Cp*Rh(III)-Catalysed Enantioselective C(sp^3)–H Functionalisation



A thesis submitted in partial fulfilment of the requirement for the degree of Doctor of Philosophy (DPhil)

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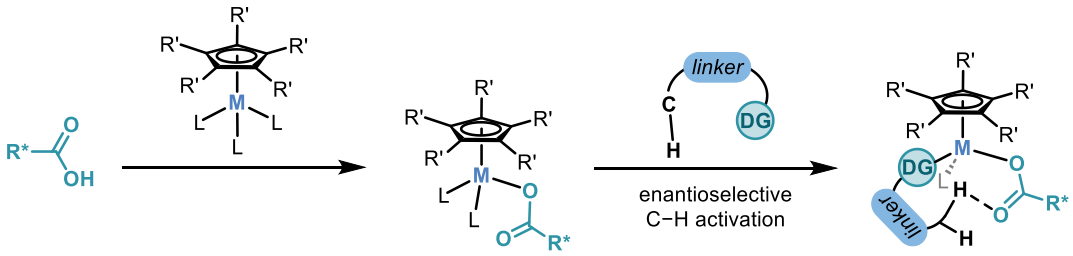
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Abstract

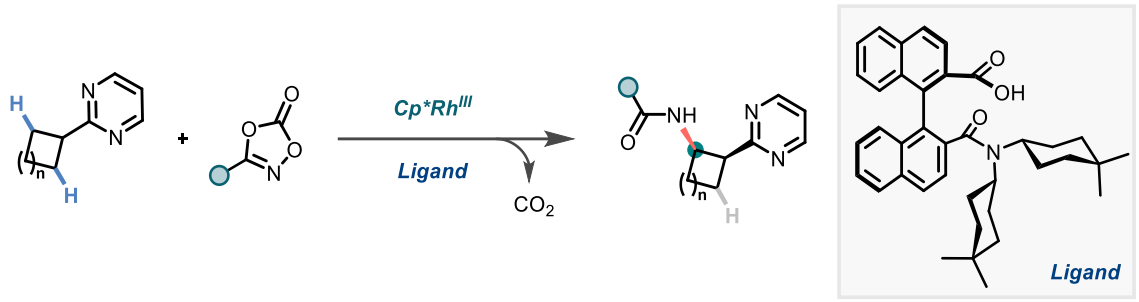
This thesis describes an enantioselective Cp*Rh(III)-catalysed intermolecular C(sp^3)–H amidation of cyclobutanes utilising azine heterocycles as directing groups, and also the preliminary discovery of an intramolecular C(sp^3)–H amidation of a newly designed dioxazolone-derived dithiane to generate the lactam products.

Chapter 1 provides a detailed overview of the theoretical foundation, as well as the evolution of C−H activation strategies and their principal mechanisms. It encapsulates a brief summary of the most widely investigated directing groups in recent years, while elucidating in detail the studies of C(sp^3)−H activation reaction using heterocyclic moieties as directing groups, such as pyridine. Furthermore, it encompasses the state-of-the-art studies of Cp^xM(III) catalysts in facilitating enantioselectivity control of desymmetrising C(sp^3)−H functionalisation reactions assisted by chiral ligands.

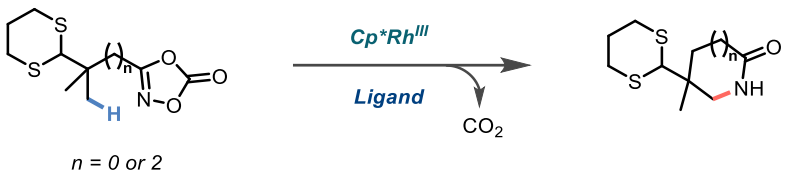


Chapter 2 introduces a new methodology to establish asymmetric cyclobutanes via the direct C−H activation strategy and demonstrates a highly enantioselective desymmetrising intermolecular C(sp^3)–H amidation of azine-linked cyclobutanes, furnishing enantioenriched *cis*-configured amido-cyclobutane scaffolds. The transformation is facilitated by an electron-deficient Cp*Rh(III*)* catalyst in synergy with a newly designed axially chiral carboxylic acid, which was found to be pivotal in attaining high levels of

enantioselectivity. Computational studies revealed the presence of multiple non-covalent interactions which contributed significantly to the high enantioselectivity that was observed.



Chapter 3 presents the synthesis of a unique class of dioxazolone-derived dithianes, as well as the initial discovery of an intramolecular dithiane-directed regio-selective C(sp^3)–H amidation reaction to generate lactam compounds. Despite the anticipated transformation process for the synthesis of cyclic amides not being achieved under our limited test conditions thus far, this work lays the foundation for a viable follow-up study based on our findings.



Declaration

The work described in this thesis was carried out in the Chemistry Research Laboratory, University of Oxford, from October 2019 until September 2023, under the supervision of Professor Darren J. Dixon. All of the work is my own unless otherwise stated and has not been submitted previously for any other degree at this or any other university.



Xing Xu

April 2024

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To my besties Xuan, Yifei, and Shuwen, I am profoundly thankful for your unwavering support, encouragement, and constant standing by my side. Your companionship has meant the world to me.

Finally, I really appreciate myself, and I wish you never get lost.

Abbreviations

Ac	acetate
Ad	adamantyl
AIBN	azobisisobutyronitrile
aq.	aqueous
AMLA	ambiphilic metal-ligand activation
Ar	aryl
Asn	l-asparagine
Bn	benzyl
Boc	*tert*-butoxycarbonyl
BQ	1,4-benzoquinone
brs	broad singlet
Bz	benzyl
cat.	catalyst
CDI	1,1'-carbonyldiimidazole
cm	centimetre
CMD	concerted metalation deprotonation
$(COCl)_2$	oxalyl chloride
cod	cyclooctadiene
COSY	correlation spectroscopy
Cp	cyclopentadiene
Cp*	1,2,3,4,5-pentamethylcyclopentadiene
CPME	cyclopentyl methyl ether
Cy	cyclohexyl
DCE	1,2-dichloroethane
DCM	dichloromethane
dd	doublet of doublets
DE	diethyl ether
DFT	density functional theory
DG	directing group

DIPEA	*N*,*N*-diisopropylethylamine
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
dppp	1,3-bis(diphenylphosphino)propane
dt	doublet of triplets
EDC	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
ee	enantiomeric excess
eq	equivalents
ES	electrophilic substitution
ESI	electrospray ionisation
Et	ethyl
Fmoc	fluorenylmethyloxycarbonyl
FT-IR	fourier transform infrared
g	grams
Glu	l-glutamic acid
Gly	l-glycine
h	hours
HATU	1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate
HFIP	hexafluoro-2-propanol
His	l-histidine
HMBC	heteronuclear multiple bond correlation
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectroscopy
HSQC	heteronuclear single quantum coupling
Hz	hertz
Ile	l-isoleucine
IPA	isopropanol
IR	infrared
J	NMR coupling constant
LDA	lithium diisopropylamide

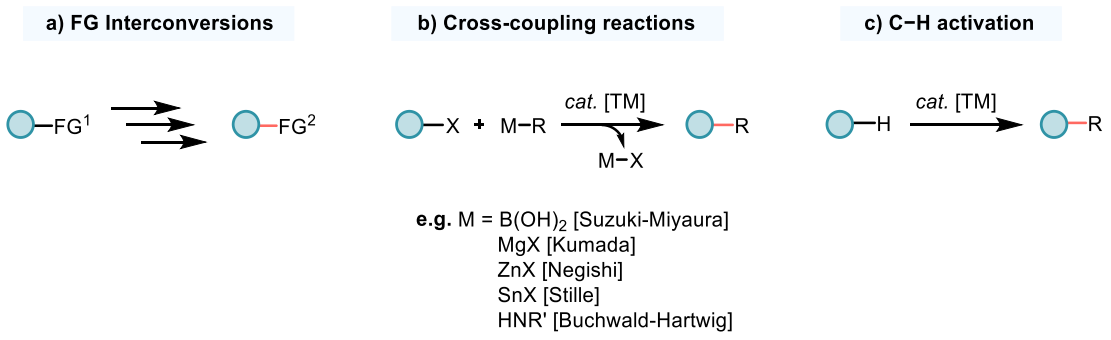
Lys	l-lysine
M	molar concentration
m	multiplet
m-	meta
Me	methyl
mg	milligram
MHz	mega hertz
min	minutes
mL	millilitre
mmol	millimoles
m.p.	melting point
MPAA	mono-*N*-protected amino acid
m/*z*	mass to charge ratio
n	*primary*, unbranched alkyl group
NBS	*N*-bromosuccinimide
*n*Bu	normal butyl
NOESY	nuclear overhauser effect spectroscopy
o-	*ortho*-
o/n	overnight
p-	*para*-
PCC	pyridinium chlorochromate
PCy_3	tricyclohexylphosphine
p-cym	*p*-cymene
PEPPSI	pyridine-enhanced precatalyst preparation stabilization and initiation
Ph	phenyl
ppm	parts per million
Pro	l-proline
Py	pyridyl
Pym	pyrimidyl
R	organic group
rt	room temperature

SBM	sigma bond metathesis
*t*Bu	tertiary butyl
T	temperature
Tf	trifluoromethanesulfonyl
Thr	l-threonine
THF	tetrahydrofuran
TLC	thin-layer chromatography
TM	transition metal
TMS	trimethylsilane
Trp	l-tryptophan
trt	trityl
Ts	4-toluenesulfonyl
^{o}C	degree(s) celsius
δ	NMR chemical shift
λ	wavelength
μ	micro

Chapter 1 General Introduction

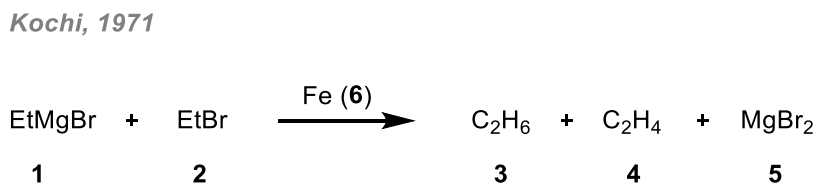
1.1 Evolution of Molecular Synthetic Strategies

Since the 1950s, the predominant approach to target-oriented organic synthesis was mainly reliant on functional group interconversions (FGI) or disconnections. This strategy involved converting one functional group into another desired functional group through a series of transformations such as substitution, addition, oxidation, reduction, elimination, and related reactions (**Scheme 1a**).[1] The core principle behind FGI was the step-wise manipulation and interconversion of existing functional groups within a molecular scaffold to progressively build complexity and introduce the desired functionalities. While this traditional approach proved effective for numerous synthetic targets, it possessed inherent limitations. The multi-step sequences often required harsh reaction conditions, generated excessive waste, and suffered from limited step- and atom-economy. Furthermore, the reliance on pre-existing functional groups as reactive handles constrained the potential disconnections and retrosynthetic avenues available to synthetic chemists.



Scheme 1 Evolution of molecular synthesis from functional group interconversions to catalytic C–H activation.

In the 1970s, inspired by Kochi's report of the cross-coupling of alkenyl halides with Grignard reagents catalysed by iron, metal-catalysed cross-coupling reactions were beginning to be studied (**Scheme 2**).[2] The earliest cross-coupling reactions typically involved the transition metal-catalysed coupling reaction of a pre-functionalised sp^2-hybridized aryl halide electrophile and a nucleophile. Although it improved synthetic efficiency compared to previous approaches, it still resulted in large amounts of undesired stoichiometric byproducts during the cross-coupling process and pre-functionalization of substrates, thereby lacking atom and step economy (**Scheme 1b**).

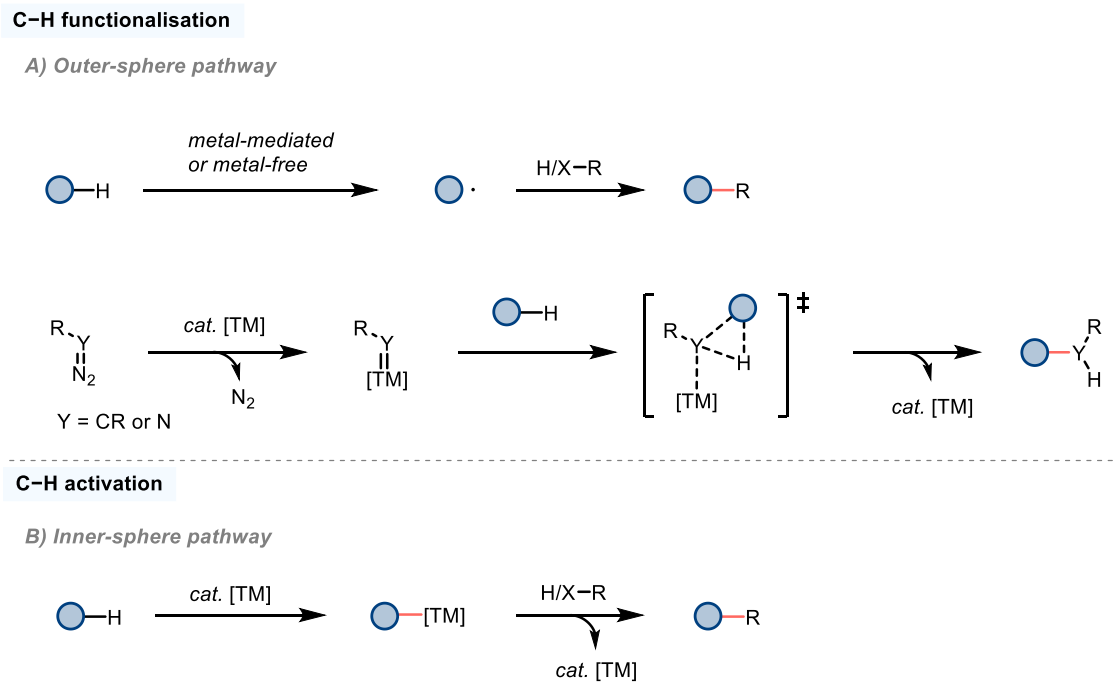


Scheme 2 Vinylation of Grignard reagents catalysis by iron.

In this context, another approach started to gain attention and focused on the direct reaction of typically unreactive carbon–hydrogen (C–H) bonds, characterized by their large thermodynamic stability (with bond dissociation energies (BDEs) ≥ 90–110 kcal/mol).[3] The BDE decreases along the order of C(sp)−H → C(sp^2)−H → C(sp^3)−H.[1] Within this burgeoning field of C−H bond cleavage and subsequent reaction leading to the formation of a new C−Y bond (e.g Y = C, N, O, S) from the C−H bond, the terminology "C−H activation" and "C−H functionalisation" are now widely used in the organic chemistry community (**Scheme 1c**).

However, within numerous academic publications, it was observed that these two terms are used inaccurately, thus it was necessary to clarify the differences of them. These two terms can be mechanistically classified into two main types. "**C−H activation**" is a specific

mechanistic step that goes through an organometallic intermediate. Here, in the presence of transition metal (TM) catalyst, a C−H bond cleaves to coordinate to the inner-sphere of the metal to form an organometallic complex intermediate with a C−TM bond, wherein the hydrocarbyl species stays in the inner-sphere during the C−H bond cleavage process (**Scheme 3B**); whereas "**C−H functionalisation**" does not have to adhere to the formation of such an organometallic intermediate, which refers to both inner-sphere and outer-sphere processes. Simply saying, it is a process involving the replacement of a C−H bond by another functional group.[4, 5] Typically, the outer-sphere C–H functionalisation can proceed through radical processes and hydrogen atom transfer (HAT) as well as the metal carbene/nitrene/oxo insertion (**Scheme 3A**).[6] While these two terms have been employed interchangeably in the literature, an emerging consensus restricts "C−H activation" usage to mechanisms involving inner-sphere pathways.



Scheme 3 C−H functionalisation and C−H activation.

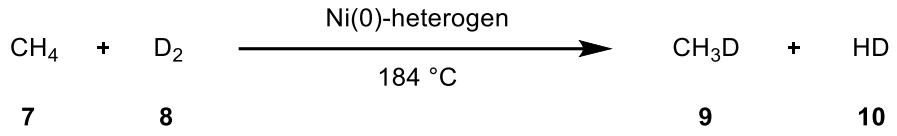
Therefore, C−H functionalisation allows for the direct functionalisation of C−H bonds without the need for pre-functionalisation of the molecule. This has become a powerful tool in the development of novel chemical transformations and the creation of complex molecules, offering significant advantages in terms of atom economy and hazardous waste reduction in organic synthesis.

1.2 Evolution of C−H Activation in Organic Chemistry

The history of C−H activation in organic chemistry is marked by a series of transformative milestones that have revolutionized the field's approach to functionalising C−H bonds. From its early origins to contemporary advancements, this section explores the key developments that have shaped the landscape of C−H activation. In this historical account, we briefly delve into the progression of this field, tracing its evolution, and highlighting the contributions of notable chemists who have played pivotal roles in advancing our understanding of C−H activation.

The first glimmerings of progress in the homogeneous catalysis of C−H activation reactions catalysed by transition metal complexes can be traced to Fenton with his seminal paper starting with the oxidation of tartaric acid in 1894.[7] Another of the earliest uses of metal-catalysed "C−H bond activation" appeared in 1936 by Taylor,[8] which described the H/D exchange in methane catalysed by a heterogeneous Ni^0 catalyst (**Scheme 4**). Despite the fact that the definition of the term was not formalised, this work indicated a new mode of chemical reactivity, enabling the cleavage of a highly unreactive alkane C−H bond at that time.

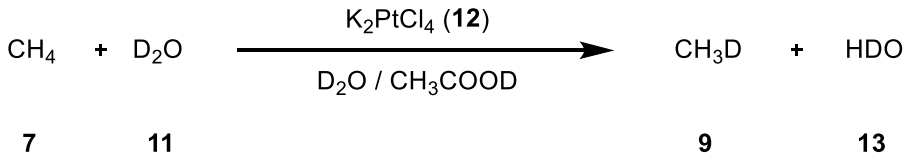
Taylor, 1936



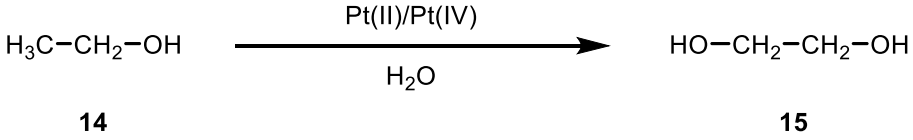
Scheme 4 H/D exchange in methane catalysed by Ni(0).

One of the most influential pioneering discoveries in this area was made by Hodges and Garnett in 1969, in which the deuteration of alkanes and arenes was found in the presence of a potassium tetrachloroplatinate (**12**) (**Scheme 5**, **top**).[9] Based on this, Shilov further extended the concept to the hydroxylation of alkanes (such as methane) by using a mixture of $K_2Pt(II)Cl_4$ and $K_2Pt(IV)Cl_6$ salts (**Scheme 5**, **bottom**).[10] This work inspired multiple mechanistic studies which suggested it proceeded through a critical C−H reductive elimination process from the alkylplatinum species to a Pt(II) intermediate. It is worth to notice that the unusual chemo-selectivity was observed in this reaction, as rate constants for the oxidation of an unactivated methyl group were at times observed to exceed those for the oxidation of an alcohol. Such new reactivity mode was described as "activation of hydrocarbons" at that time.

