_{\frac{1}{2}}(rac) = \frac{\ln(2)}{k_{rac}} = 22 \text{ min}$$

7.1.22 Barrier to Rotation of 260



time (h)	time (s)	major ent. (%)	minor ent. (%)	e.e. (%)	$\ln(\frac{100}{\text{e.e.}})$
0.00	0	96.97	3.03	93.94	0.06
0.08	300	93.66	6.34	87.32	0.14
0.17	600	90.36	9.64	80.72	0.21

time (h)	time (s)	major ent. (%)	minor ent. (%)	e.e. (%)	$\ln(\frac{100}{e.e.})$
0.25	900	87.60	12.40	75.20	0.29
0.35	1260	84.58	15.42	69.16	0.37
0.42	1500	82.57	17.43	65.14	0.43
0.50	1800	80.46	19.54	60.92	0.50
0.58	2100	78.30	21.70	56.60	0.57
0.67	2400	76.34	23.66	52.68	0.64
0.83	3000	72.69	27.31	45.38	0.79
1.00	3600	69.46	30.54	38.92	0.94
1.25	4500	65.39	34.61	30.78	1.18
1.52	5460	61.97	38.03	23.94	1.43
1.75	6300	59.65	40.35	19.30	1.65
2.00	7200	57.65	42.35	15.30	1.88
2.25	8100	56.11	43.89	12.22	2.10
2.77	9960	53.92	46.08	7.84	2.55



$$\ln \left(\frac{100}{e.e.} \right) = k_{rac} \times t + \ln \left(\frac{100}{e.e., t=0} \right)$$

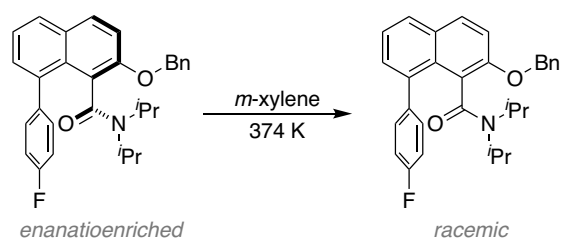
$$\text{and } k_{ent} = \frac{1}{2}k_{rac}$$

$$\text{Therefore } k_{ent} = \frac{1}{2}slope = 1.26 \times 10^{-4}$$

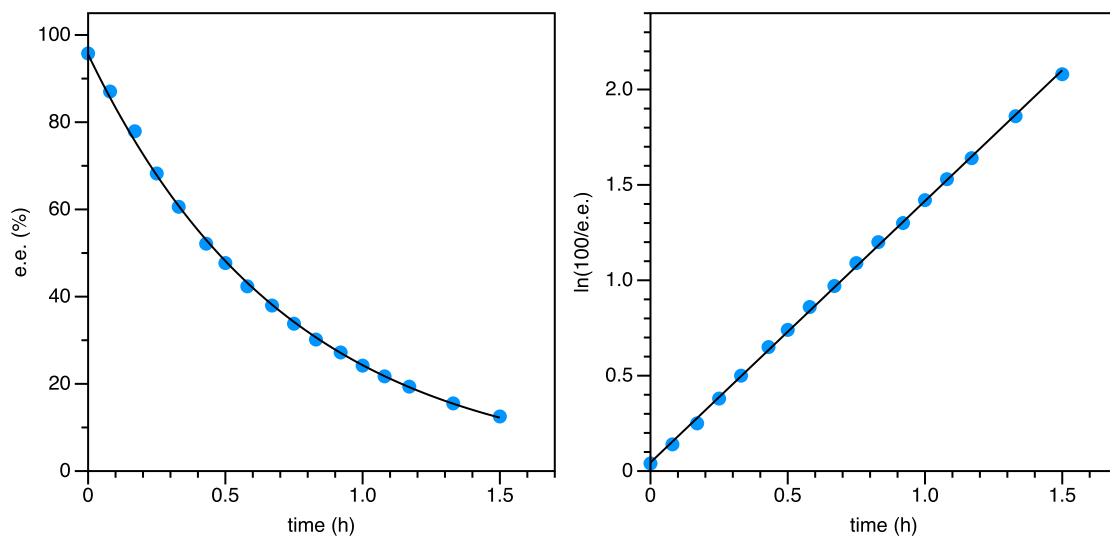
$$\Delta G_T^\ddagger = \ln \left(\frac{k_B T}{h \times k_{ent}} \right) RT = 28.7 \text{ kcal mol}^{-1}$$

$$t_{\frac{1}{2}}(rac) = \frac{\ln(2)}{k_{rac}} = 46 \text{ min}$$

7.1.23 Barrier to Rotation of 261



time (h)	time (s)	major ent. (%)	minor ent. (%)	e.e. (%)	$\ln(\frac{100}{\text{e.e.}})$
0.00	0	97.88	2.12	95.76	0.04
0.08	300	93.52	6.48	87.04	0.14
0.17	600	88.96	11.04	77.92	0.25
0.25	900	84.12	15.88	68.24	0.38
0.33	1200	80.30	19.70	60.60	0.50
0.43	1560	76.07	23.93	52.14	0.65
0.50	1800	73.85	26.15	47.70	0.74
0.58	2100	71.18	28.82	42.36	0.86
0.67	2400	68.98	31.02	37.96	0.97
0.75	2700	66.90	33.11	33.79	1.09
0.83	3000	65.08	34.92	30.16	1.20
0.92	3300	63.60	36.40	27.20	1.30
1.00	3600	62.09	37.91	24.18	1.42
1.08	3900	60.86	39.14	21.72	1.53
1.17	4200	59.68	40.32	19.36	1.64
1.33	4800	57.76	42.24	15.52	1.86
1.50	5400	56.26	43.74	12.52	2.08



$$\ln \left(\frac{100}{\text{e.e.}} \right) = k_{rac} \times t + \ln \left(\frac{100}{\text{e.e.}_{t=0}} \right)$$