Hodges & Garnett, 1969

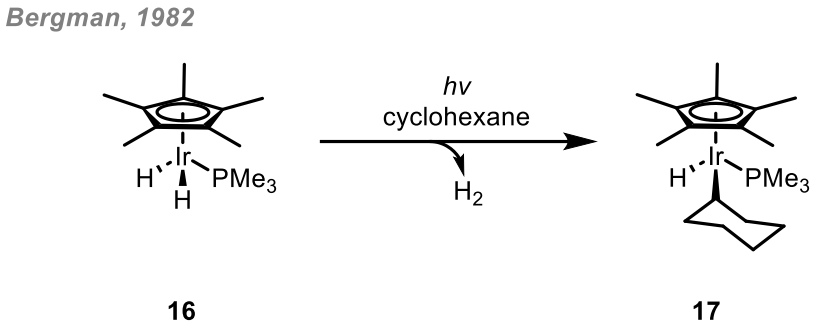


Shilov, 1969



Scheme 5 Methanol from methane *via* homogenous catalysis.

A subsequent major breakthrough was demonstrated by Bergman in 1982,[11] which depicted the first example of an intermolecular addition of an unactivated C–H bond of saturated cyclohexane to obtain corresponding low valent iridium complex (**Scheme 6**). The most important point of the work is that there was a remarkable selectivity among the C−H bond, where the Cp*Ir(PMe_3) (**16**) metal centre showed a favourable cleavage of C−H bonds in the order: aryl > 1° > 2° >> 3°.

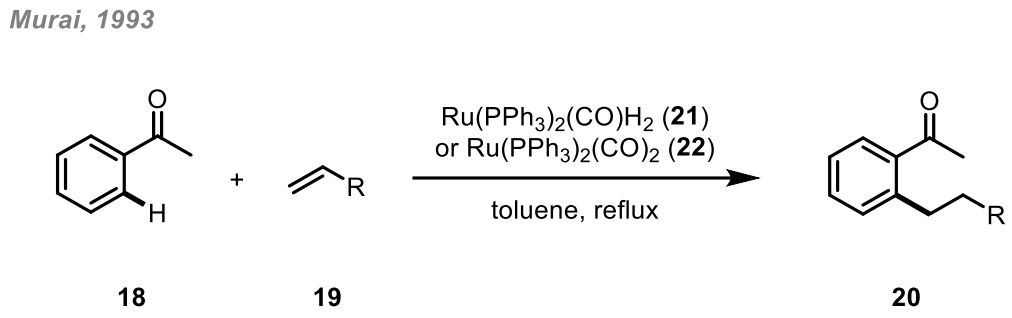


Scheme 6 Alkane C–H bond oxidaitve addition to the transition metal complex.

This major issue of selectivity was subsequently studied by Graham,[12] Jones,[13] Flood,[14] Baker.[15] All of their results supported that both the kinetics and thermodynamics of C−H addition to the metal complex preferred to occur on the less-bulky alkyl group, thus constituting the very first studies of selectivity in C−H activation.

In 1993, the arguably most remarkable milestone in this field was reported by Murai, where the concept of a directing group was introduced into the catalytic C−H functionalisation for the first time.[16] In the presence of $Ru(PPh_3)_3(CO)_2$ (**21**) or $Ru(PPh_3)_3(CO)H_2$ (**22**) as the catalyst, the olefin substrates (**19**) could insert into C−H bonds of aromatic ketones in the *ortho* position (**Scheme 7**). A variety of unsaturated alkynes were also compatible to the catalytic system in high yields. Most importantly, the selectivity of the Ru-catalysed insertions was controlled by the proximity of the C(sp^3)–H bond of the aryl substrates, aided

by of directing groups (either N- or O-coordinating). This discovery was considered a major milestone and laid the groundwork for the transition metal catalysed site-selective C−H activation.



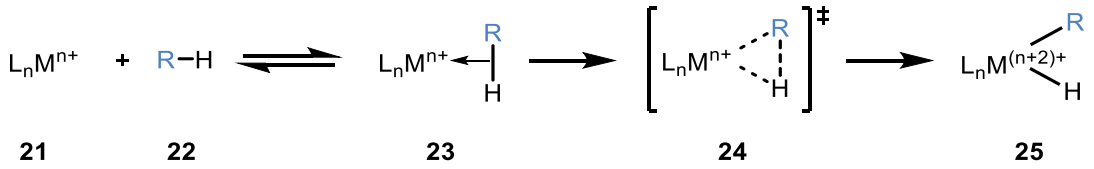
Scheme 7 Ruthenium catalysed *ortho*-C–H olefination of aromatic ketones.

1.3 Mechanisms of C−H Activation Reactions

Since these initial discoveries in the field of catalytic C−H activation, significant efforts have been made to study not only the transformation and reaction conditions but also the mechanisms of the elementary steps involved in activating the C−H bond. Four main reaction modes have been well investigated: oxidative addition, electrophilic activation, σ-bond metathesis, and radical rebound mechanism.[17, 18]

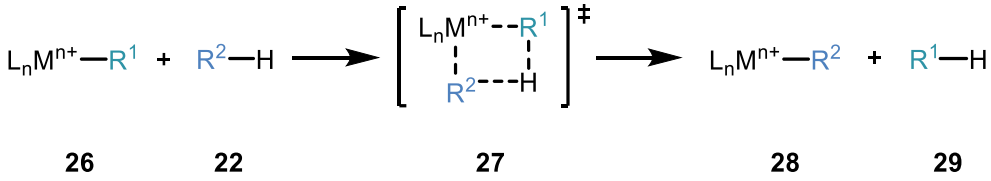
Oxidative addition (OA): this pathway predominates where the electron-rich metal centre is in a low oxidation state, which interacts synergistically with the C–H bond. Namely, in this process, a σ-C–H bond coordinates to the low-valent transition metal centre through an electron back-donation from dπ orbital of metal to the σ^* orbital of the coordinated C−H bond. This lowers the C−H bond order, leading to the bond cleavage in a homolytic fashion and the coordination number of the metal is increased by two units (**Scheme 8**). As the result,

a reactive organometallic species is formed featuring both a hydride and an alkyl/aryl ligand attached to the oxidized metal centre (**25**).[17, 19]



Scheme 8 Oxidative addition (OA).

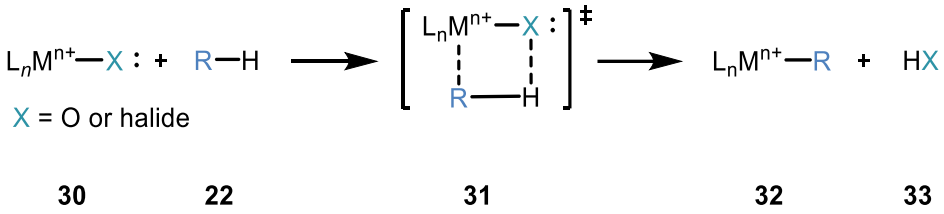
***σ*-bond metathesis (*σ*-BM):** early transition metals with d^0 configuration in a high oxidation state, including lanthanide and actinide metals (such as complexes of Sc(III), Zr(IV), Nb(V), Ta(V)) lacking available d electrons, thus are not able to undergo oxidative additions. However, they can interact with a C−H bond *via* *σ*-bond metathesis (*σ*-BM). In the process of *σ*-BM, it undergoes C−H bond cleavage and new C−M bond formation through a concerted reaction process *via* a four-membered metallacycle transition state formed by [2σ+2σ] cycloaddition of a metal−ligand bond with that of substrate, involving no change of the oxidation state at the metal centre (**Scheme 9**).[20]



Scheme 9 σ-bond metathesis (σ-BM).

Electrophilic activation (ES and AMLA/CMD): The key feature of the electrophilic type of mechanism for C−H activation is the abstraction of a proton by a lone pair on an adjacent heteroatom during the four-membered transition state (**Scheme 10**). It distinguishes the

electrophilic substitution (ES) mechanism from the σ-BM mechanism which does not operate *via* a lone pair.[21-24]

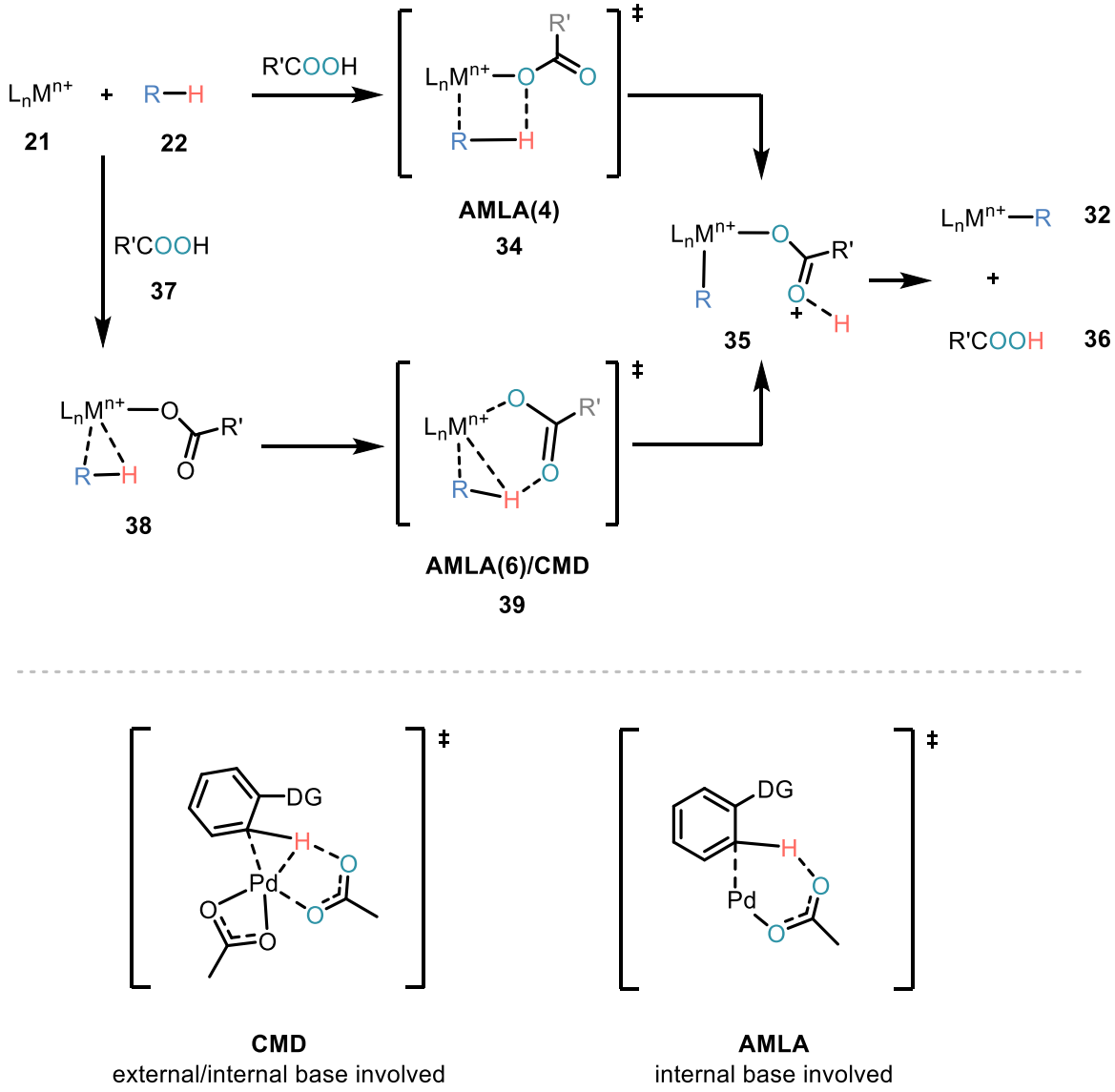


Scheme 10 Electrophilic substitution mechanism.

Apart from ES, there is a number of classifications for electrophilic type mechanisms, such as ambiphilic metal-ligand activation (AMLA),[25] concerted metalation deprotonation (CMD),[26] electrophilic concerted metalation deprotonation (eCMD),[27] ligand to ligand hydrogen transfer (LLHT)[28] among others. Arguably the most significantly investigated reaction mechanisms in C−H activation work are CMD processes coined by Fagnou and AMLA process coined by Macgregor and Davis (**Scheme 11**). CMD describes the processes that occur during the C−H bond activation: the formation of a C−M bond concurrent with the deprotonation of the C−H bond. Both an internal and external base could participate in the CMD mechanism. Despite the AMLA being similar to the CMD, it highlights the cleavage of the C–H bond by a metal catalyst with the assistance of an internal base (**Scheme 11 bottom**).[29] The base must be a ligand possessing chelating ability (e.g. carboxylates), which is necessarily bound to the metal centre. AMLA commonly involves 4-membered transition states (AMLA(4)) and 6-membered transition states (AMLA(6)) as shown in **Scheme 11 top**. The mechanism including an internal base is called AMLA/CMD, which is commonly used in carboxylate-assisted C−H activation.

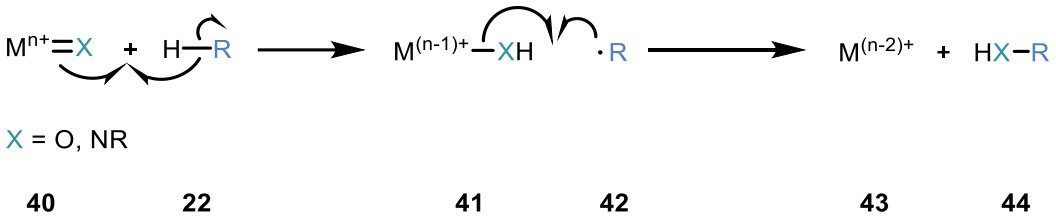
Differing from the ES pathway, during the process of AMLA/CMD, a sigma bond is first formed between a high-valent late transition metal (such as Pd^{II}, Ir^{II}, Rh^{III}) and an alkyl C−H

bond (**Scheme 11 top**). The formation of this sigma complex induces polarization of the C−H bond, leading to the increase of the acidity of the proton. Next, a weak base (i.e. a carboxylate ligand) deprotonates the hydrocarbon to generate a new C−M bond and a carboxylic acid. AMLA can be regarded as more amphiphilic (to be both nucleophilic and electrophilic), while CMD is more either nucleophilic or oxidative.[30]



Scheme 11 General CMD/AMLA mechanism (top); examples showing the general difference between CMD and AMLA in the system catalysed by $Pd(OAc)_2$ (bottom).

Radical rebound mechanism: It is commonly proposed for metal-oxo catalysts in enzyme catalysis.[31] Here, C−H activation is promoted through a metalloradical pathway, which involves a hydrogen radical abstraction process from an alkane by the oxo species (**Scheme 12**). It is followed by a rapid rebound of the radical species onto the metal hydroxo intermediate, resulting in a M−XH intermediate and a carbon-centred radical species.



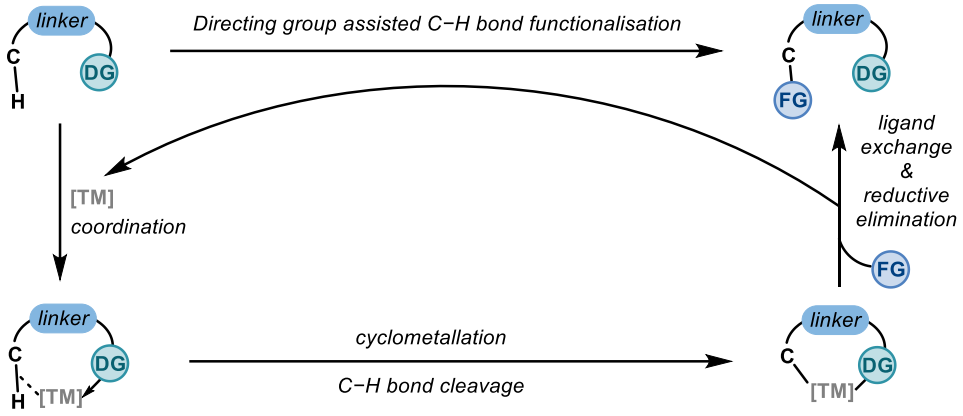
Scheme 12 Radical rebound mechanism.

1.4 Directing Groups – Key for Control of Regioselectivity

1.4.1 Overview of directing groups

Given their ubiquity in all organic molecules, gaining exquisite control of the unactivated C−H bond is a challenge of the highest degree, further complicated by issues of the precise control of chemoselectivity and site- (regio- and stereo-) selectivity encountered in more complex substrates. The site-selectivity can be controlled by considering the electronic and steric effects or exploiting some chelation assistance. Among the diverse strategies developed for C−H activation, the use of directing groups (DGs) has emerged as a powerful and dominant approach, which is able to exquisitely control the site of reactivity. The dominant class of directing groups (DGs) are Lewis-basic functional groups containing non-

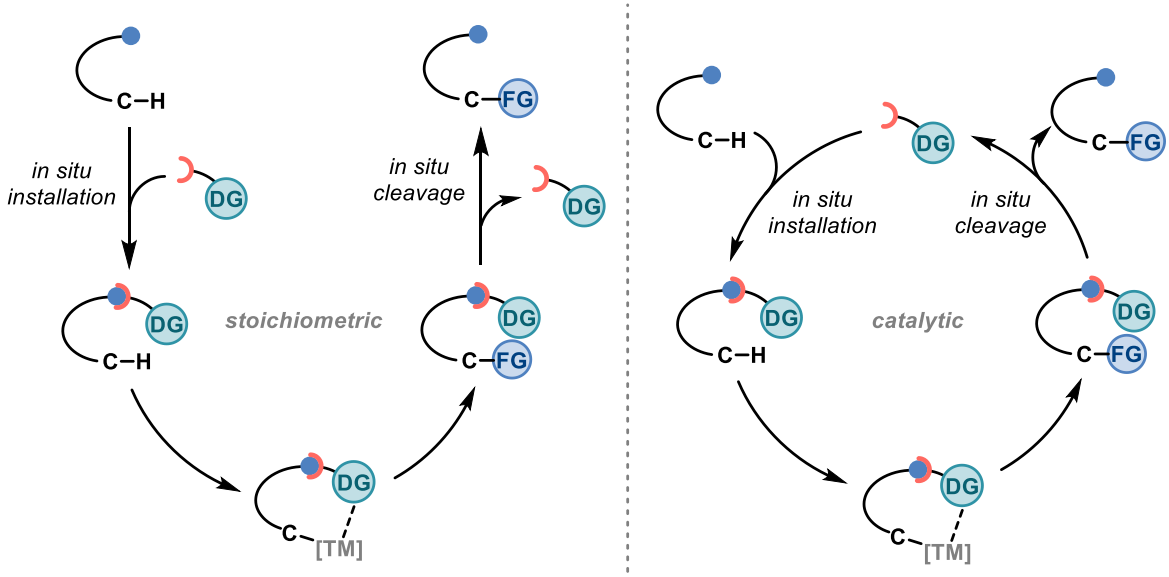
bonding lone pair electrons, that initially coordinate the transition metal centre to the substrate to form a [C–H···M] σ-complex and deliver the metal centre into close proximity with a single specific C−H bond (**Scheme 13**). Moreover, the effective concentration between metal and C−H bond can be increased by binding with the DG, which promotes the downstream agostic interaction eventually.



Scheme 13 Directing group for selective C–H activation.

Multiple functional groups such as ketones, esters, alcohols, amides, amines, pyridines, pyrimidines, oxazolines among others have been investigated as directing groups in C−H activation reactions.[32-34] It is found that a good DG coordinates to the transition metal in a strong but reversible manner, because it needs to promote the selective C−H activation, as well as to allow the dissociation of the intermediate metalated complex to complete a round of the catalytic cycle. DGs can be sorted into two categories according to their coordinating strength: strongly coordinating DGs (i.e. DGs that readily form stoichiometric cyclometalated complexes) and weakly coordinating DGs (i.e. DGs resulting metallacycles which are less thermodynamically stable and are not necessarily isolable, but generally possess higher reactivity than the metallacycles formed with strong DGs).

When selecting an appropriate DG for C−H activation reactions, it is necessary to consider if the DG is an intrinsic part embedded into the substrate and the desirable part of the product. If not, facile removal or alteration of the DG, following C−H functionalisation, is of critical importance. However, as alluded to in the former case, sometimes it would be beneficial to use a DG which is an intrinsic part of the target molecule but synthetically restrictive to be introduced in later steps. A further classification of DG, the transient directing group, which avoids the extra pre-installation and removal, is receiving widespread attention in recent decades.[35]



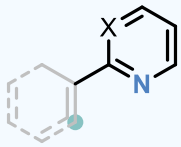
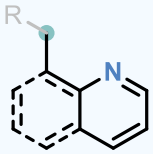
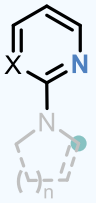
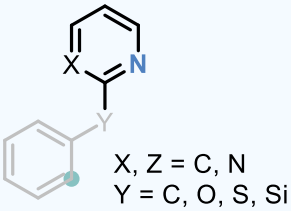
Scheme 14 Transient directing group for selective C–H activation.

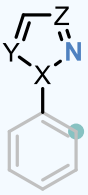
The transient directing mediators could be added into the reaction individually in either stoichiometric or catalytic amounts (**Scheme 14**). Installation of the transient directing mediator occurs initially in situ, and subsequently coordinates the transition metal centre, bringing it into close proximity with a C−H bond on the substrate. C−H activation occurs, and the metal centre dissociates and repeats the same process mentioned above on additional substrate molecules. Finally, the transient directing group can cleave in situ to release the

desired functionalized product as well as the same amount of transient directing mediator being added in the beginning, ideally. It's worth noting that the catalytic cycle needs a stoichiometric amount of transient directing mediator when the functional groups in the substrates would inhibit the catalytic activity; otherwise, it could proceed with catalytic amounts of transient directing mediators. Thereby, in the final step after the transient directing mediator is released, in the catalytic case (i.e., catalytic in transient DG and catalytic in TM), the transient directing mediator continues to proceed to the next catalytic cycle after being released from the last catalytic cycle (**Scheme 14, right**). However, in the stoichiometric case, the catalytic cycle stops (**Scheme 14, left**). The most commonly employed transient directing group relies on imine intermediates, which are generated in situ by the amine moiety of amino acids reacting with the aldehyde group on the substrates.

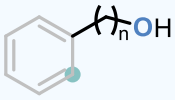
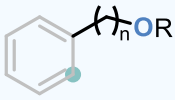
The huge library of DGs can also be divided in some other ways (**Scheme 15**), such as monodentate carbonyl-containing DGs, bidentate DGs, heterocyclic DGs and heteroatom-based DGs (N, S, P, Si…).[36, 37]

Heterocyclic DGs

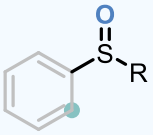
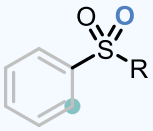
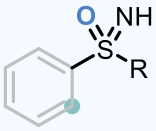







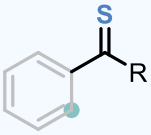
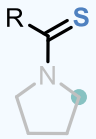
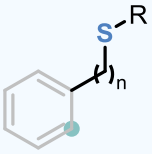
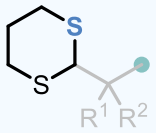
OH- and OR-based DGs

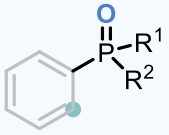
Sulfoxide, sulfones, sulfonamides & sulfoximines as DGs

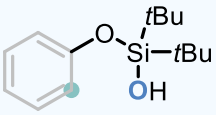
S-based DGs

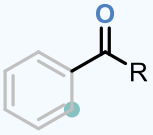
P-based DGs



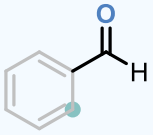
Si-based DGs



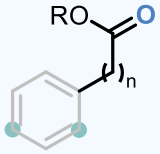
Ketone as DGs



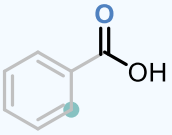
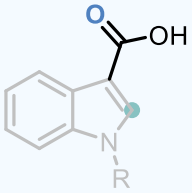
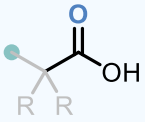
Aldehydes as DGs



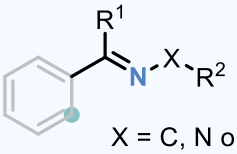
Esters as DGs



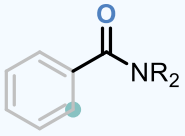
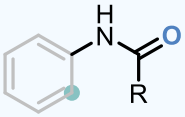
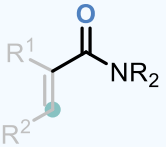
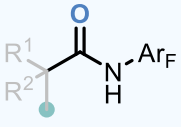
Carboxylic acids as DGs

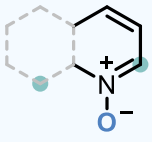
Imines, oximes, hydrazine and hydrazone derivatives as DGs



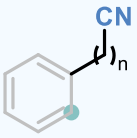
Monodentate amides as DGs

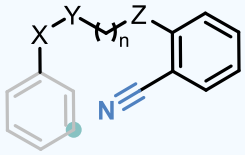





N-oxides as DGs

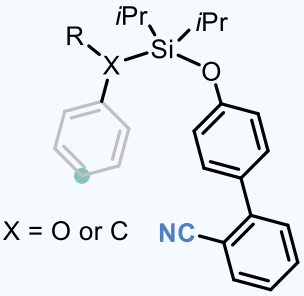


Nitriles as DGs



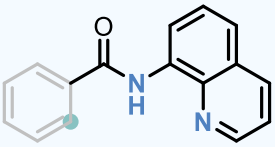


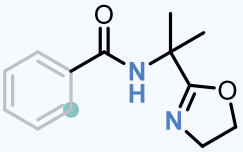
X, Y, Z:
1 or 2 heteroatoms.
often a C=O group

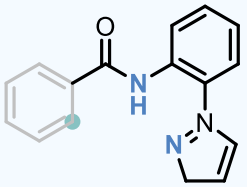


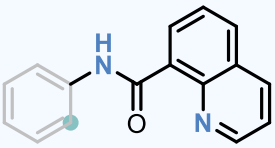
Bidentate DGs

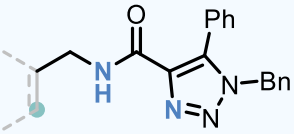
N,N bidentate DGs

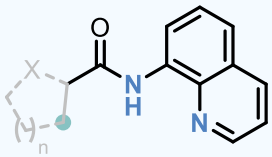




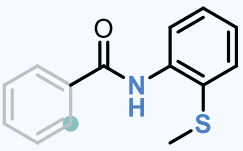


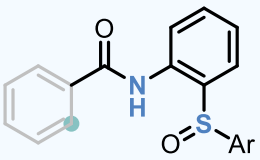


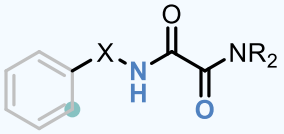


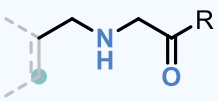


O,N,S bidentate DGs







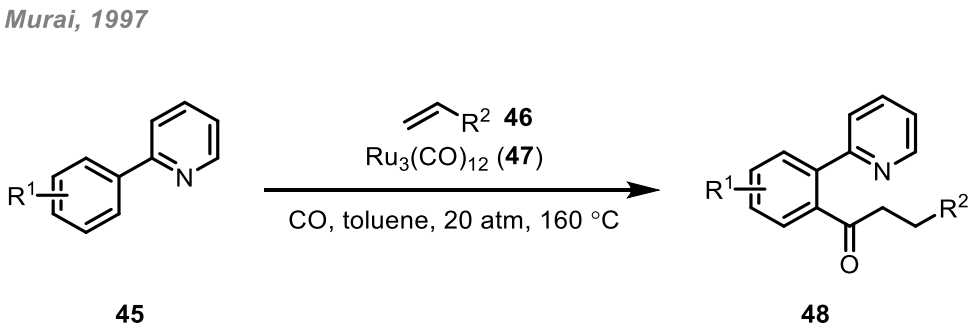


Scheme 15 Selected widely-used directing groups.

1.4.2 Pyrimidine directing groups

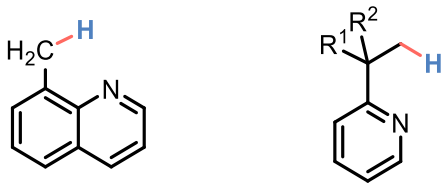
Heterocycles featuring a sp^2-hybridised nitrogen atom such as pyridine, pyrazole, pyrimidine, are one of the most commonly used directing groups. This popularity can be attributed to three key factors: (i) heterocycles are valuable skeletons commonly found in bio-active and pharmaceutical molecules, which avoids the further DG removal after functionalisation or specific pre-installation; (ii) the introduction of heterocycles is synthetically feasible and well-developed; (iii) they are strongly coordinating, and that strength can be controlled by changing heterocycle ring substitution.

The pyridyl group is one of the most commonly applied DGs in C−H functionalisation, especially for C(sp^2)−H bond activation. The use of pyridine as a DG dates back to the 1990s in pioneering work by Murai.[38] In the presence of $Ru_3(CO)_{12}$ as the catalyst, the first C(sp^2)−H carbonylation reaction occurred on the *ortho* position of benzene rings (**45**) using a pyridyl DG with CO (20 atm) and alkenes (**46**) as carbonylative source in toluene at 160 °C (**Scheme 16**). Subsequently, a variety of C(sp^2)−H functionalisation works were rapidly developed in the following decades, mainly utilising Pd, Ru, Rh, Mn, Co, Cu, Ir complexes as catalysts, which mostly focused on using phenyl pyridine as substrate.[36]



Scheme 16 Ru-catalysed C−H carbonylation of pyridylbenzenes with CO.

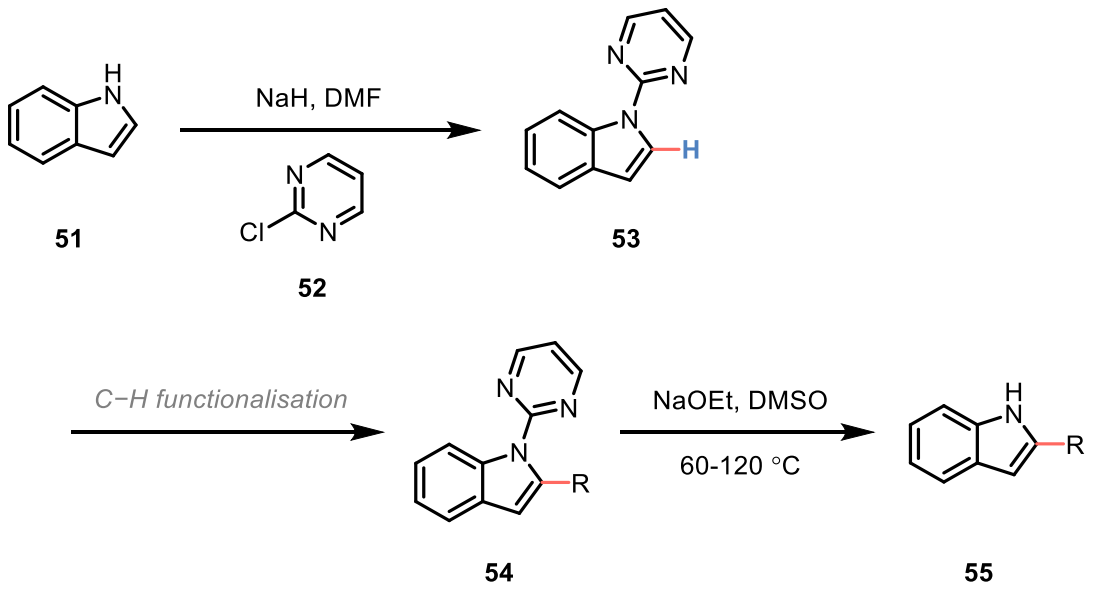
In comparison, the C−H functionalisation of more inert C(sp^3)−H bonds has always been considered more difficult, not just due to its demanding higher bond dissociation energy, but also due to the typically far greater selectivity challenges. So far, the investigation of the C(sp^3)-H activation with substrates bearing azine-based DGs have mainly focussed on 8-methylquinoline (**49**) and 2-ethylpyridine derivatives (**50**). Due to the benzylic nature of 8-methylquinoline, it is generally easier to undergo the terminal methyl C(sp^3)−H functionalisation than that of 2-ethylpyridine (**Scheme 17**).



49 **50**

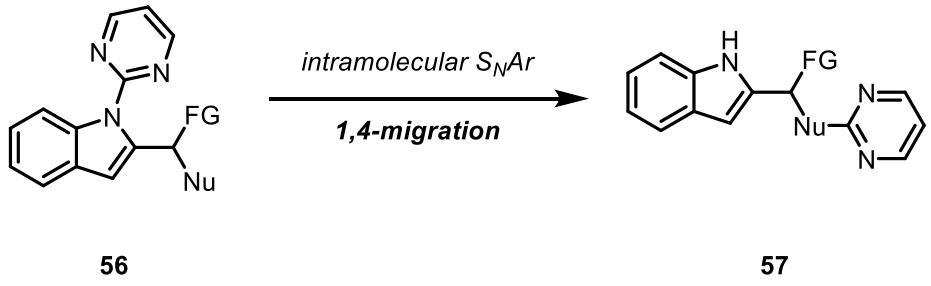
Scheme 17 8-methylquinoline and 2-ethylpyridine derivatives.

Complementary to these approaches, the application of pyrimidine as a DG has often been tested in reactions which initially using pyridine as DG. In most cases, pyrimidine and pyridine can both work under similar conditions in comparable systems. For instance, the pyrimidine directing group has been attached to nitrogen atom of indoles or pyrroles to enable the C−H functionalisation of the C2 position, and notably, can also be readily removed after reaction.[39] For example, the cleavage of pyrimidine group is typically not possible when it is attached by a C−C bond, but when it is attached to the nitrogen of indole (**51**), the pyrimidine-free C2-functionalised indole products (**55**) can be obtained by simply heating the C−H functionalisation product (**54**) with NaOEt in DMSO (**Scheme 18**).



Scheme 18 Selected example of installation and removal of pyrimidine DG on indoles.

However, there are still many cases where only the pyrimidine directing group features specially. For instance, pyrimidine has been observed several times to undergo an intramolecular nucleophilic aromatic substitution (S_NAr), which results in the 1,4-migration of the pyrimidine ring, when a pendant nucleophile is appropriately positioned (**Scheme 19**).[40]



Scheme 19 Pyrimidine DG migration on indoles.

1.5 Enantioselective Rhodium(III)-Catalysed C−H Functionalisation

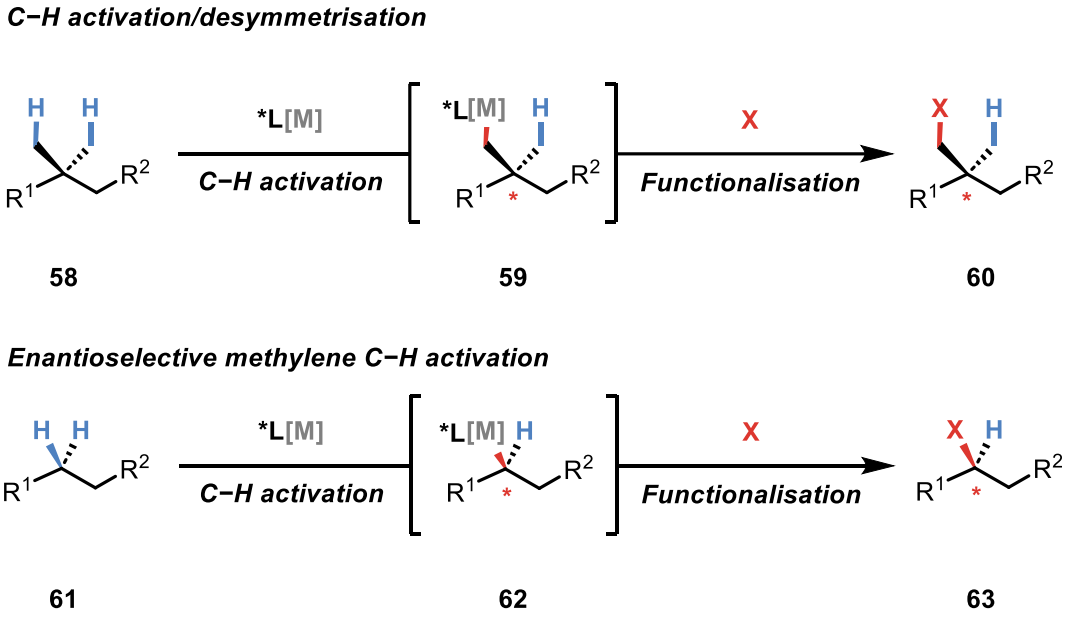
Transition metal catalysed directing-group-assisted C−H activation has been shown to be one of the most useful and successful strategies to realize the selective functionalisation in synthetic chemistry. Over the past decades, a plethora of transition metal complexes containing precious 4d, 5d and earth-abundant 3d block transition metals have been developed and investigated, where the most popular transition metals are Pd, Ru, Ni, Fe, Cu, Co, and Ir.[41, 42]

1.5.1 Enantioselective C(sp^3)–H functionalisation

Despite the fact that directing effects and electronic biases can provide a direct and efficient option to control the chemo- and regio-selectivity in transition metal-catalysed C−H functionalisation reactions,[43-45] unfortunately, the application of C−H activation in drug or bioactive molecules is still hardly realised due to enantioselectivity issues. Notably, small molecule drugs frequently contain chiral motifs critical to their mode of action, given the inherent chirality of target biomolecules such as proteins.[46] Therefore, precise selective C−H bond modification that can establish chirality in high enantiomeric excess, in one step, have drawn significant attention in recent years.