$$\text{and } k_{ent} = \frac{1}{2} k_{rac}$$

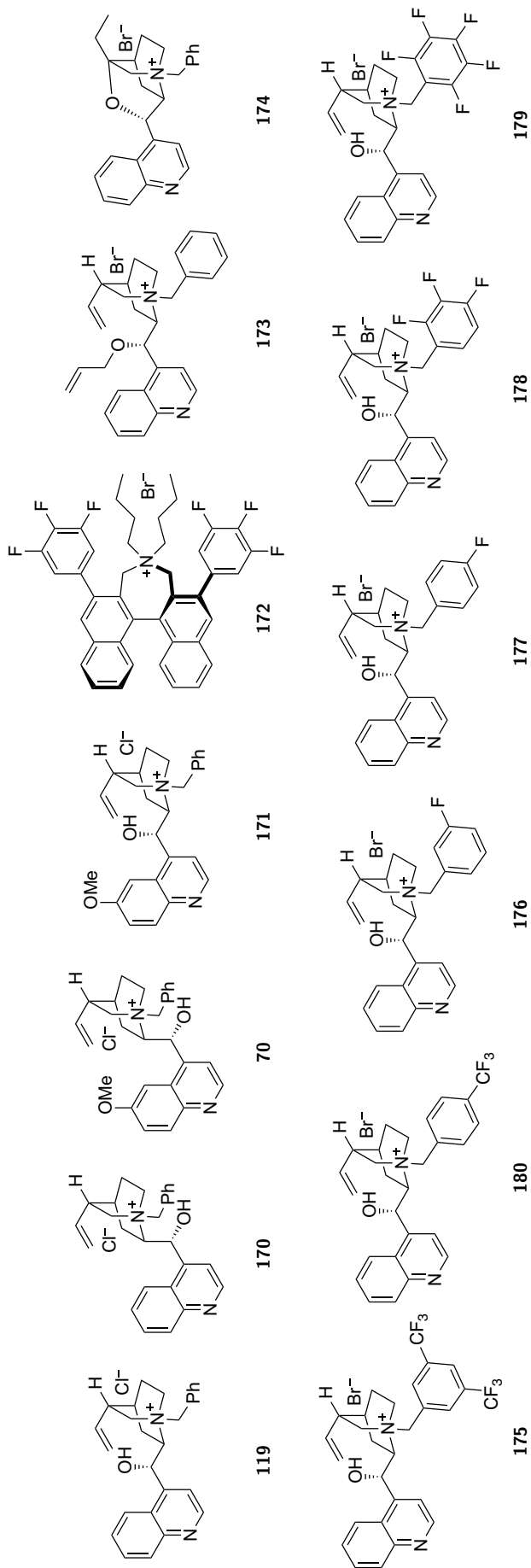
$$\text{Therefore } k_{ent} = \frac{1}{2} \text{slope} = 1.90 \times 10^{-4}$$

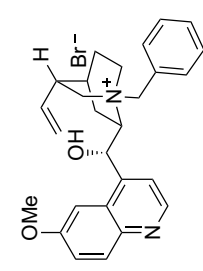
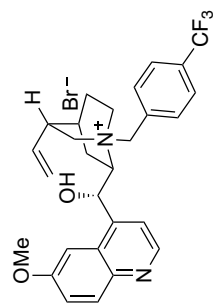
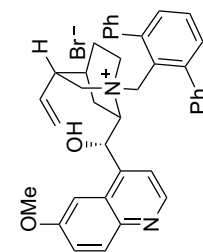
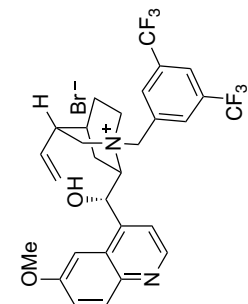
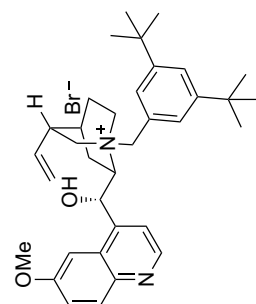
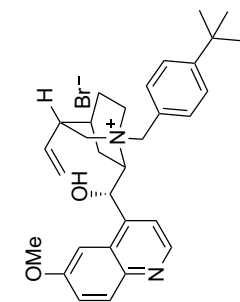
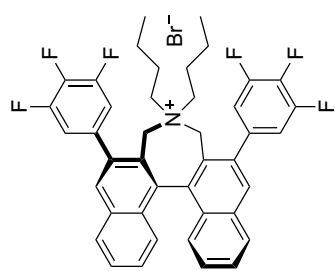
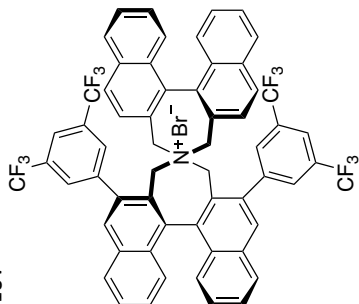
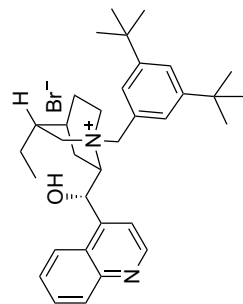
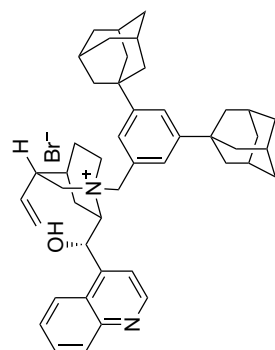
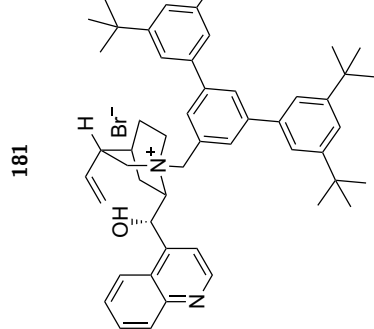
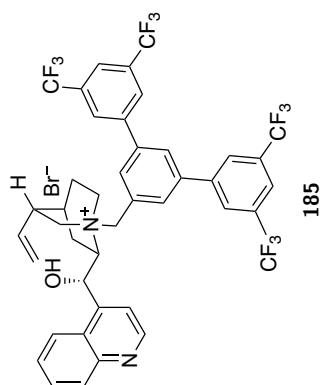
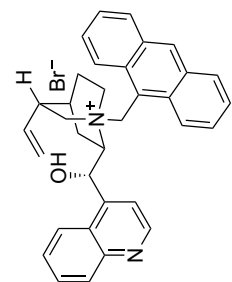
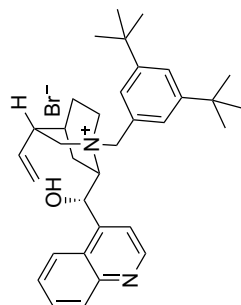
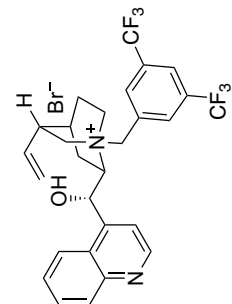
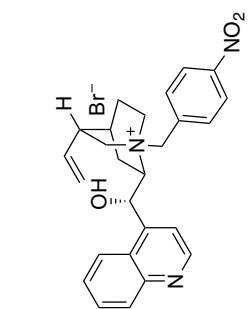
$$\Delta G_T^\ddagger = \ln \left(\frac{k_B T}{h \times k_{ent}} \right) RT = 28.4 \text{ kcal mol}^{-1}$$