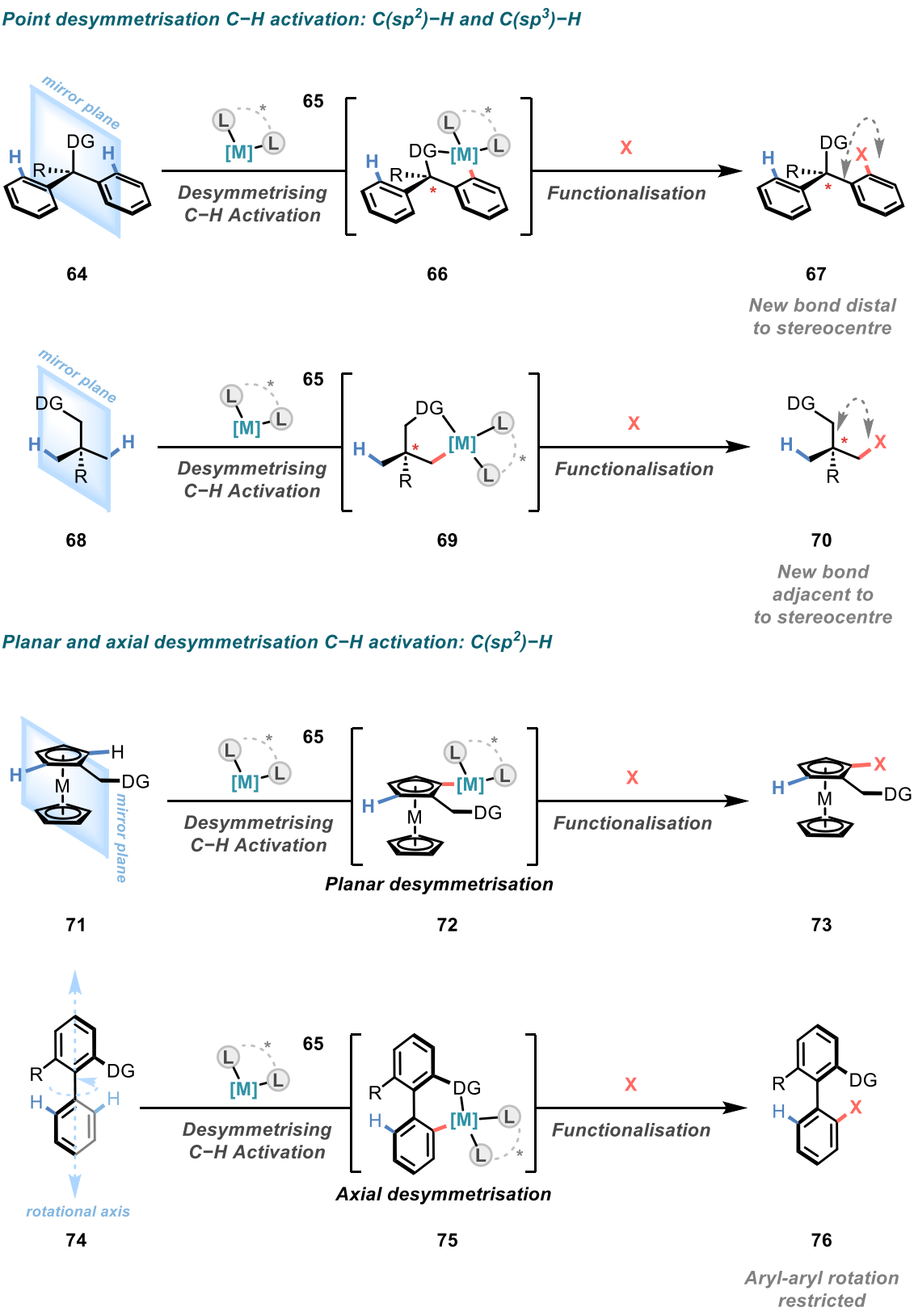
To date, multiple approaches have been developed to achieve enantioselective C–H functionalisation, including: (a) biomimetic approaches[47] or metal-oxo H-atom abstractions;[48] (b) metallonitrene/metallocarbene C−H bond insertion;[49, 50] and (c) transition metal induced C−H activation process[51] which is the approach we focus in this thesis.

According to different environment of chiral carbon centres, two categories are revealed to be effective for the transition metal-mediated enantioselective C−H activation. One is a desymmetrisation of prochiral molecular entity (such as isopropyl desymmetrisation), in which the newly-developed chiral carbon centre is not bound to the metal centre (**Scheme 20 top**). Another one is functionalisation of enantiotopic methylene C−H bond using transition metal complex bound to the chiral carbon sterocentre directly (**Scheme 20 bottom**).



Scheme 20 Transition metal-catalysed enantioselective functionalisation of C(sp^3)−H bond in different environment.

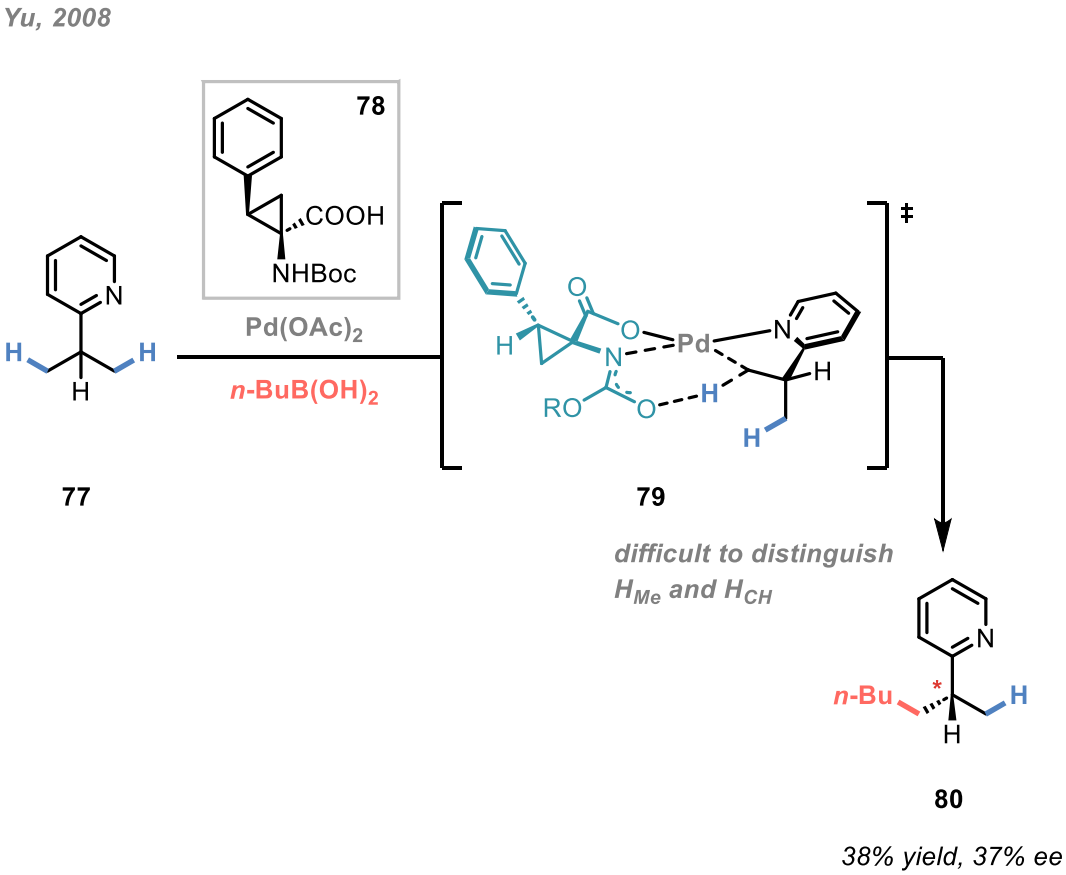
Enantioselective C−H activation by desymmetrisation generally divides into two categories. The first is the C−H point desymmetrisation, where the new bond generated by C−H activation is distal to the stereocentre (in C(sp^2)−H desymmetrisation), or adjacent to introduced stereocentre (in C(sp^3)−H desymmetrisation) (**Scheme 21A**). The second one is the planar or axis C−H desymmetrisation, such as the desymmetrisation of metallocene[52, 53] and biphenyl compounds by C−H activation (**Scheme 21B**).[54] Herein, we only focus on the C(sp^3)−H point desymmetrisation type.



Scheme 21 Symmetry differentiation of transition metal-catalysed desymmetrisation C–H activation.

Inspired by a series of initial studies on mono-*N*-protected amino acids (MPAAs) for the enantioselective C(sp^2)–H activation of 2-benzhydrylpyridines by Yu,[55] the bidentate cyclopropyl MPAA (**78**) was shown to be applicable for the enantioselective C(sp^3)–H bond alkylation of 2-isopropyl pyridine (**77**) catalysed by palladium(II) acetate (**Scheme 22**). Compared to the C(sp^2)–H functionalisation of 2-benzhydrylpyridines they previously reported in similar system, this one yielded the product in only 38% yield and 37% enantiomeric excess respectively.[56] This poor selectivity might be due to the challenge of differentiating between a methyl group and the methine proton, owing to insufficient size difference (in comparison with an aryl group and a methine proton of 2-benzhydrylpyridines).

Subsequently, it was found that the pyridine-directed C–H activation still occurred in the absence of a chiral ligand, leading to racemic product formation. It indicated that such strongly-coordinating DGs might favour to bind to the metal centre first rather than chiral ligands (especially since in many systems the concentration of substrates is significantly higher than that of the ligands), while a strongly-coordinating DG can also establish a thermodynamically more stable cyclometallation intermediate that terminates the catalytic cycle.[57]

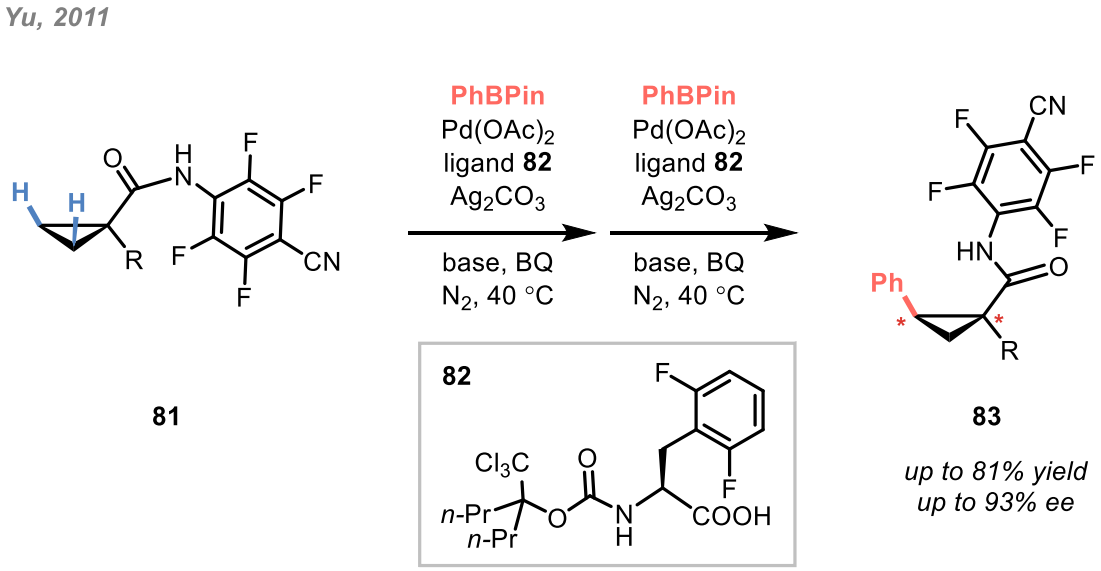


Scheme 22 Initial studies on enantioselective C(sp^3)–H activation with strong DG.

In order to avoid the unanticipated coordination between strong DGs and metal, the rigid cyclopropyl and cyclobutyl compound containing weakly coordinating monodentate DGs were then explored in the presence of the MPAA ligands in the Pd(II)/Pd(0) catalytic systems.[58, 59]

Using acidic *N*-arylamides as weakly coordinating directing groups, the first example of palladium catalysed cross-coupling of cyclopropane C−H bond with phenylboronic acid pinacol ester (Ph-BPin) was achieved to afford the *cis*-substituted chiral cyclopropane amides in the presence of ligand **82** by Yu and coworkers in 2011 (**Scheme 23**).[58] To give the optimal yield and enantiomeric excess, the reaction needed to be performed twice for it to reach the maximum conversion (i.e. all the reagents excluding the substrates needed to be

added in two batches separately). Gratifyingly, this methodology could be expanded to an enantioselective variant.

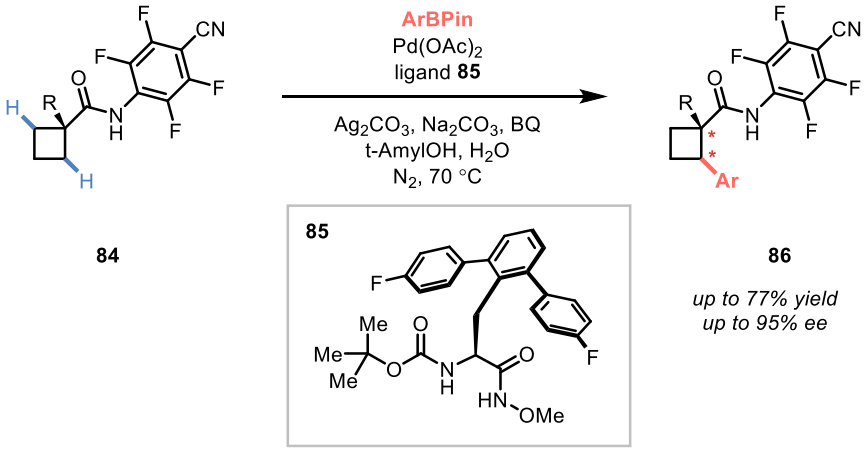


Scheme 23 Pd(II)-catalysed enantioselective C(sp^3)–H activation of cyclopropanes.

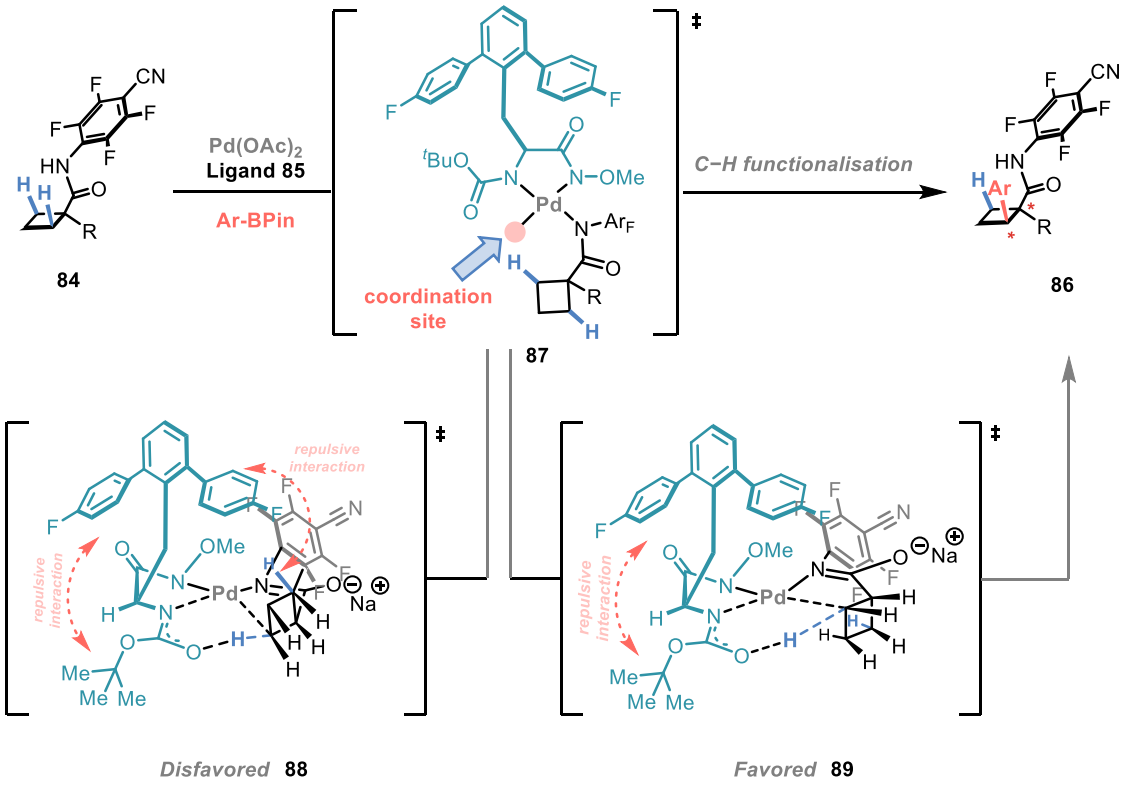
In 2014, a library of chiral mono-*N*-protected α-amino-*O*-methylhydroxamic acid (MPAHA) ligands, with a larger side chain and *N*-protecting group modified from MPAA, were applied for the intermolecular C(sp^3)–H arylation of C1-substituted cyclobutanecarboxylic acid derivative (**84**) (**Scheme 24 top**). With the optimal MPAHA (**85**), the corresponding *cis*-arylated products were attained in up to 77% yield, with high enantio-control of up to 95% ee.

This novel work provided a new approach to synthesize functionalised four membered rings, avoiding the more traditional and predominating [2+2] cycloaddition method.[59] The computational studies explained that the main repulsive interaction between *N*-protecting group and the MPAHA side chain could effectively push the MPAHA side chain to be orthogonal with the Pd(II) plane, which further established the favourable configuration **89** (**Scheme 24 bottom**).

Yu, 2014



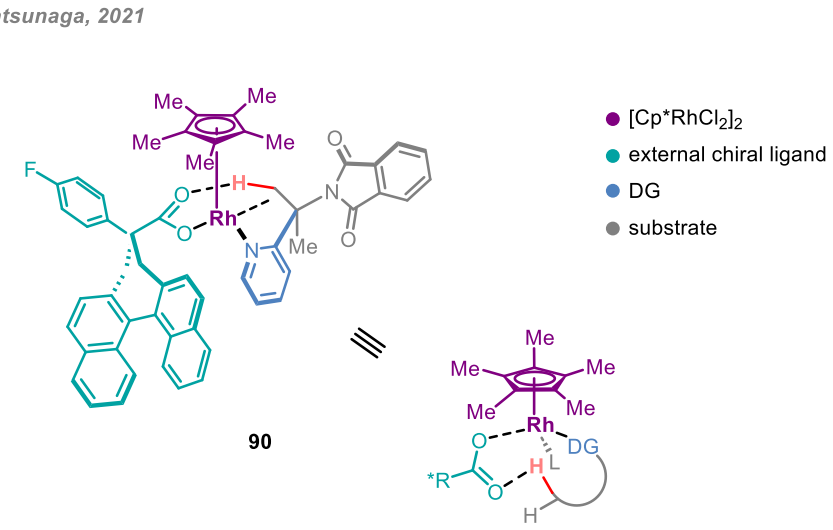
Computational Studies



Scheme 24 Intermolecular enantioselective C(sp^3)–H arylation of cyclobutanes using weakly coordinating DG.

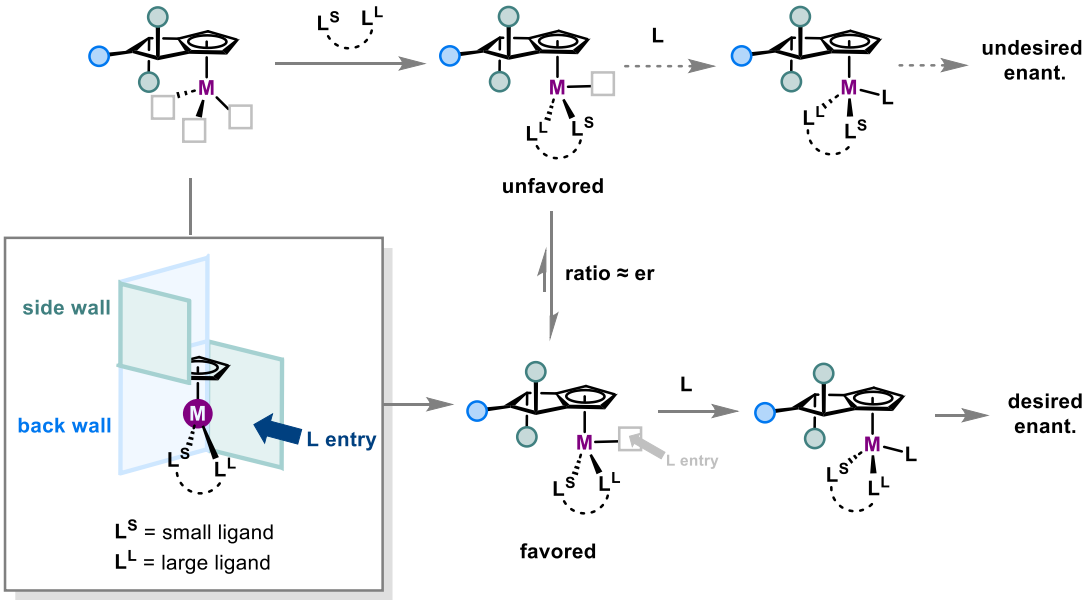
1.5.2 Cp*Rh(III) and Cp^{x}Rh(III) type catalysis in C−H functionalisation

In recent years, numerous remarkable methodologies in rhodium catalysed C−H functionalisation have been discovered.[60] Rhodium, a precious transition metal belonging to the group 9, has garnered significant attention as a catalyst in various organic transformations, particularly in the realm of C−H functionalisation.[61-64] Rhodium complexes, containing a diversity of ligands, are able to exist in the oxidation states of 0, +1, +2 to +3, such as $Rh_4(CO)_{12}$, $RhCl(PPh_3)_3$, $[Rh(OAc)_2]_2$, and $[Cp^*RhCl_2]_2$. In lower oxidation states rhodium remains stable solely when suitable ligands are present.[65] The trivalent rhodium metal attached with a pentamethylcyclopentadienyl (Cp*) or the chiral cyclopentadienyl (Cp^x) ligands are prominently utilised in various catalytic asymmetric reactions given their remarkable stability and high reactivity. Cp*Rh(III) catalyst is generally employed in presence of external chiral ligands to control the stereoselectivity. For instance, in a recent work reported by Matsunaga group,[66] the computational studies revealed that a chiral binaphthyl monocarboxylic acid combined with the rhodium centre forming a reactive Cp*−Rh metallocyclic intermediate, which could establish a defined chiral environment upon ligand exchange, leading to the favourable reaction conformation that can achieve control of stereoselectivity (**Scheme 25**). In addition, the Cp* can also play an important role in increasing the steric repulsion, further tuning the appropriate conformation during the reaction.



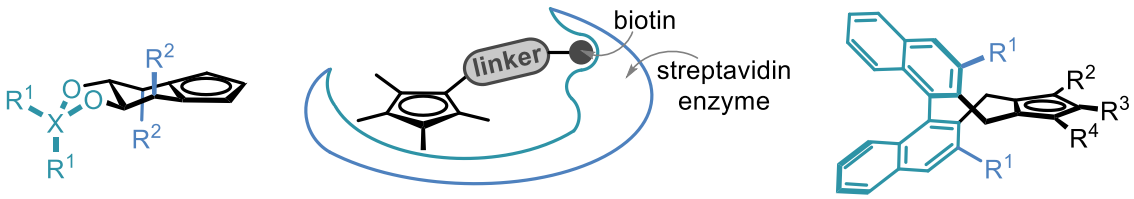
Scheme 25 Selected example: favored TS structure of the Cp*Rh(III)-catalysed C–H activation assisted by external chiral ligand.

Another privileged strategy is using the Cp^{x}Rh(III) catalysis. This approach is still based on the concept of building the special chiral environment around the metal centre, but differently in this case, the chiral environment is derived from an exquisitely designed chiral Cp-type ring rather than through the additional complexation of an external chiral ligands (**Scheme 26**).



Scheme 26 Cramer's design concept for Cp^{x}M(III) complex.

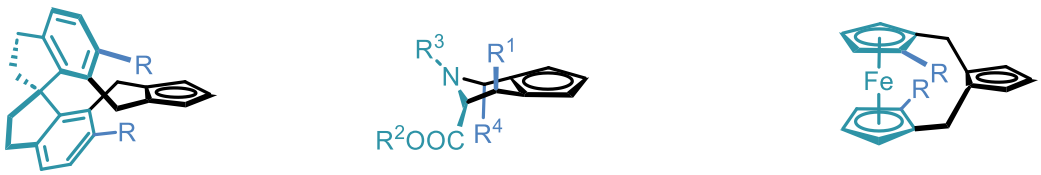
A series of leading papers in C−H activation has been demonstrated by Cramer using an elegant design concept for chiral Cp^x ligands (initially, Mannitol-Cp (**91**),[67] and then BINOL-Cp (**93**)[68]) since 2012, and then by Ward & Rovis (SavCp (**92**)),[69] You (SCp (**94**)),[70] Antonchick & Waldmann (JasCp (**95**)),[71] and Wang (FcCp (**96**)).[72] which have enabled a wide range of asymmetric C−H functionalisation reactions building on this strategy (**Scheme 27**).[73] This strategy has been shown to control the enantioselectivity effectively, however, the preparation of the chiral Cp^X can be highly synthetically challenging, which typically requires 6 to 12 steps. Especially, during the ligand screening and optimization project phases, this brings significant challenges and inconvenience for reaction discovery/optimisation.



Mannitol-Cp (91)
Cramer, 2012

SavCp (92)
Ward&Rovis, 2012

BINOL-Cp (93)
Cramer, 2013



SCp (94)
You, 2016

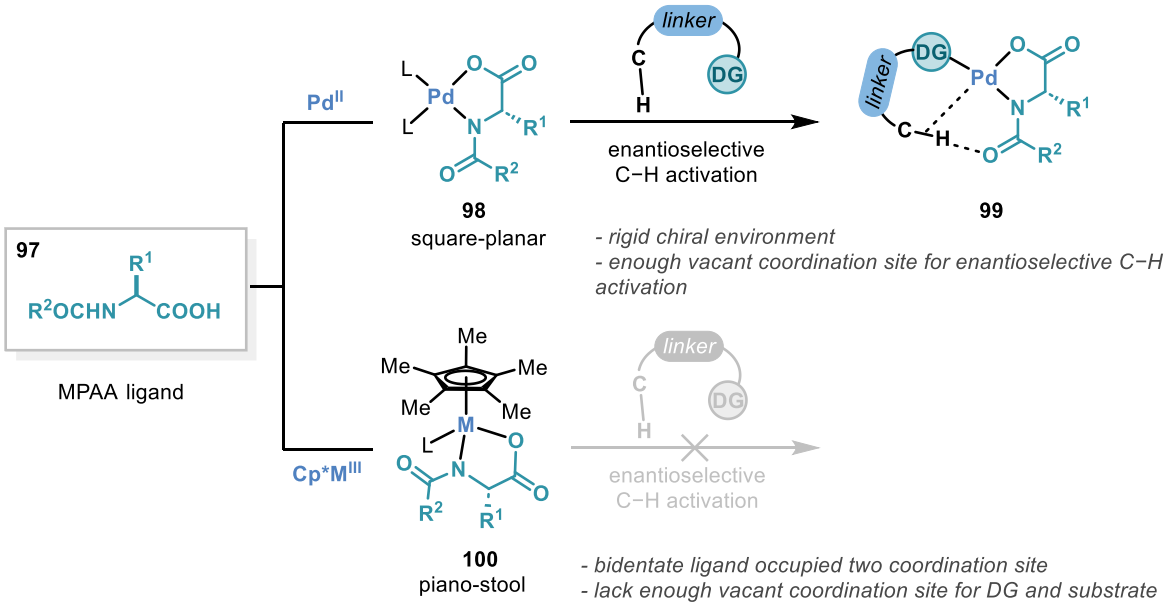
JasCp (95)
Antonchick&Waldmann, 2017

FcCp (96)
Wang, 2020

Scheme 27 Overview of Cp^X ligands in asymmetric C−H functionalisation reactions.

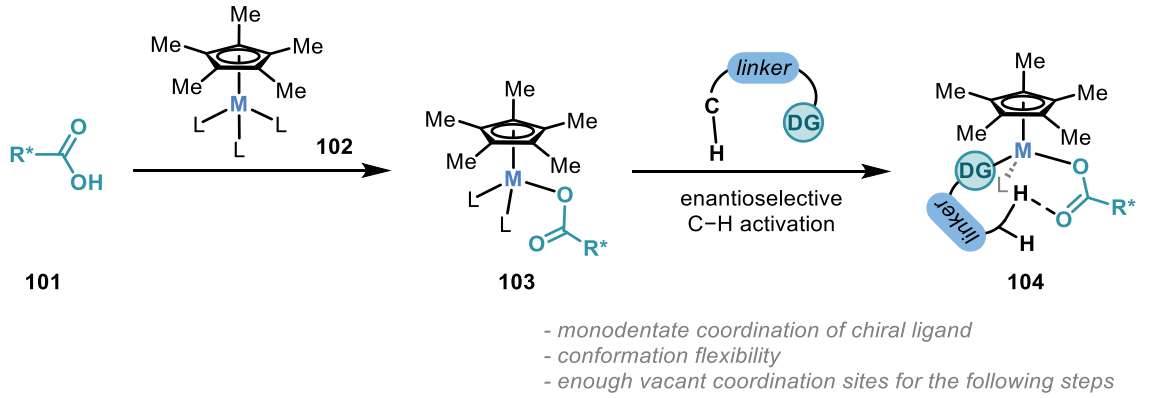
1.5.3 Cp*Rh(III)-catalysed enantioselective C−H functionalisation assisted by chiral carboxylic acid ligands

The mechanistic pathways of Cp*M(III) catalysed C−H activation reaction assisted by carboxylate or coordinating bases have been studied broadly in recent years *via* quantum chemical calculations and *via* experimental mechanistic investigations.[30, 74, 75] It has been determined that the mechanism of such C−H activation is generally observed to be amphiphilic metal ligand activation (AMLA), base-assisted internal electrophilic substitution (BIES), and concerted metalation deprotonation (CMD) pathways. The agostic interactions between the C−H bond and the electrophilic rhodium centre can weaken the C−H bond, acidifying the hydrogen atom and thereby facilitating C-M bond formation. Therefore, the nature of the introduced chiral coordinating base ligand is vital for the control of enantioselectivity by forming an appropriate sterically enforced transition state. In 2018, Yu and co-workers reported a Pd(II)-catalysed enantioselective C(sp^2)−H and C(sp^3)−H alkylation using mono-*N*-protected amino acids (MPAAs) as chiral ligands, in which the rigid chiral environment was controlled *via* a bidentate coordination (**Scheme 28 top**).[55] In this strategy, such bidentate MPAA ligands were specifically designed for application in palladium(II) catalysis, which required occupation of two vacant coordination sites of the total four coordination sites available at the Pd(II) centre. However, these ligands have not been successfully applied in Cp*M(III) catalysis directly so far, because the Cp*M(III) complexes adopt a piano-stool geometry (**100**) with only three empty coordination sites (**Scheme 28 bottom**), therefore, if the bidentate ligand occupied two vacant coordination sites, the utilisation of directing groups is prohibited in this system.[76]



Scheme 28 Different coordination modes of bidentate ligands with Pd^{II} and Cp^*M^{III} complexes.

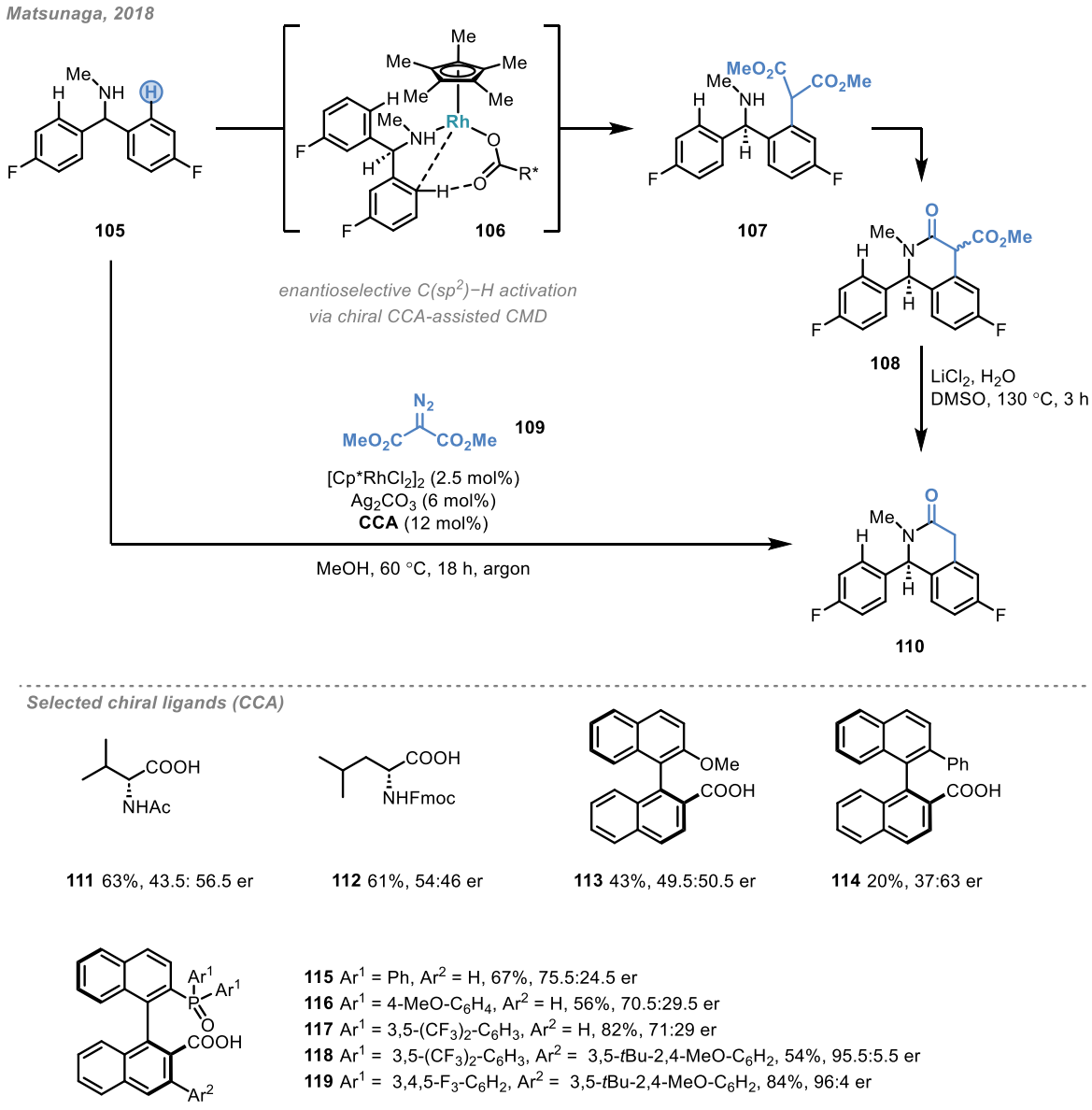
Given this restriction, monodentate coordinating chiral ligands have to date been employed in achiral Cp*M(III) catalysed C−H activation (**Scheme 29**). Since there is only one coordination site on the metal centre occupied by the chiral ligand leading to the conformational flexibility in the binding of the substrate, the construction of a favourable chiral environment is rendered more challenging. A series of seminal work was conducted using Cp*Ir(III), Cp*Rh(III) and Cp*Co(III) catalysts combination with monodentate coordinating chiral ligands, by Chang,[77] and Matsunaga[76] since 2015.



Scheme 29 Monodentate chiral ligand assisted enantioselective C−H activation catalysed by Cp^*M^{III}.

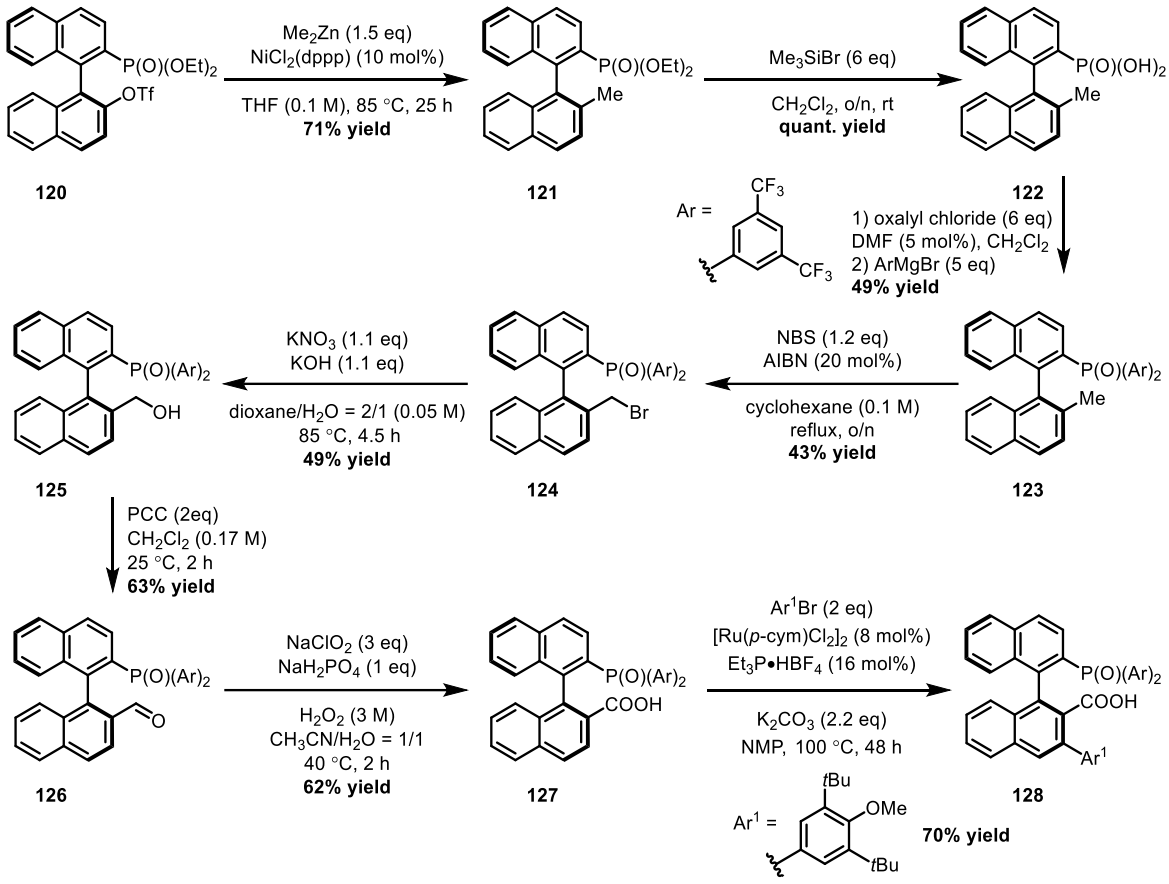
As the chiral binaphthyl backbone is one of the most effective and privileged skeletons in asymmetric synthetic chemistry, it was prioritized to be selected for establishing a chiral carboxylic acid (CCA) ligand library by Matsunaga,[78] which was for the first time utilised in a $Cp^xRh(III)$/CCA catalytic system. Subsequently, a series of enantioselective $C(sp^2)$−H and $C(sp^3)$−H functionalisation reactions catalysed by many other $Cp^xM(III)$ complexes were discovered successively.