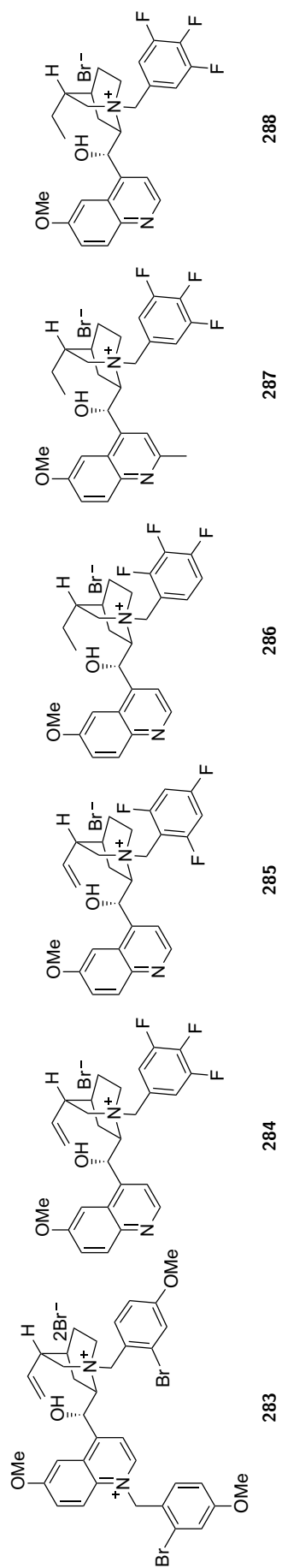
$$t_{\frac{1}{2}}(rac) = \frac{\ln(2)}{k_{rac}} = 30 \text{ min}$$

7.2 Full Optimisation

7.2.1 Index of Phase-Transfer Catalysts







7.2.2 Optimisation Table for Enantioselective *O*-Alkylation of Naphthols

Cat.	Cat. eq.	Base	Base eq.	Electrophile	Solvent	Conc. (M)	Temp. (°C)	e.r.	Conversion (%)
119	0.05	50% aq. KOH	2.5	BnBr	toluene	0.1	rt	50:50	N/A
170	0.05	50% aq. KOH	2.5	BnBr	toluene	0.1	rt	50:50	N/A
70	0.05	50% aq. KOH	2.5	BnBr	toluene	0.1	rt	50:50	N/A
171	0.05	50% aq. KOH	2.5	BnBr	toluene	0.1	rt	50:50	N/A
119	0.05	50% aq. K ₂ CO ₃	2.5	BnBr	toluene	0.1	rt	75:25	N/A
170	0.05	50% aq. K ₂ CO ₃	2.5	BnBr	toluene	0.1	rt	25:75	N/A
70	0.05	50% aq. K ₂ CO ₃	2.5	BnBr	toluene	0.1	rt	36:64	N/A
171	0.05	50% aq. K ₂ CO ₃	2.5	BnBr	toluene	0.1	rt	64:36	N/A
182	0.05	50% aq. K ₂ CO ₃	2.5	BnBr	toluene	0.1	rt	78:22	N/A
182	0.1	50% aq. K ₂ CO ₃	2.5	BnBr	toluene	0.1	rt	76:24	N/A
182	0.2	50% aq. K ₂ CO ₃	2.5	BnBr	toluene	0.1	rt	75:25	N/A
182	0.025	50% aq. K ₂ CO ₃	2.5	BnBr	toluene	0.1	rt	85:15	N/A
119	0.05	50% aq. NaOH	2.5	BnBr	toluene	0.1	rt	50:50	N/A
119	0.05	50% aq. K ₃ PO ₄	2.5	BnBr	toluene	0.1	rt	70:30	N/A
119	0.05	50% aq. Cs ₂ CO ₃	2.5	BnBr	toluene	0.1	rt	77:23	N/A
119	0.05	25% aq. CsOH·H ₂ O	2.5	BnBr	toluene	0.1	rt	52:48	N/A
119	0.05	25% aq. RbOH·H ₂ O	2.5	BnBr	toluene	0.1	rt	54:46	N/A
119	0.05	50% aq. K ₂ CO ₃	2.5	BnBr	toluene	0.1	rt	74:26	N/A
119	0.05	50% aq. Cs ₂ CO ₃	2.5	BnBr	toluene	0.1	rt	77:23	N/A
180	0.05	50% aq. Cs ₂ CO ₃	2.5	BnBr	toluene	0.1	rt	72:28	N/A

Cat.	Cat. eq.	Base	Base eq.	Electrophile	Solvent	Conc. (M)	Temp. (°C)	e.r.	Conversion (%)
176	0.05	50% aq. Cs ₂ CO ₃	2.5	BnBr	toluene	0.1	rt	73:27	N/A
174	0.05	50% aq. Cs ₂ CO ₃	2.5	BnBr	toluene	0.1	rt	51:49	N/A
182	0.05	50% aq. Cs ₂ CO ₃	2.5	BnBr	toluene	0.1	rt	82:18	N/A
177	0.05	50% aq. Cs ₂ CO ₃	2.5	BnBr	toluene	0.1	rt	68:32	N/A
181	0.05	50% aq. Cs ₂ CO ₃	2.5	BnBr	toluene	0.1	rt	70:30	N/A
179	0.05	50% aq. Cs ₂ CO ₃	2.5	BnBr	toluene	0.1	rt	60:40	N/A
178	0.05	50% aq. Cs ₂ CO ₃	2.5	BnBr	toluene	0.1	rt	75:25	N/A
184	0.05	50% aq. Cs ₂ CO ₃	2.5	BnBr	toluene	0.1	rt	72:28	N/A
173	0.05	50% aq. Cs ₂ CO ₃	2.5	BnBr	toluene	0.1	rt	50:50	N/A
172	0.05	50% aq. Cs ₂ CO ₃	2.5	BnBr	toluene	0.1	rt	57:43	N/A
275	0.05	50% aq. Cs ₂ CO ₃	2.5	BnBr	toluene	0.1	rt	49:51	N/A
276	0.05	50% aq. Cs ₂ CO ₃	2.5	BnBr	toluene	0.1	rt	67:33	N/A
182	0.05	50% aq. Cs ₂ CO ₃	2.5	BnBr	toluene	0.1	rt	84:16	N/A
182	0.05	25% aq. Cs ₂ CO ₃	2.5	BnBr	toluene	0.1	rt	82:18	N/A
182	0.05	50% aq. K ₃ PO ₄	2.5	BnBr	toluene	0.1	rt	77:23	N/A
182	0.05	K ₃ PO ₄	2.5	BnBr	toluene	0.1	rt	64:36	N/A
182	0.05	Cs ₂ CO ₃	2.5	BnBr	toluene	0.1	rt	53:47	N/A
182	0.05	Cs ₂ CO ₃	1.5	BnBr	toluene	0.1	rt	53:47	N/A
182	0.05	15% aq. Na ₃ PO ₄	2.5	BnBr	toluene	0.1	rt	86:14	N/A
182	0.05	Li ₂ CO ₃	2.5	BnBr	toluene	0.1	rt	N/A	N/A
182	0.05	Ag ₂ CO ₃	2.5	BnBr	toluene	0.1	rt	80:20	N/A
182	0.05	Na ₂ CO ₃	2.5	BnBr	toluene	0.1	rt	92:8	N/A
182	0.05	2 M aq. Na ₂ CO ₃	2.5	BnBr	toluene	0.1	rt	87:13	N/A

Cat.	Cat. eq.	Base	Base eq.	Electrophile	Solvent	Conc. (M)	Temp. (°C)	e.r.	Conversion (%)
182	0.05	Na ₃ PO ₄	2.5	BnBr	toluene	0.1	rt	88:12	N/A
182	0.05	K ₂ CO ₃	2.5	BnBr	toluene	0.1	rt	75:25	N/A
182	0.05	Ag ₂ CO ₃	2.5	BnBr	toluene	0.1	rt	91:9	N/A
182	0.05	25% aq. KF	2.5	BnBr	toluene	0.1	rt	75:25	N/A
182	0.05	Ag ₂ CO ₃	2.5	BnBr	toluene	0.1	rt	90:10	N/A
182	0.05	Ag ₂ CO ₃	2.5	BnBr	benzene	0.1	rt	90:10	N/A
182	0.05	Ag ₂ CO ₃	2.5	BnBr	<i>p</i> -xylene	0.1	rt	91:9	N/A
182	0.05	Ag ₂ CO ₃	2.5	BnBr	<i>m</i> -xylene	0.1	rt	91:9	N/A
182	0.05	Ag ₂ CO ₃	2.5	BnBr	CCl ₄	0.1	rt	87:13	N/A
182	0.05	Ag ₂ CO ₃	2.5	BnBr	CHCl ₃	0.1	rt	77:23	N/A
182	0.05	Ag ₂ CO ₃	2.5	BnBr	CH ₂ Cl ₂	0.1	rt	83:17	N/A
182	0.05	Ag ₂ CO ₃	2.5	BnBr	1,2-DCE	0.1	rt	83:17	N/A
182	0.05	Ag ₂ CO ₃	2.5	BnBr	Trichloroethane	0.1	rt	86:14	N/A
182	0.05	Ag ₂ CO ₃	2.5	BnBr	Tetrachloroethane	0.1	rt	N/A	N/A
182	0.05	Ag ₂ CO ₃	2.5	BnBr	Et ₂ O	0.1	rt	87:13	N/A
182	0.05	Ag ₂ CO ₃	2.5	BnBr	<i>i</i> Pr ₂ O	0.1	rt	88:12	N/A
182	0.05	Ag ₂ CO ₃	2.5	BnBr	TBME	0.1	rt	84:16	N/A
171	0.05	50% aq. Cs ₂ CO ₃	2.5	BnBr	toluene	0.1	rt	66:34	N/A
277	0.05	50% aq. Cs ₂ CO ₃	2.5	BnBr	toluene	0.1	rt	66:34	N/A
278	0.05	50% aq. Cs ₂ CO ₃	2.5	BnBr	toluene	0.1	rt	81:19	N/A
279	0.05	50% aq. Cs ₂ CO ₃	2.5	BnBr	toluene	0.1	rt	79:21	N/A
280	0.05	50% aq. Cs ₂ CO ₃	2.5	BnBr	toluene	0.1	rt	70:30	N/A
281	0.05	50% aq. Cs ₂ CO ₃	2.5	BnBr	toluene	0.1	rt	67:33	N/A

Cat.	Cat. eq.	Base	Base eq.	Electrophile	Solvent	Conc. (M)	Temp. (°C)	e.r.	Conversion (%)
282	0.05	50% aq. Cs ₂ CO ₃	2.5	BnBr	toluene	0.1	rt	78:22	N/A
283	0.05	50% aq. Cs ₂ CO ₃	2.5	BnBr	toluene	0.1	rt	68:32	N/A
284	0.05	50% aq. Cs ₂ CO ₃	2.5	BnBr	toluene	0.1	rt	64:36	N/A
285	0.05	50% aq. Cs ₂ CO ₃	2.5	BnBr	toluene	0.1	rt	61:39	N/A
286	0.05	50% aq. Cs ₂ CO ₃	2.5	BnBr	toluene	0.1	rt	66:34	N/A
287	0.05	50% aq. Cs ₂ CO ₃	2.5	BnBr	toluene	0.1	rt	69:31	N/A
288	0.05	50% aq. Cs ₂ CO ₃	2.5	BnBr	toluene	0.1	rt	68:32	N/A
185	0.05	50% aq. Cs ₂ CO ₃	2.5	BnBr	toluene	0.1	rt	90:10	N/A
175	0.05	50% aq. Cs ₂ CO ₃	2.5	BnBr	toluene	0.1	rt	82:18	N/A
183	0.05	50% aq. Cs ₂ CO ₃	2.5	BnBr	toluene	0.1	rt	87:13	N/A
186	0.05	50% aq. Cs ₂ CO ₃	2.5	BnBr	toluene	0.1	rt	83:17	N/A
183	0.05	50% aq. Cs ₂ CO ₃	2.5	BnBr	toluene	0.1	rt	80:20	N/A
183	0.05	25% aq. Cs ₂ CO ₃	2.5	BnBr	toluene	0.1	rt	81:19	N/A
183	0.05	50% aq. K ₃ PO ₄	2.5	BnBr	toluene	0.1	rt	77:23	N/A
183	0.05	K ₃ PO ₄	2.5	BnBr	toluene	0.1	rt	73:27	N/A
183	0.05	Cs ₂ CO ₃	2.5	BnBr	toluene	0.1	rt	54:46	N/A
183	0.05	15% aq. Na ₃ PO ₄	2.5	BnBr	toluene	0.1	rt	89:11	N/A
183	0.05	Li ₂ CO ₃	2.5	BnBr	toluene	0.1	rt	N/R	N/A
183	0.05	Ag ₂ CO ₃	2.5	BnBr	toluene	0.1	rt	83:17	N/A
183	0.05	Na ₂ CO ₃	2.5	BnBr	toluene	0.1	rt	94:6	N/A
183	0.05	2 M aq. Na ₂ CO ₃	2.5	BnBr	toluene	0.1	rt	84:16	N/A
183	0.05	Na ₃ PO ₄	2.5	BnBr	toluene	0.1	rt	93:7	N/A
183	0.05	K ₂ CO ₃	2.5	BnBr	toluene	0.1	rt	82:18	N/A