Initially, an asymmetric $C(sp^2)$−H alkylation process using an achiral $Cp^xRh(III)$/CCA catalytic system was developed (**Scheme 30**), which first enabled the intramolecular C−H functionalisation of diarylmethane amines **105** with diazomalonate **109** through a cyclometalated intermediate **106** forming alkylated-diarylmethane amines **107**, followed by cyclization and Krapcho decarboxylation, ultimately yielding 1,4-dihydroisoquinolin-3(2H)-one derivatives. Multiple chiral carboxylic acids were investigated; initially, MPAA ligands only afforded the product in low enantioselectivity, which indicated that the MPAA ligands **111 & 112** could promote the CMD process but were unable to enforce high enantioselectivity with the Cp*Rh(III) catalyst. Subsequently, in the case of binaphthyl-type CCA **113**, featuring an ether group at the C2' position, the reaction afforded almost racemic product. However, the more sterically hindered CCA **114** exhibited promising selectivity control with an enantiomeric ratio of 37:63. The bulkier CCA **119** containing a phosphine oxide moiety was eventually found to be the optimal ligand providing the product in 96:4 er. The further investigation revealed that the substituents at both C2'- and C3-positions played a crucial role in enhancing the enantioselectivity, which achieved up to 98.5:1.5 er with bis-CF_3 substituents on the *ortho* position of aromatic rings of substrate. This reaction demonstrated that the CCA ligand alone in such systems could serve as the sole source of chirality, thereby opening a new door in this area.



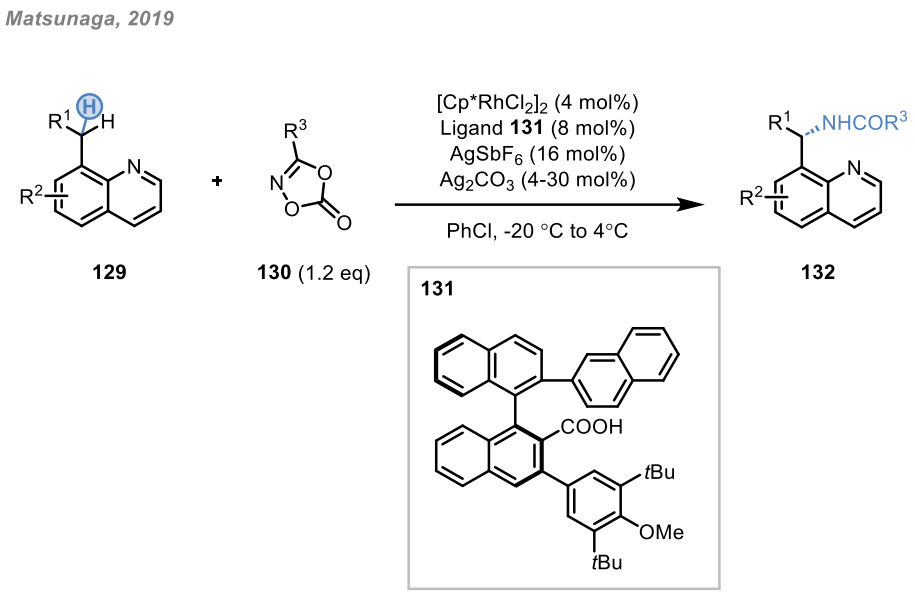
Scheme 30 Cp*Rh^{III}-catalysed enantioselective C(sp^2)−H alkylation/cyclization assisted by chiral CCA.

However, while this fine-tuning of the CCA demonstrated impressive effects on the enantioselectivity control, its synthesis required over 8 steps, highlighting a lack of the synthetic efficiency, greatly hindering the ligand screening phase of reaction development (**Scheme 31**).



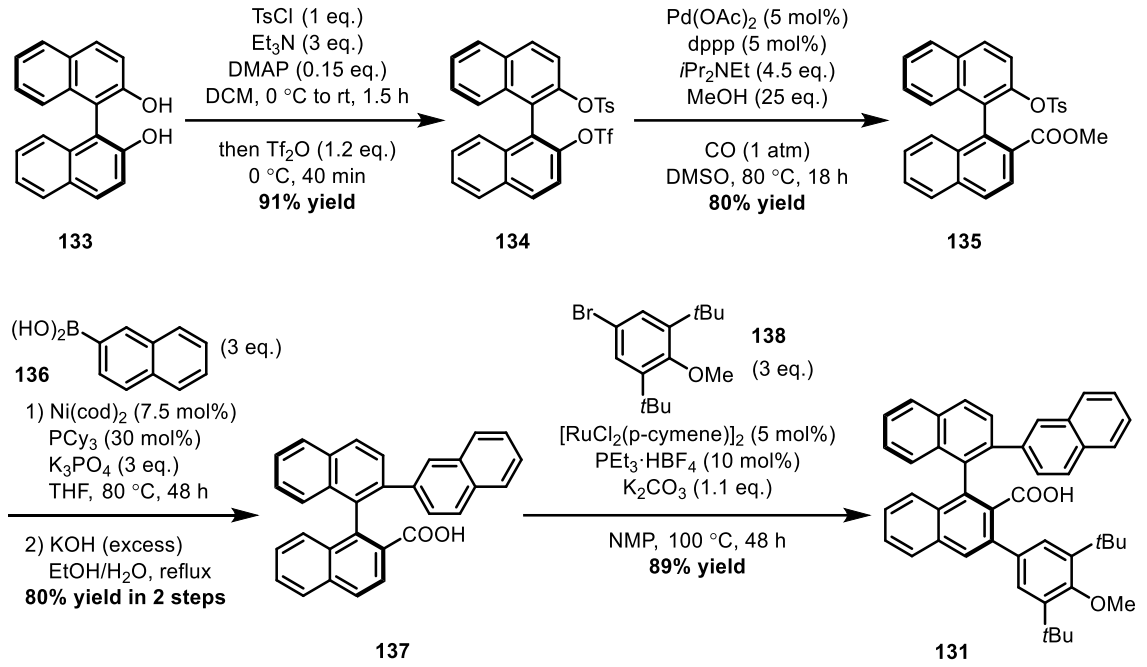
Scheme 31 Synthetic route of chiral carboxylic acid.

Advancing beyond C−C bond formation, the barely explored formation of C−N bonds by C(sp3)−H bond activation was subsequently investigated, featuring enantiocontrol by Matsunaga in 2019.[79] Using readily-available dioxazolones as the amide source, a newly designed binaphthyl-based chiral carboxylic acid **131** bearing aryl substituents at the C2' and C3 positions, and with the Cp*$RhCl_2$ dimer as the catalyst, the methylene C(sp^3)−H amidation of 8-alkylquinolines **129** was achieved, furnishing the targeted enantiomer **132** in up to 94:6 enantiomeric ratio (**Scheme 32**).



Scheme 32 Enantioselective methylene C(sp^3)−H amidation of 8-alkylquinolines.

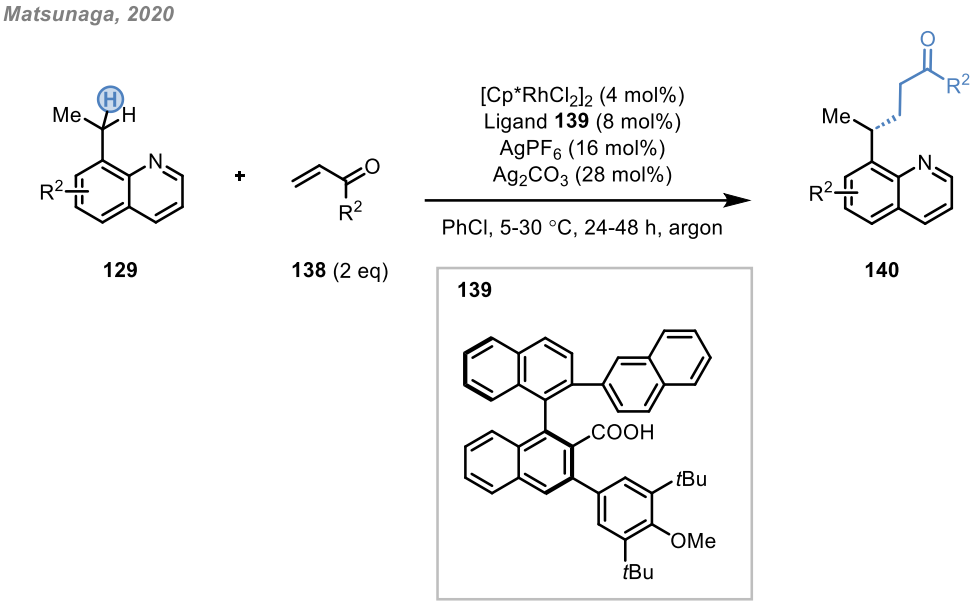
The reaction proceeded under mild conditions at low reaction temperatures between -20 to 4 °C and in comparison to the previous work mentioned above, the synthesis of the CCA **131** here was much simpler - completed in five steps starting from commercial (*S*)-BINOL (**133**) (**Scheme 33**). Treated separately with TsCl and Tf_2O respectively, the (*S*)-BINOL (**133**) was transformed into the monotosylated and monotriflated compound **134**. Selective carbonylation catalysed by $Pd(OAc)_2$ then yielded the compound **135**. After the Ni-catalysed Suzuki−Miyaura coupling with naphthalen-2-ylboronic acid (**136**), carboxylic acid **137** was released. Finally, the desired CCA **131** was generated through a Ru-catalysed *ortho* C−H arylation using carboxyl group as directing group.



Scheme 33 Synthetic route to chiral ligand **131**.

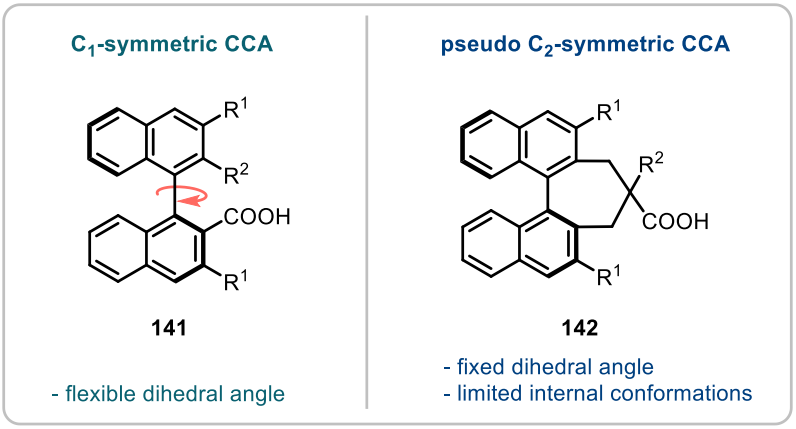
Furthermore, α,β-unsaturated carbonyl compounds **138** were shown to be effective electrophiles in place of the dioxazolones, leading to the enantioselective C(sp^3)−H alkylation products on similar substrates (**Scheme 34**).[80] Silver salts were screened in this work and found to be key for improving the reactivity without compromising the enantioselectivity. Instead of using previously employed $AgSbF_6$, $AgPF_6$ was found to improve the yield from 26% to 80% in the presence of additional 28 mol% of Ag_2CO_3 reagent.

In addition, an H/D exchange experiment was performed by employing the substrate **129** with CD_3OD or AcOD under the standard reaction conditions. There was almost no H/D exchange observed, indicating that the C−H bond cleavage step is likely the irreversible enantio-determining step.



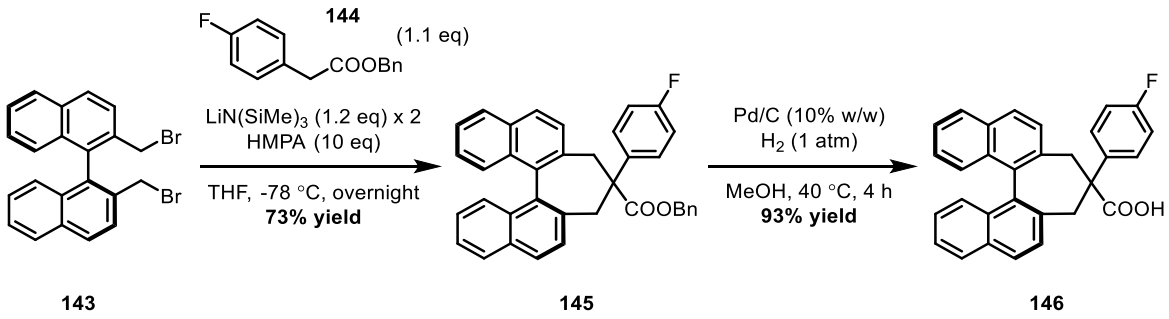
Scheme 34 Cp*Rh(III)/CCA-catalysed enantioselective C(sp^3)–H alkylation reaction of 8-ethylquinolines.

While C1-symmetric binaphthyl CCAs offer tuneable flexibility in various reactions, their inherent structural feature poses a challenge. The less restricted dihedral angle between the two naphthyl rings allows for more flexible rotation, leading to the conformational flexibility and ambiguity of possible transition-state geometries during the C−H activation step. Precisely controlling enantioselectivity becomes intricate as favourable and unfavourable transition states compete amidst this conformational complexity (**Scheme 35 left**).



Scheme 35 Comparison of C1-symmetric and pseudo-C2-symmetric CCAs.

In this context, the Matsunaga group further developed a binaphthyl-based pseudo-C2-symmetric CCA in assisting the enantioselective C−H functionalisation, in which there was more restricted conformational flexibility (**Scheme 35 right**). Starting from the commercial or readily prepared bromides **143**, the synthesis of such CCA can be completed in two steps *via* a double alkylation with a nitrile or ester to afford compound **145** followed by benzyl deprotection. This strategy not only decreased the conformational ambiguity for the transition states, but expedited the ligand synthesis, resulting in convenience for the ligand screening/optimisation compared to other complex ligands (**Scheme 36**).

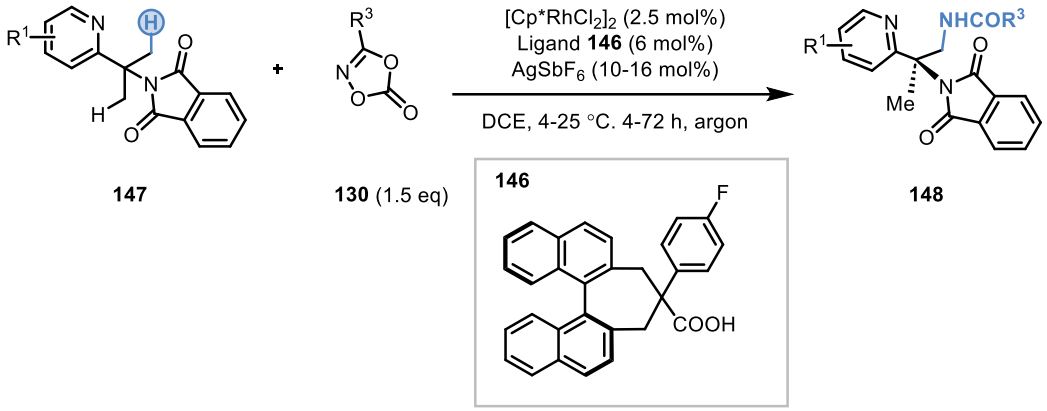


Scheme 36 Synthesis of CCA **146**.

This type of CCA was subsequently applied to an enantioselective C(sp^3)−H desymmetrising amidation of 2-alkylpyridine derivatives **147** bearing a phthalimide-protected amine (**Scheme 37**).[66] Using dioxazolones **130** as the amide reagent, pyridine, isoquinoline and benzimidazole could be used as efficient directing groups in combination with the Cp*Rh(III) or Cp*$^{t\text{Bu}}$Rh(III) catalysts, which improved the enantioselectivity up to 96:4 er. The sterically hindered phthalimide moiety used here mainly increased the steric hinderance, which was beneficial for distinguishing the enantio determining transition states during the

C−H activation step, however the necessary presence of such a group limited the diversity of substrates and further applications.

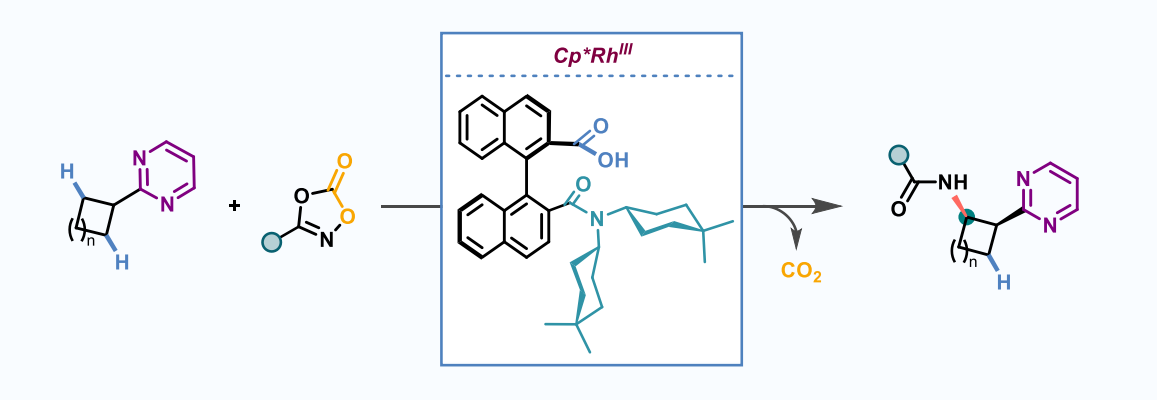
Matsunaga, 2021



Scheme 37 Enantioselective methyl C(sp^3)−H amidation of 2-alkylpyridines.

Chapter 2 Discovery and Development of Enantioselective Cp*Rh-Catalysed C(sp^3)–H Amidation of Azine-Substituted Cyclobutanes

2.1 Chapter Overview



Scheme 38 Cp*Rh(III)-catalysed enantioselective C(sp^3)–H amidation of azine-substituted cyclobutanes.