Cat.	Cat. eq.	Base	Base eq.	Electrophile	Solvent	Conc. (M)	Temp. (°C)	e.r.	Conversion (%)
183	0.05	Ag ₂ CO ₃	2.5	BnBr	toluene	0.1	rt	91:9	N/A
183	0.05	25% aq. KF	2.5	BnBr	toluene	0.1	rt	92:8	N/A
183	0.05	50% aq. K ₂ CO ₃	2.5	BnBr	toluene	0.1	rt	81:19	N/A
183	0.05	25% aq. KF	2.5	BnBr	toluene	0.1	rt	93:7	N/A
183	0.05	25% aq. KF	2.5	BnBr	benzene	0.1	rt	94:6	N/A
183	0.05	25% aq. KF	2.5	BnBr	<i>p</i> -xylene	0.1	rt	88:12	N/A
183	0.05	25% aq. KF	2.5	BnBr	<i>m</i> -xylene	0.1	rt	90:10	N/A
183	0.05	25% aq. KF	2.5	BnBr	CCl ₄	0.1	rt	90:10	N/A
183	0.05	25% aq. KF	2.5	BnBr	CHCl ₃	0.1	rt	87:13	N/A
183	0.05	25% aq. KF	2.5	BnBr	CH ₂ Cl ₂	0.1	rt	86:14	N/A
183	0.05	25% aq. KF	2.5	BnBr	1,2-dichloroethane	0.1	rt	80:20	N/A
183	0.05	25% aq. KF	2.5	BnBr	Trichloroethane	0.1	rt	92:8	N/A
183	0.05	25% aq. KF	2.5	BnBr	<i>o</i> -xylene	0.1	rt	91:9	N/A
183	0.05	25% aq. KF	2.5	BnBr	Et ₂ O	0.1	rt	79:21	N/A
183	0.05	25% aq. KF	2.5	BnBr	iPr ₂ O	0.1	rt	60:40	N/A
183	0.05	25% aq. KF	2.5	BnBr	MTBE	0.1	rt	80:20	N/A
183	0.05	25% aq. KF	2.5	BnCl	benzene	0.1	rt	94:6	N/A
183	0.05	25% aq. KF	2.5	BnBr	benzene	0.1	rt	93:7	N/A
183	0.05	25% aq. KF	2.5	BnI	benzene	0.1	rt	95:5	N/A
183	0.05	25% aq. KF	2.5	BnOTs	benzene	0.1	rt	85:15	N/A
183	0.05	25% aq. KF	2.5	allyl bromide	benzene	0.1	rt	75:25	N/A
183	0.05	25% aq. KF	2.5	allyl iodide	benzene	0.1	rt	73:27	N/A
183	0.05	25% aq. KF	2.5	MeI	benzene	0.1	rt	73:27	N/A

Cat.	Cat. eq.	Base	Base eq.	Electrophile	Solvent	Conc. (M)	Temp. (°C)	e.r.	Conversion (%)
183	0.05	25% aq. KF	2.5	propargyl bromide	benzene	0.1	rt	64:36	N/A
183	0.05	25% aq. KF	2.5	prenyl bromide	benzene	0.1	rt	90:10	N/A
183	0.05	25% aq. KF	2.5	1-bromonaphthalene	benzene	0.1	rt	90:10	N/A
183	0.05	25% aq. KF	2.5	2-bromonaphthalene	benzene	0.1	rt	92:8	N/A
183	0.05	25% aq. KF	2.5	Ac ₂ O	benzene	0.1	rt	44:56	N/A
183	0.05	25% aq. KF	2.5	BnI	benzene	0.01	rt	97:3	N/A
183	0.05	25% aq. KF	2.5	BnI	benzene	0.05	rt	96:4	N/A
183	0.05	25% aq. KF	2.5	BnI	benzene	0.1	rt	95:5	N/A
183	0.05	25% aq. KF	2.5	BnI	benzene	0.2	rt	94:6	N/A
183	0.05	25% aq. KF	2.5	BnI	benzene	0.5	rt	NR	N/A
183	0.05	25% aq. KF	2.5	BnI	benzene	1.0	rt	85:15	N/A
183	0.05	50% aq. Cs ₂ CO ₃	2.5	BnI	benzene	0.1	rt	89:11	N/A
183	0.05	50% aq. KF	2.5	BnBr	benzene	0.1	rt	93:7	N/A
186	0.05	25% aq. KF	2.5	BnI	benzene	0.1	rt	96:4	N/A
183	0.1	25% aq. KF	2.5	BnI	benzene	0.01	rt	97:3	36
183	0.1	25% aq. KF	2.5	BnI	benzene	0.05	rt	95:5	36
183	0.1	25% aq. KF	2.5	BnI	benzene	0.1	rt	94:6	50
183	0.1	25% aq. KF	2.5	BnI	benzene	0.2	rt	93:7	33
183	0.2	25% aq. KF	2.5	BnI	benzene	0.01	rt	96:4	37
183	0.2	25% aq. KF	2.5	BnI	benzene	0.05	rt	94:6	42
183	0.2	25% aq. KF	2.5	BnI	benzene	0.1	rt	92:8	34
183	0.2	25% aq. KF	2.5	BnI	benzene	0.2	rt	87:13	22
183	0.1	25% aq. KF	5.0	BnI	benzene	0.1	rt	93:7	63

Cat.	Cat. eq.	Base	Base eq.	Electrophile	Solvent	Conc. (M)	Temp. (°C)	e.r.	Conversion (%)
183	0.1	50% aq. KF	2.5	BnI	benzene	0.1	rt	94:6	60
186	0.1	25% aq. KF	2.5	BnI	benzene	0.1	rt	96:4	38
183	0.1	25% aq. KF	2.5	BnI	10% CH ₂ Cl ₂ /benzene	0.1	rt	94:6	54
183	0.1	25% aq. KF	2.5	BnI	10% CHCl ₃ /benzene	0.1	rt	94:6	45
186	0.1	25% aq. CsF	2.5	BnI	benzene	0.1	rt	94:6	14
183	0.05	50% aq. Cs ₂ CO ₃	5.0	BnI	benzene	0.05	rt	94:6	82
183	0.1	50% aq. Cs ₂ CO ₃	5.0	BnI	benzene	0.05	rt	94:6	90
186	0.05	50% aq. Cs ₂ CO ₃	5.0	BnI	benzene	0.05	rt	95:5	95
183	0.1	50% aq. Cs ₂ CO ₃	5.0	BnI	benzene	0.05	rt	93:7	68
274	0.1	50% aq. Cs ₂ CO ₃	5.0	BnI	benzene	0.05	rt	93:7	68
186	0.05	50% aq. Cs ₂ CO ₃	5.0	BnI	benzene	0.05	rt	95:5	73
193	0.05	50% aq. Cs ₂ CO ₃	5.0	BnI	benzene	0.05	rt	96:4	65
183	0.1	50% aq. Cs ₂ CO ₃	5.0	BnI	benzene	0.05	10	94:6	59
186	0.05	50% aq. Cs ₂ CO ₃	5.0	BnI	benzene	0.05	10	93:7	69
193	0.05	50% aq. Cs ₂ CO ₃	5.0	BnI	benzene	0.05	10	95:5	56
183	0.1	50% aq. Cs ₂ CO ₃	5.0	BnI	benzene	0.05	30	94:6	77
186	0.05	50% aq. Cs ₂ CO ₃	5.0	BnI	benzene	0.05	30	94:6	79
193	0.05	50% aq. Cs ₂ CO ₃	5.0	BnI	benzene	0.05	30	96:4	N/A
183	0.1	50% aq. Cs ₂ CO ₃	5.0	BnI	benzene	0.05	40	90:10	100
186	0.05	50% aq. Cs ₂ CO ₃	5.0	BnI	benzene	0.05	40	92:8	96
193	0.05	50% aq. Cs ₂ CO ₃	5.0	BnI	benzene	0.05	40	92:8	85
183	0.05	50% aq. Cs ₂ CO ₃	5.0	BnI	benzene	0.05	rt	94:6	65
183	0.1	50% aq. Cs ₂ CO ₃	5.0	BnI	benzene	0.05	rt	93:7	69

Cat.	Cat. eq.	Base	Base eq.	Electrophile	Solvent	Conc. (M)	Temp. (°C)	e.r.	Conversion (%)
193	0.05	50% aq. Cs ₂ CO ₃	5.0	BnI	benzene	0.05	rt	95:5	65
193	0.1	50% aq. Cs ₂ CO ₃	5.0	BnI	benzene	0.05	rt	95:5	66
183	0.1	50% aq. Cs ₂ CO ₃	5.0	BnI	benzene	0.025	rt	96:4	56
186	0.05	50% aq. Cs ₂ CO ₃	5.0	BnI	benzene	0.025	rt	96:4	70
193	0.05	50% aq. Cs ₂ CO ₃	5.0	BnI	benzene	0.025	rt	97:3	40
183	0.1	50% aq. Cs ₂ CO ₃	5.0	BnI	benzene	0.01	rt	97:3	42
186	0.05	50% aq. Cs ₂ CO ₃	5.0	BnI	benzene	0.01	rt	97:3	57
193	0.05	50% aq. Cs ₂ CO ₃	5.0	BnI	benzene	0.01	rt	97:3	25
186	0.05	50% aq. Cs ₂ CO ₃	5.0	BnI	benzene	0.025	rt	96:4	97
186	0.05	50% aq. Cs ₂ CO ₃	5.0	BnI	benzene	0.01	rt	96:4	96
186	0.025	50% aq. Cs ₂ CO ₃	5.0	BnI	benzene	0.05	rt	95:5	93
186	0.025	50% aq. Cs ₂ CO ₃	5.0	BnI	benzene	0.025	rt	94:6	97
193	0.05	50% aq. Cs ₂ CO ₃	5.0	BnI	benzene	0.025	rt	95:5	94
193	0.05	50% aq. Cs ₂ CO ₃	5.0	BnI	benzene	0.01	rt	97:3	83

Bibliography

- [1] G. H. Christie, J. Kenner, *J. Chem. Soc., Trans.* **1922**, 121.
- [2] M. Oki, *Top. Stereochem.* **1983**, 14, 1.
- [3] E. L. Eliel, S. H. Wilen, *Stereochemistry of Organic Compounds*, Wiley, **1994**.
- [4] G. Bringmann, A. J. Price Mortimer, P. A. Keller, M. J. Gresser, J. Garner, M. Breuning, *Angew. Chem. Int. Ed.* **2005**, 44, 5384.
- [5] J. E. Smyth, N. M. Butler, P. A. Keller, *Nat. Prod. Rep.* **2015**, 32, 1562.
- [6] C. M. Harris, H. Kopecka, T. M. Harris, *J. Am. Chem. Soc.* **1983**, 105, 6915.
- [7] K. Dodou, *Expert Opin. Investig. Drugs* **2005**, 14, 1419.
- [8] J. Xiong, J. Li, Q. Yang, J. Wang, T. Su, S. Zhou, *Breast Cancer Res.* **2017**, 19, 27.
- [9] S. R. LaPlante, L. D. Fader, K. R. Fandrick, D. R. Fandrick, O. Hucke, R. Kemper, S. P. F. Miller, P. J. Edwards, *J. Med. Chem.* **2011**, 54, 7005.
- [10] J. Clayden, W. Moran, P. Edwards, S. LaPlante, *Angew. Chem. Int. Ed.* **2009**, 48, 6398.
- [11] N. Murugesan, Z. Gu, S. Spergel, M. Young, P. Chen, A. Mathur, L. Leith, M. Hermsmeier, E. C.-K. Liu, R. Zhang, E. Bird, T. Waldron, A. Marino, B. Koplowitz, W. G. Humphreys, S. Chong, R. A. Morrison, M. L. Webb, S. Moreland, N. Trippodo, J. C. Barrish, *J. Med. Chem.* **2003**, 46, 125.
- [12] Y. S. Zhou, L. K. Tay, D. Hughes, S. Donahue, *J. Clin. Pharmacol.* **2004**, 44, 680.
- [13] M. Berthod, G. Mignani, G. Woodward, M. Lemaire, *Chem. Rev.* **2005**, 105, 1801.
- [14] H. Takahashi, S. Wakamatsu, H. Tabata, T. Oshitari, A. Harada, K. Inoue, H. Nat-sugari, *Org. Lett.* **2011**, 13, 760.
- [15] M. Reist, B. Testa, P.-A. Carrupt, M. Jung, V. Schurig, *Chirality* **1995**, 7, 396.
- [16] M. Rickhaus, L. Jundt, M. Mayor, *Chimia* **2016**, 192.
- [17] C. Wolf, *Dynamic Stereochemistry of Chiral Compounds. Principles and Applications*, RSC Publishing, **2008**.
- [18] M. Sakamoto, A. Unosawa, S. Kobaru, K. Fujita, T. Mino, T. Fujita, *Chem. Commun.* **2007**, 3586.
- [19] M. Rieger, F. H. Westheimer, *J. Am. Chem. Soc.* **1950**, 72, 19.
- [20] D. M. Hall, M. M. Harris, *J. Chem. Soc.* **1960**, 490.
- [21] A. Ahmed, R. A. Bragg, J. Clayden, W. L. Lai, C. McCarthy, J. H. Pink, N. Westlund, S. A. Yasin, *Tetrahedron* **1998**, 54, 13277 .
- [22] R. Adams, H. C. Yuan, *Chem. Rev.* **1933**, 12, 261.
- [23] J. Clayden, J. H. Pink, *Angew. Chem. Int. Ed.* **1998**, 37, 1937.