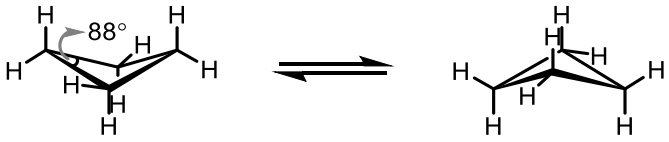
This chapter reviews the modern methodologies developed to synthesize cyclobutane rings *via* direct C(sp^3)–H activation tactics, which confer significant synthetic advantages when compared to alternative strategies. The development of a novel pyrimidine-directed intermolecular C(sp^3)–H amidation of cyclobutanes utilising a Cp*Rh(III) catalyst and readily-available dioxazolones will then be discussed. In order to improve the reactivity and enantioselectivity of the preliminary result (64% yield, 51:49 er), a library of chiral ligands was synthesised. It was found that a binaphthyl-based chiral carboxylic acid (CCA) bearing a pendant *N*,*N*-4,4-dimethylcyclohexyl amide was optimal for the highly-enantioselective

desymmetrisation process, affording the desired amidation products in up to 94% yield and 99:1 er after optimisation. A good range of dioxazolones substituted with diverse functional groups were compatible with this unique transformation, giving moderate to excellent enantioselectivity and yield. It is noteworthy that a variety of amidated cycloalkylpyrimidines and cyclobutanes with other N-containing directing groups could also be attained using this catalytic system. In addition, the enantioenriched *bis*-amidated cyclobutanes were found to be accessible under the standard conditions. Detailed computational mechanistic studies suggested that a key $n{-}\pi^*$ interaction between the pyrimidine directing group and the ligand amide, in tandem with additional CH−π interactions with the *gem*-dimethyl groups on the cyclohexane rings, play a vital role in enforcing a rigid conformation in the enantio-determining transition state.

2.2 Cyclobutanes in Small-Molecule Drug Candidates

Cyclobutane is referred to as the "Cinderella" among carbocyclic compounds,[81] as it is the second most strained saturated monocarbocycle behind cyclopropane, with a strain energy of 26.3 kcal mol^{-1}.[82, 83] The four carbon atoms of cyclobutane are not entirely in the same plane since it adopts a butterfly or puckered conformation. This means that the bond angle is slightly reduced from the theoretical 90° to 88°, which further increases the angular strain but relieves the torsional strain (**Scheme 39**). As a result, the C−C bonds show slightly increased *p*-character, and the C−H bonds show increased *s*-character.[84] This slightly increased s-character leads to the unique reactivity of cyclobutane, which is placed between the very reactive cyclopropane and relatively inert cyclopentane. Moreover, due to the

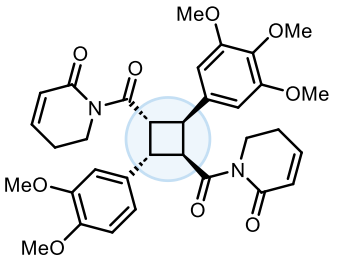
inherent ring strain, cyclobutanes undergo reactions such as ring opening to acyclic products (ca 23–26 kcal mol^{-1} exothermic), ring enlargement towards five-/ six-membered ring products (ca 20 and 25 kcal mol−1, respectively) and ring contraction to cyclopropanes.[85] This implies that reactions involving cyclobutyl compounds may vary in their feasibility, presenting specific challenges.



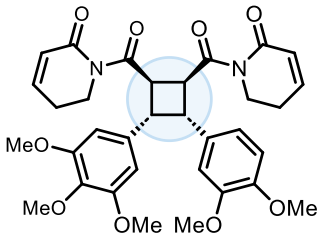
149 **150**

Scheme 39 Interconversion of the two puckered conformations of cyclobutane.

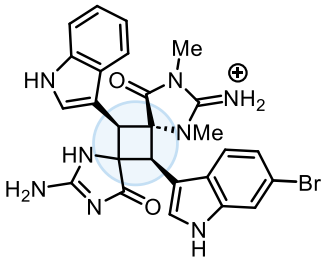
In recent years, the saturated cyclobutane scaffold has been increasingly utilised to replace the planar aromatic rings in pharmaceutical compounds due to its unique conformational constraints, which can better complement the spatial arrangements within target proteins, and because it can block metabolically labile sites.[83] The increased degree of saturation also leads to higher water solubility and lower melting points, which are important considerations in drug development.[86] Moreover, the cyclobutyl ring can serve as the key pharmacophore in lead compounds,[87-92] occupying a hydrophobic pocket within the target enzyme,[87, 92-98] avoid cis/trans-isomerisation,[99-101] strengthen the metabolic stability,[102-104] conformationally restrict the molecule[105-107] or replace the aryl group to reduce the fractional degree of planarity of compounds.[108, 109] It is therefore apparent that cyclobutanes can confer valuable physical and pharmacological properties to biologically-active compounds, and thus the synthesis of cyclobutane building blocks has drawn a large amount of attention in recent years, yet remains a formidable challenge to date.



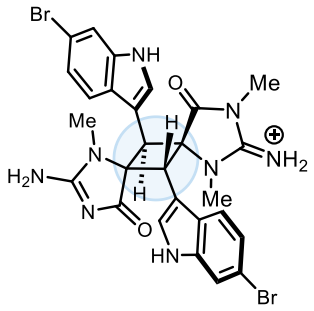
piperarborenine B
151



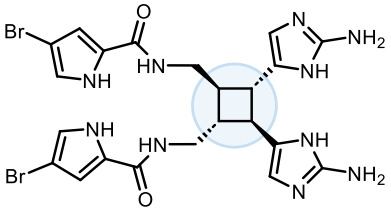
piperarborenine D
152



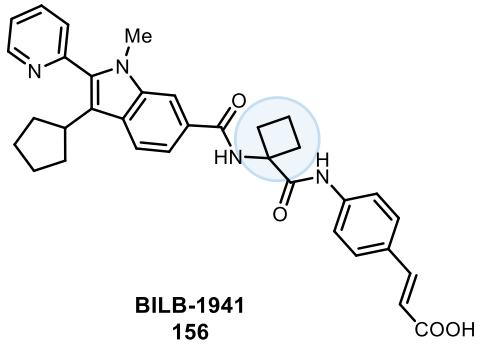
dictazole A
153



dictazole B
154



(±)-Sceptrin
155



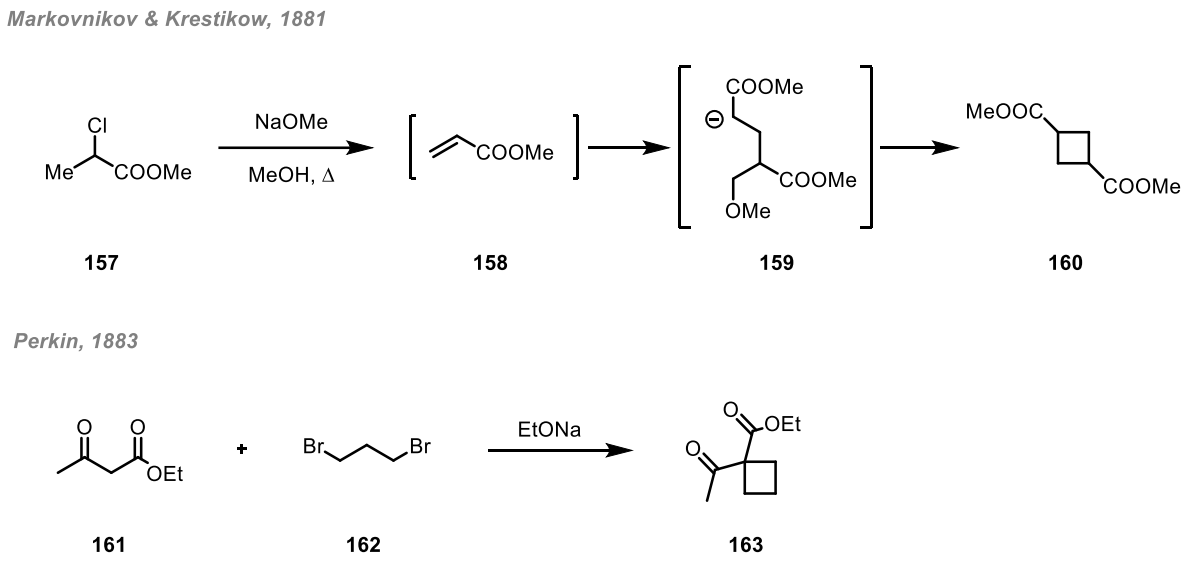
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156

Scheme 40 Biologically-active molecules containing cyclobutanes.

Cyclobutanes are core units prevalent in many natural products, as well as important motifs embedded in a variety of biologically-active molecules. **Scheme 40** shows a selection of natural products containing the cyclobutyl scaffold that have been reported in the literature.[110-114] The stereocontrolled synthesis of such complex cyclobutanes is an unavoidable problem that is still being addressed. Concurrently, the control of regioselectivity during the construction of cyclobutane building blocks is also a longstanding problem in synthetic organic chemistry.

2.3 Traditional Methods for Cyclobutane Construction

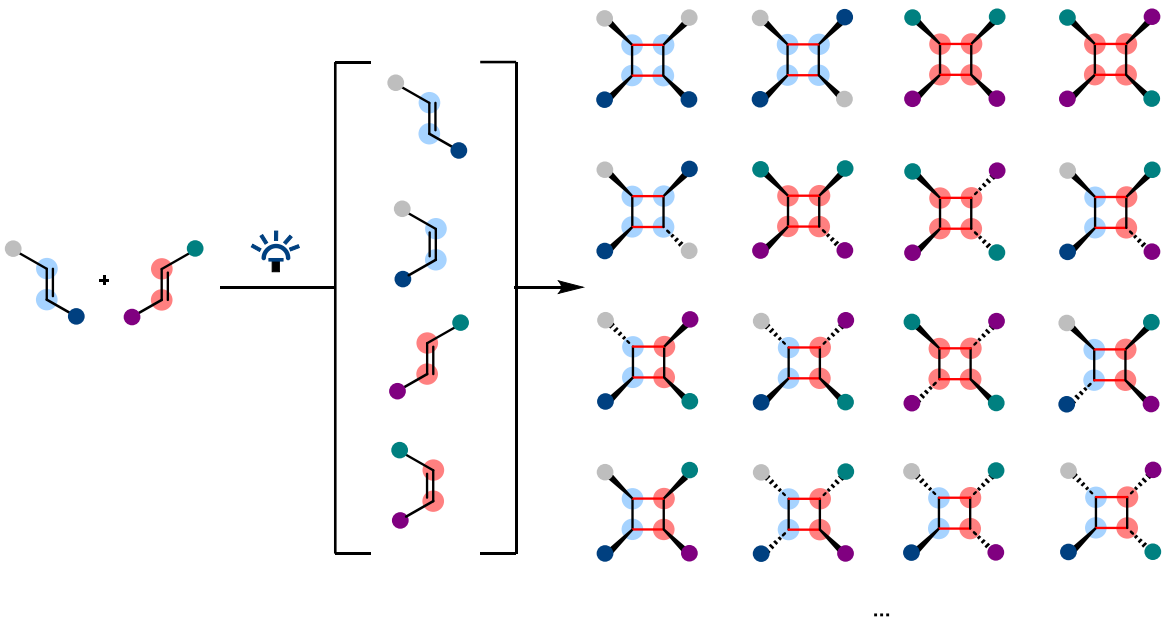
The earliest reported synthesis of symmetric cyclobutanes was represented by the homocondensation of ethyl 3-chloropropionate by Markovnikov and Krestikow in 1881 (**Scheme 41, top**),[115] and the condensation of diethyl malonate with the 1,3-dibromopropane by Perkin in 1883 (**Scheme 41, bottom**).[116]



Scheme 41 Initial synthesis of symmetric cyclobutanes.

To date, the fundamental strategies for the construction of four-membered rings mainly involve [2+2] photocycloadditions, intramolecular cyclizations of acyclic precursors and derivatization of cyclobutene/ cyclobutanone/ bicyclo[1.1.0]butane.[117, 118] Among all of them, cyclobutanones particularly stand out, because they offer a convenient four-carbon ring motif that allows for further structural elaboration, and each position on the ring has the potential for functionalisation. Arguably the most commonly considered approach to cyclobutane skeletons is through an intermolecular [2+2] photocycloaddition of two olefins

(**Scheme 42**).[85, 119-124] However, this method is generally associated with significant chemo-, regio-, and stereoselectivity issues, since the two monomers can undergo heterodimerization and homodimerization. Although the selectivity could be influenced by the steric and electronic effects of the olefins, it could also form a potentially complex mixtures of corresponding dimeric products with different configurational isomers due to the facile E/Z isomerism of the starting materials under the photochemical conditions. As the above-mentioned functionalisation of cyclobutene/ cyclobutanone/ bicyclo[1.1.0]butane, and the [2+2] photocycloaddition are not relevant to the main strategies developed within this thesis, these topics will not be reviewed further.

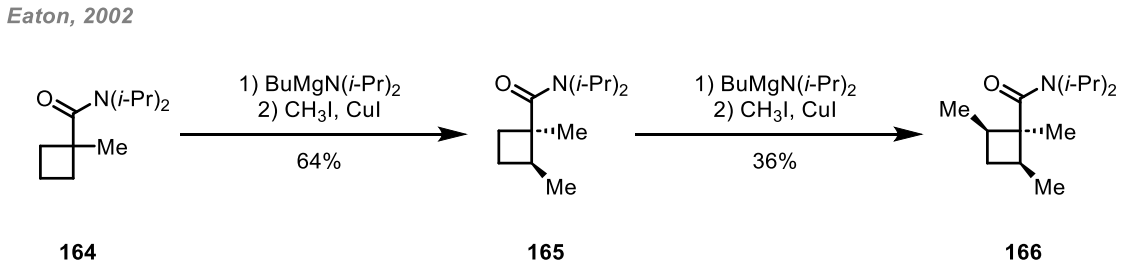


Scheme 42 Potential products of a [2+2] photocycloaddition reaction from two different olefins.

2.4 C–H Functionalisation Approach to Cyclobutanes

As introduced in chapter 1, the utilisation of direct C(sp^3)–H activation logic presents a viable alternative to photocycloadditions that could facilitate more accurate control over the products obtained, offering the potential to bypass the significant aformentioned limitations associated with direct [2+2] cycloaddition strategies, and facilitating the efficient synthesis of a broad array of functionalised cyclic scaffolds.

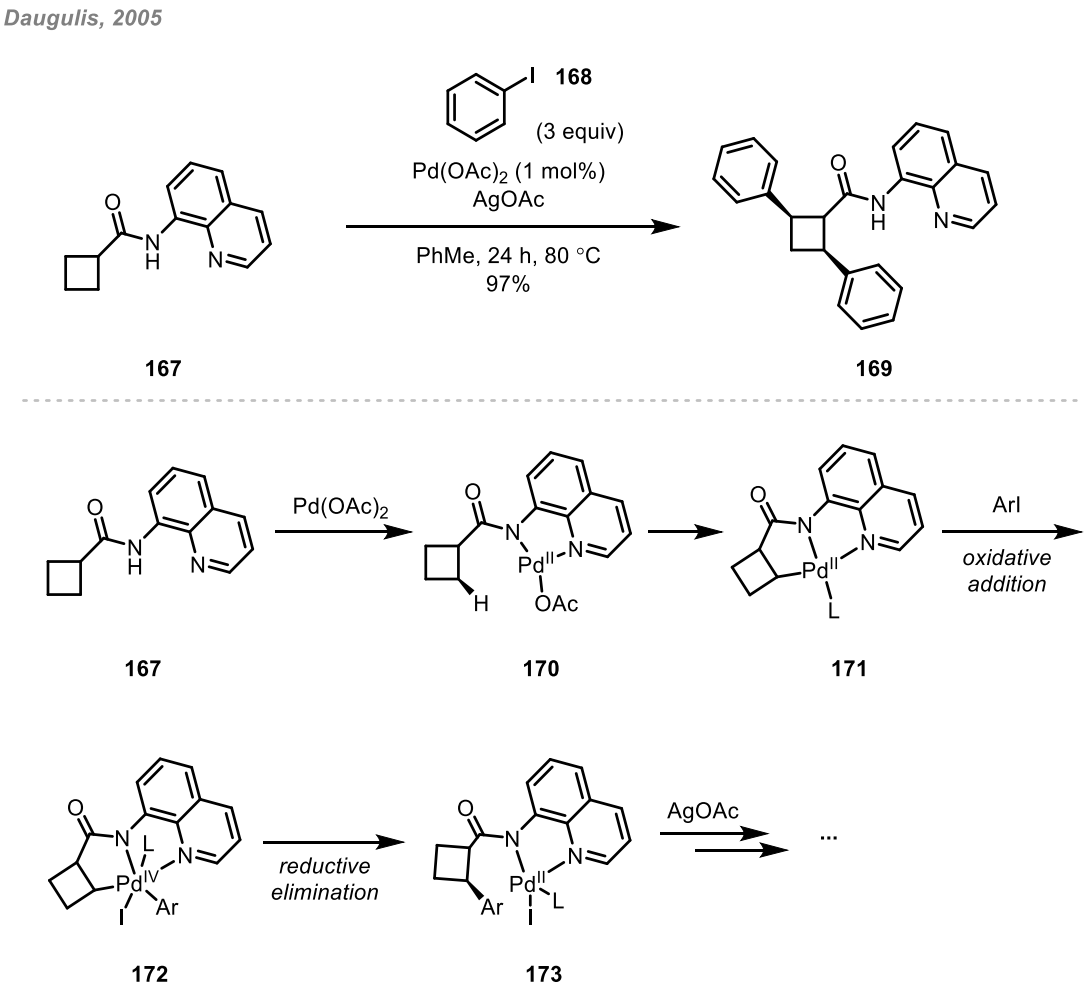
In spite of the fact that the C–H functionalisation of cyclopropanes has received extensive attention in the literature,[125-128] analogous examples of direct cyclobutene C−H functionalisation are extremely limited. One of the early examples of C(sp^3)−H functionalisation in cyclobutanes was reported by Eaton and coworkers in 2002 (**Scheme 43)**. A harsh magnesiation procedure is essential for the transformation, the products were obtained in moderate yield, and no enantioselective reaction was disclosed.[129, 130]



Scheme 43 Direct C–H methylation of cyclobutane.

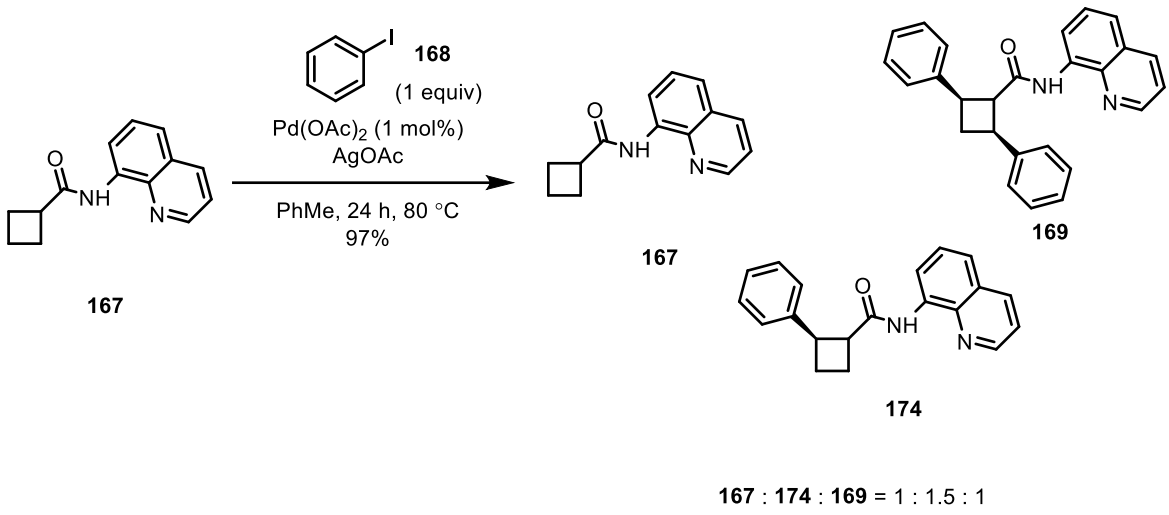
In 2005, Daugulis and coworkers disclosed a seminal work, in which an aminoquinoline-amide was assembled on the saturated cyclobutane **167**, which acted as DG to assist the C(sp^3)−H arylation of four membered rings in the presence of iodobenzene **168** (3 equiv.) catalysed by 1 mol% $Pd(OAc)_2$ (Scheme **44**, top). A single bis-arylated cyclobutane diastereomer **169** was obtained in an excellent 97% yield. This was the first time such a

transformation was performed on a cyclobutane ring under palladium (II/IV) catalysis.[131] The proposed reaction mechanism involves the complexation of the DG and palladium catalyst, and subsequent insertion into the adjacent cyclobutane C−H bond to form a five membered palladacycle **171** which is favoured under kinetic control.[132] A palladium(IV) intermediate **172** is then generated after oxidative addition with an aryl iodide, which is then followed by reductive elimination to release the arylated cyclobutane **169** and subsequent palladium dissociation from intermediate **173**. The stoichiometric silver salt is used to turn over the generated palladium(II) iodide to palladium(II) acetate (**Scheme 44, bottom**).