- [24] J. Clayden, C. McCarthy, M. Helliwell, *Chem. Commun.* **1999**, 2059.
- [25] D. Bright, I. E. Maxwell, J. de Boer, *J. Chem. Soc., Perkin Trans. 2* **1973**.
- [26] W. B. Schweizer, G. Procter, M. Kaftory, J. D. Dunitz, *Helv. Chim. Acta* **1978**, *61*, 2783.
- [27] M. A. Cuyegkeng, A. Mannschreck, *Chemische Berichte* **1987**, *120*, 803.
- [28] C. Kashima, A. Katoh, *J. Chem. Soc., Perkin Trans. 1* **1980**, 1599.
- [29] M. Sakamoto, F. Yagishita, M. Ando, Y. Sasahara, N. Kamataki, M. Ohta, T. Mino, Y. Kasashimaa, F. T., *Org. Biomol. Chem.* **2010**, *8*, 5418.
- [30] W. E. Stewart, T. H. Siddall, *Chem. Rev.* **1970**, *70*, 517.
- [31] C. Roussel, M. Adjimi, A. Chemlal, A. Djafri, *J. Org. Chem.* **1988**, *53*, 5076.
- [32] B. E. Dial, R. D. Rasberry, B. N. Bullock, M. D. Smith, P. J. Pellechia, S. Profeta, K. D. Shimizu, *Org. Lett.* **2011**, *13*, 244.
- [33] B. E. Dial, P. J. Pellechia, M. D. Smith, K. D. Shimizu, *J. Am. Chem. Soc.* **2012**, *134*, 3675.
- [34] Y. Suzuki, M. Kageyama, R. Morisawa, Y. Dobashi, H. Hasegawa, S. Yokojima, O. Kitagawa, *Chem. Commun.* **2015**, 51.
- [35] Y. Iwasaki, R. Morisawa, Y. Satoshi, H. Hasegawa, C. Roussel, N. Vanthuyne, E. Caytan, O. Kitagawa, *Chem. Eur. J.* **2018**, *24*, 4453.
- [36] P. Bowles, J. Clayden, M. Tomkinson, *Tetrahedron Lett.* **1995**, *36*, 9219 .
- [37] P. Bowles, J. Clayden, M. Helliwell, C. McCarthy, M. Tomkinson, N. Westlund, *J. Chem. Soc., Perkin Trans. 1* **1997**, 2607.
- [38] S. Thayumanavan, P. Beak, D. P. Curran, *Tetrahedron Lett.* **1996**, *37*, 2899.
- [39] H. Koide, M. Uemura, *Chem. Commun.* **1998**, 2483.
- [40] H. Koide, T. Hata, M. Uemura, *J. Org. Chem.* **2002**, *67*, 1929.
- [41] J. Clayden, W. L. Lai, *Angew. Chem. Int. Ed.* **1999**, *38*, 2556.
- [42] J. Clayden, W. L. Lai, *Tetrahedron Lett.* **2001**, *42*, 3163 .
- [43] J. Clayden, W. L. Lai, M. Helliwell, *Tetrahedron* **2004**, *60*, 4399.
- [44] J. Clayden, D. Mitjans, L. H. Youssef, *J. Am. Chem. Soc.* **2002**, *124*, 5266.
- [45] M. S. Betson, J. Clayden, M. Helliwell, D. Mitjansa, *Org. Biomol. Chem.* **2005**, *3*, 3898.
- [46] J. Clayden, P. Johnson, J. H. Pink, M. Helliwell, *J. Org. Chem.* **2000**, *65*, 7033.
- [47] J. Clayden, P. Johnson, J. H. Pink, *J. Chem. Soc., Perkin Trans. 1* **2001**, 371.
- [48] R. Rios, C. Jimeno, P. J. Carroll, P. J. Walsh, *J. Am. Chem. Soc.* **2002**, *124*, 10272.
- [49] T. Suda, K. Noguchi, M. Hirano, K. Tanaka, *Chem. Eur. J.* **2008**, *14*, 6593.
- [50] K. Tanaka, Y. Takahashi, Y. Suda, M. Hirano, *Synlett* **2008**, 2008, 1724.
- [51] K. T. Barrett, S. J. Miller, *J. Am. Chem. Soc.* **2013**, *135*, 2963.

- [52] K. T. Barrett, A. J. Metrano, P. R. Rablen, S. J. Miller, *Nature* **2014**, *509*, 71.
- [53] C. M. Starks, C. L. Liotta, M. E. Halpern, *Phase-Transfer Catalysis*, Chapman & Hall, **1994**.
- [54] C. M. Starks, *J. Am. Chem. Soc.* **1971**, *93*, 195.
- [55] D. Landini, A. Maia, F. Montanari, *J. Chem. Soc., Chem. Commun.* **1977**, 112.
- [56] R. J. Armstrong, M. D. Smith, *Angew. Chem. Int. Ed.* **2014**, *53*, 12822.
- [57] S. Shirakawa, K. Liu, K. Maruoka, *J. Am. Chem. Soc.* **2012**, *134*, 916.
- [58] J. D. Jolliffe, R. J. Armstrong, M. D. Smith, *Nat. Chem.* **2017**, *9*, 558.
- [59] M. Sakamoto, A. Unosawa, S. Kobaru, A. Saito, T. Mino, T. Fujita, *Angew. Chem. Int. Ed.* **2005**, *44*, 5523.
- [60] J. D. Jolliffe, *Cation-Directed Atropselective Synthesis of BINOL Derivatives*, Ph.D. thesis, University of Oxford, **2017**.
- [61] E. Kumarasamy, R. Raghunathan, M. P. Sibi, J. Sivaguru, *Chem. Rev.* **2015**, *115*, 11239.
- [62] A. Kouvarakism, H. E. Katerinopoulos, *Synth. Commun.* **1995**, *25*, 3035.
- [63] A. J. Grenning, J. A. Tunge, *J. Am. Chem. Soc.* **2011**, *133*, 14785.
- [64] T. A. Moss, A. Alba, D. Hepworth, D. J. Dixon, *Chem. Commun.* **2008**, 2474.
- [65] W. J. Wheeler, D. D. O'Bannon, S. Swanson, T. A. Gillespie, D. L. Varie, *J. Label. Compd. Radiopharm.* **2005**, *48*, 149.
- [66] T.-S. Mei, D.-H. Wang, J.-Q. Yu, *Org. Lett.* **2010**, *12*, 3140.
- [67] D. B. G. Williams, M. Lawton, *J. Org. Chem.* **2010**, *75*, 8351.
- [68] H. Mayr, M. Breugst, A. R. Ofial, *Angew. Chem. Int. Ed.* **2011**, *50*, 6470.
- [69] R. Gompper, H.-U. Wagner, *Angew. Chem. Int. Ed.* **1976**, *15*, 321.
- [70] W. J. Le Noble, H. F. Morris, *J. Org. Chem.* **1969**, *34*, 1969.
- [71] N. Kornblum, P. J. Berrigan, W. J. Le Noble, *J. Am. Chem. Soc.* **1963**, *85*, 1141.
- [72] H. Wynberg, B. Greijdanus, *J. Chem. Soc., Chem. Commun.* **1978**, 427.
- [73] S. Colonna, A. Re, H. Wynberg, *J. Chem. Soc., Perkin Trans. 1* **1981**, 547.
- [74] U. H. Dolling, P. Davis, E. J. J. Grabowski, *J. Am. Chem. Soc.* **1984**, *106*, 446.
- [75] D. L. Hughes, U. H. Dolling, K. M. Ryan, E. F. Schoenewaldt, E. J. J. Grabowski, *J. Org. Chem.* **1987**, *52*, 4745.
- [76] A. Kurts, A. Macias, I. Beletskaya, O. Reutov, *Tetrahedron* **1971**, *27*, 4759.
- [77] A. Kurts, A. Macias, I. Beletskaya, O. Reutov, *Tetrahedron* **1971**, *27*, 4777.
- [78] R. G. Pearson, J. Songstad, *J. Am. Chem. Soc.* **1967**, *89*, 1827.
- [79] K. N. Houk, M. N. Paddon-Row, *J. Am. Chem. Soc.* **1986**, *108*, 2659.
- [80] M. E. Jones, S. R. Kass, J. Filley, R. M. Barkley, G. B. Ellison, *J. Am. Chem. Soc.* **1985**, *107*, 109.

- [81] E. V. Dehmlow, S. Schrader, *Z. Naturforsch. B Chem. Sci.* **1990**, *45*, 409.
- [82] A. Sepsey, D. R. Németh, G. Németh, A. Felinger, *J. Chromatogr. A* **2018**, *1564*, 155 .
- [83] O. Trapp, G. Schoetz, V. Schurig, *Chirality* **2001**, *13*, 403.
- [84] O. Trapp, *J. Chromatogr. B* **2008**, *875*, 42 .
- [85] D.-H. Wang, K. M. Engle, B.-F. Shi, J.-Q. Yu, *Science* **2010**, *327*, 315.
- [86] K. M. Engle, D.-H. Wang, J.-Q. Yu, *J. Am. Chem. Soc.* **2010**, *132*, 14137.
- [87] C. G. Seitz, H. Zhang, Y. Mo, J. M. Karty, *J. Org. Chem.* **2016**, *81*, 3711.
- [88] K. Shishido, A. Yamashita, K. Hiroya, K. Fukumoto, T. Kametani, *Tetrahedron Lett.* **1989**, *30*, 111.
- [89] P. G. M. Wuts, *Greene's Protective Groups in Organic Synthesis*, Wiley, **2014**.
- [90] S. Fletcher, P. T. Gunning, *Tetrahedron Lett.* **2008**, *49*, 4817.
- [91] W.-M. Dai, Y. Zhang, Y. Zhang, *Tetrahedron: Asymmetry* **2004**, *15*, 525.
- [92] M. L. Huggins, *J. Org. Chem.* **1936**, *01*, 407.
- [93] D. E. Patterson, S. Xie, L. A. Jones, M. H. Osterhout, C. G. Henry, T. D. Roper, *Org. Process Res. Dev.* **2007**, *11*, 624.
- [94] L. Vial, M.-H. Gonçalves, P.-Y. Morgantini, J. Weber, G. Bernardinelli, J. Lacour, *Synlett* **2004**, *2004*, 1565.
- [95] T. Onoda, R. Shirai, S. Iwasaki, *Tetrahedron Lett.* **1997**, *38*, 1443.
- [96] P. J. Kocienski, *Protecting Groups*, Thieme, **1994**.
- [97] L. M. Deck, Q. Mgani, A. Martinez, A. Martinic, L. J. Whalen, D. L. Vander Jagt, R. E. Royer, *Tetrahedron Lett.* **2012**, *53*, 373 .
- [98] J. Ichikawa, M. Yokota, T. Kudo, S. Umezaki, *Angew. Chem. Int. Ed.* **2008**, *47*, 4870.
- [99] S. K. Guha, B. Wu, B. S. Kim, W. Baik, S. Koo, *Tetrahedron Lett.* **2006**, *47*, 291.
- [100] J. P. Wolfe, R. A. Singer, V. H. Yang, S. L. Buchwald, *J. Am. Chem. Soc.* **1999**, *121*, 9550.
- [101] A. F. Littke, C. Dai, G. C. Fu, *J. Am. Chem. Soc.* **2000**, *122*, 4020.
- [102] J. Yin, M. P. Rainka, X.-X. Zhang, S. L. Buchwald, *J. Am. Chem. Soc.* **2002**, *124*, 1162.
- [103] S. L. Chien, R. Adams, *J. Am. Chem. Soc.* **1934**, *56*, 1787.
- [104] J. A. Hirsch, *Top. Stereochem.* **1967**, *3*, 199.
- [105] F. R. Jensen, C. H. Bushweller, B. H. Beck, *J. Am. Chem. Soc.* **1969**, *91*, 344.
- [106] J. E. Anderson, *J. Chem. Soc., Perkin Trans. 2* **1974**, *10*.
- [107] H. J. Schneider, V. Hoppen, *J. Org. Chem.* **1978**, *43*, 3866.
- [108] A. Cooke, M. M. Harris, *J. Chem. Soc. C* **1967**, *0*, 988.

- [109] A. B. Pangborn, M. A. Giardello, R. H. Grubbs, R. K. Rosen, F. J. Timmers, *Organometallics* **1996**, *15*, 1518.
- [110] W. L. F. Armarego, D. D. Perrin, *Purification of Laboratory Chemicals*, Butterworth-Heinemann, **1996**.
- [111] T. Perrard, J.-C. Plaquevent, J.-R. Desmurs, D. Hébrault, *Org. Lett.* **2000**, *2*, 2959.
- [112] M. Lian, Z. Li, J. Du, Q. Meng, Z. Gao, *Eur. J. Org. Chem.* **2010**, 6525.
- [113] R. Ceccarelli, S. Insogna, M. Bella, *Org. Biomol. Chem.* **2006**, *4*, 4281.
- [114] C. G. Bashore, I. J. Samardjiev, J. Bordner, J. W. Coe, *J. Am. Chem. Soc.* **2003**, *125*, 3268.
- [115] M. Chaumontet, R. Piccardi, N. Audic, J. Hitce, J.-L. Peglion, E. Clot, O. Baudoin, *J. Am. Chem. Soc.* **2008**, *130*, 15157.
- [116] G. Xia, X. Han, X. Lu, *Org. Lett.* **2014**, *16*, 6184.
- [117] M. J. Frisch, et al., *Gaussian 09, Revision D.01*, Gaussian Inc., Wallingford CT, **2009**.
- [118] H. Lin, D. G. Truhlar, *Theor. Chem. Acc.* **2006**, *117*, 185.
- [119] W. J. Hehre, R. Ditchfield, J. A. Pople, *J. Chem. Phys.* **1972**, *56*, 2257.
- [120] A. G. Baboul, L. A. Curtiss, P. C. Redfern, K. Raghavachari, *J. Chem. Phys.* **1999**, *110*, 7650.
- [121] B. Mennucci, E. Cancès, J. Tomasi, *J. Phys. Chem. B* **1997**, *101*, 10506.
- [122] S. Grimme, *Chem. Eur. J.* **2012**, *18*, 9955.
- [123] C. Y. Legault, *Comput. Programs Biomed.* **2010**, *18*, 99.