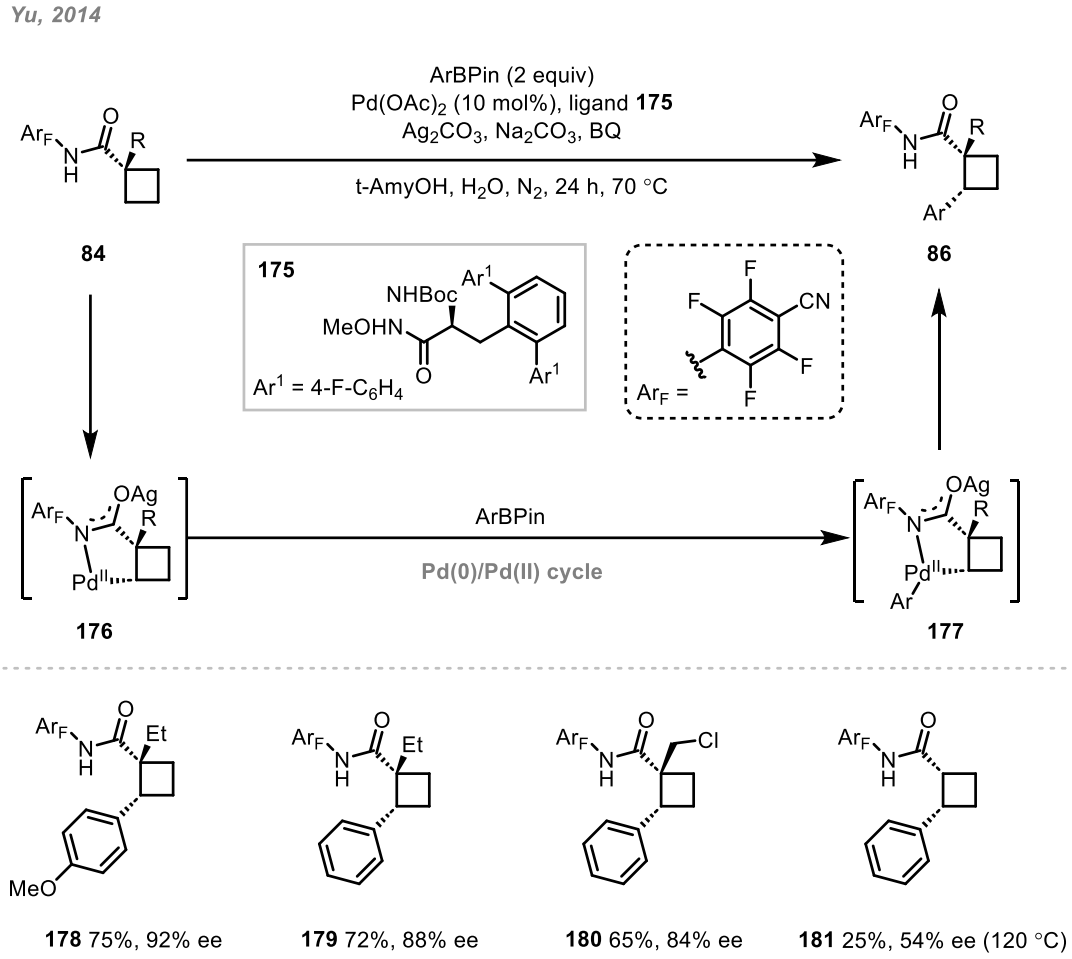
Scheme 44 Direct C–H arylation of cyclobutane and proposed Pd(II/IV) mechanism.

The authors also tested the feasibility of generating the mono-arylation product by using only one equivalent of iodobenzene (**Scheme 45**), but they obtained a mixture of starting material **167**, mono-arylated cyclobutane **174** and bis-arylated cyclobutane **169** in the ratio of 1:1.5:1. This indicated that the rate of the second arylation step is almost the same as the first arylation step.



Scheme 45 Arylation of cyclobutane **167** with one equivalent of iodobenzene.

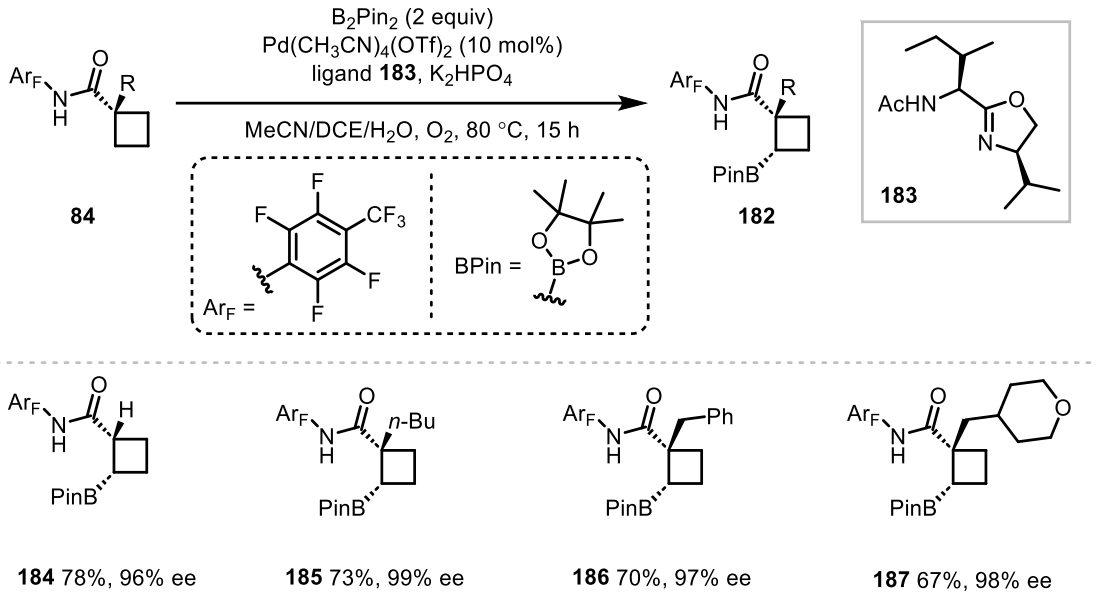
Until 2014, only synthesis of racemic substituted cyclobutanes had been reported in the literature, but then Yu and coworkers reported the first Pd-catalysed enantioselective C(sp^3)−H arylaton of cyclobutyl carboxylic acid derivatives **84** using polyfluorophenyl amides as a weakly coordinating monodentate directing group (**Scheme 46**).[59] A unique chiral bidentate monoprotected amino acid (MPAA) ligand **175** was developed to achieve the requisite enantiocontrol. In this reaction, substrates bearing a fully-substituted α-position obtained good results (up to 77% yield with up to 95% ee), while the cyclobutanes with α-tertiary stereocenters only gave low yield and enantioselectivity (**181**).



Scheme 46 Enantioselective C(sp^3)–H arylation of cyclobutyl carboxylic acid derivatives.

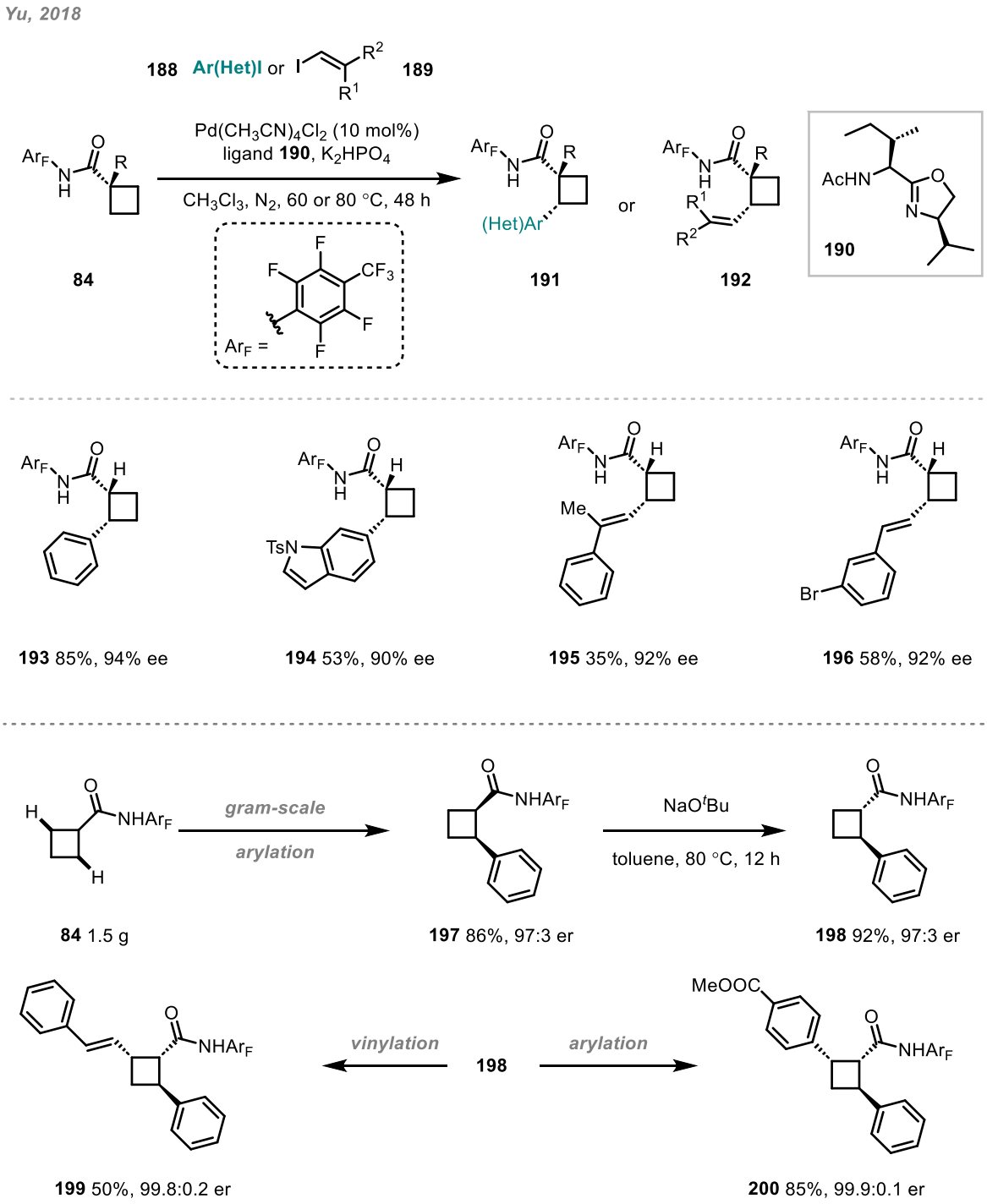
Based on those studies, Yu subsequently (in 2017) achieved the enantioselective C(sp^3)–H borylation reaction of the similar cyclobutanecarboxylic acid derivatives **84** with a newly designed chiral acetyl-protected aminomethyl oxazoline ligand **183** (**Scheme 47**).[133] Catalysed by 10 mol% of $Pd(CH_3CN)_4(OTf)_2$, the borylated products **182** were obtained in moderate to good yield and good to excellent ee (up to 78% yield and up to > 99% ee). Unlike the previous report, this reaction proved to be less sensitive the extent of substitution at the α-position, and O_2 was used as the only oxidant for the Pd(II)/Pd(0) catalytic cycle.

Yu, 2017



Scheme 47 Enantioselective C(sp^3)–H borylation of cyclobutyl carboxylic acid derivatives.

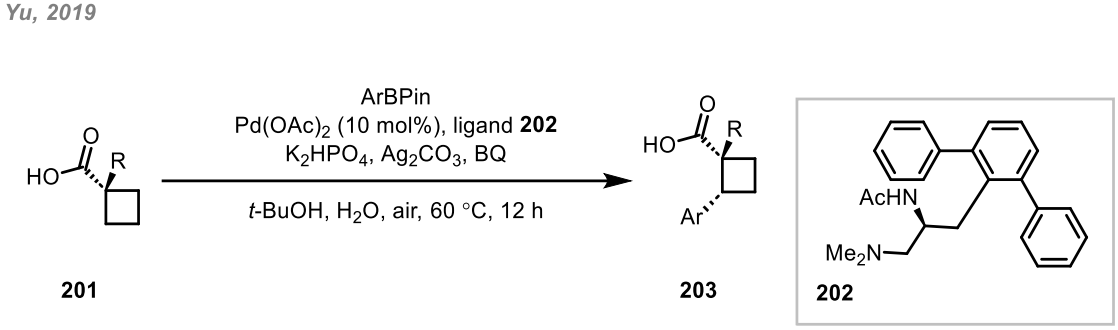
Subsequently, the Yu lab further demonstrated an efficient $Pd(CH_3CN)_4Cl_2$ catalysed enantioselective C(sp^3)–H arylation and vinylation of the same substrates **84** with tertiary stereocentres (**Scheme 48, top**).[134] Notably, this transformation was also performed to construct three contiguous chiral centres on the sterically-congested cyclobutane rings (**Scheme 48, bottom**), which further highlighted that this reaction provided a versatile strategy for the synthesis of chiral cyclobutanes. The reaction could be performed on 1.5 gram-scale, affording the corresponding arylated product in 86% isolated yield with 97:3 er - subsequent treatment with 2 equivalents of sodium *tert*-butoxide was demonstrated to provide access to the corresponding *trans*-epimer **198**, which was obtained in 92% yield and 97:3 er. It's worth mentioning that the compound **198** can process both arylation and vinylation reactions smoothly with excellent enantioselectivity up to 99.9:0.1 er. These chiral cyclobutanes possessing three contiguous stereogenic centres were difficult to access based on previously reported approaches.



Scheme 48 Enantioselective C(sp^3)–H arylation and vinylation of cyclobutyl carboxylic acid derivatives.

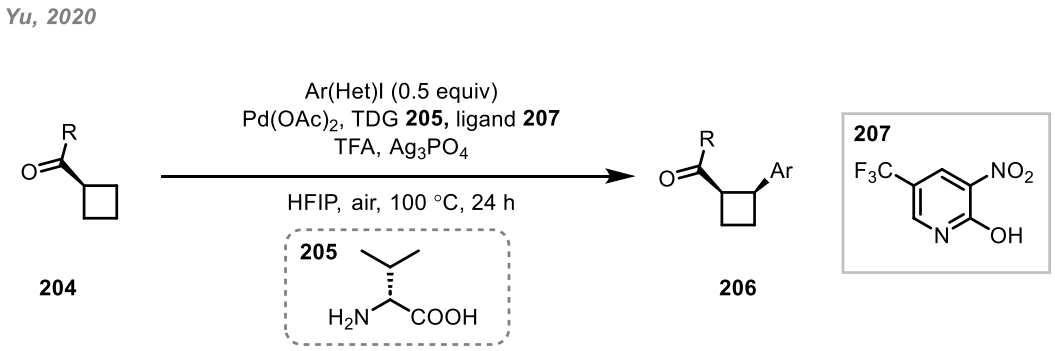
In 2019, Yu demonstrated that the amide directing group could be replaced with a free carboxylic acid to achieve the enantioselective C(sp^3)–H arylation on cyclobutane rings **201** (**Scheme 49**).[135] The mono-protected amino acid or mono-protected aminoethyl amine was

applied to the reaction as the chiral ligand, which obtained moderate to good enantiomeric ratio up to 95:5.



Scheme 49 Enantioselective C(sp^3)−H arylation of free cyclobutyl carboxylic acid.

In 2020, the Yu lab developed the first example of a Pd(II)-catalysed enantioselective C(sp^3)−H arylation of ketones using D-valine as a chiral transient directing group (**Scheme 50**).[136] The electron-deficient 2-pyridone **207** was utilised as the chiral ligand, which was key to efficiently introduce chirality to the cyclobutyl ketone with different silver salts.

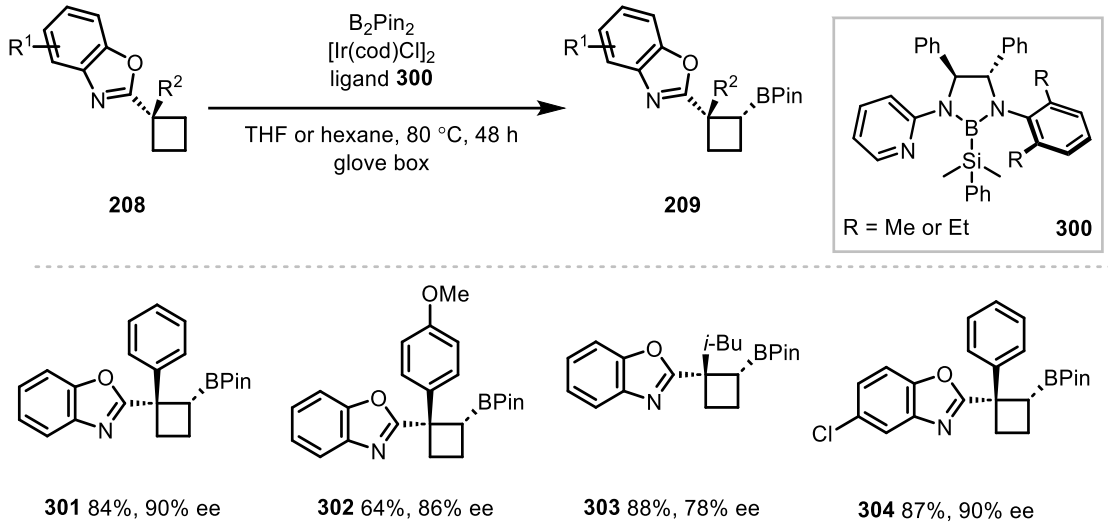


Scheme 50 Enantioselective C(sp^3)−H arylation and vinylation of cyclobutyl ketones.

Around the same time, Xu and coworkers reported the first example of a benzoxazoline-directed iridium-catalysed enantioselective C(sp^3)–H borylation of cyclobutanes **208** using an unique chiral bidentate boryl ligand **300** (**Scheme 51**).[137] In this reaction, the α-substituents on the cyclobutanes were not limited to alkyl groups like the work by Yu,[133]

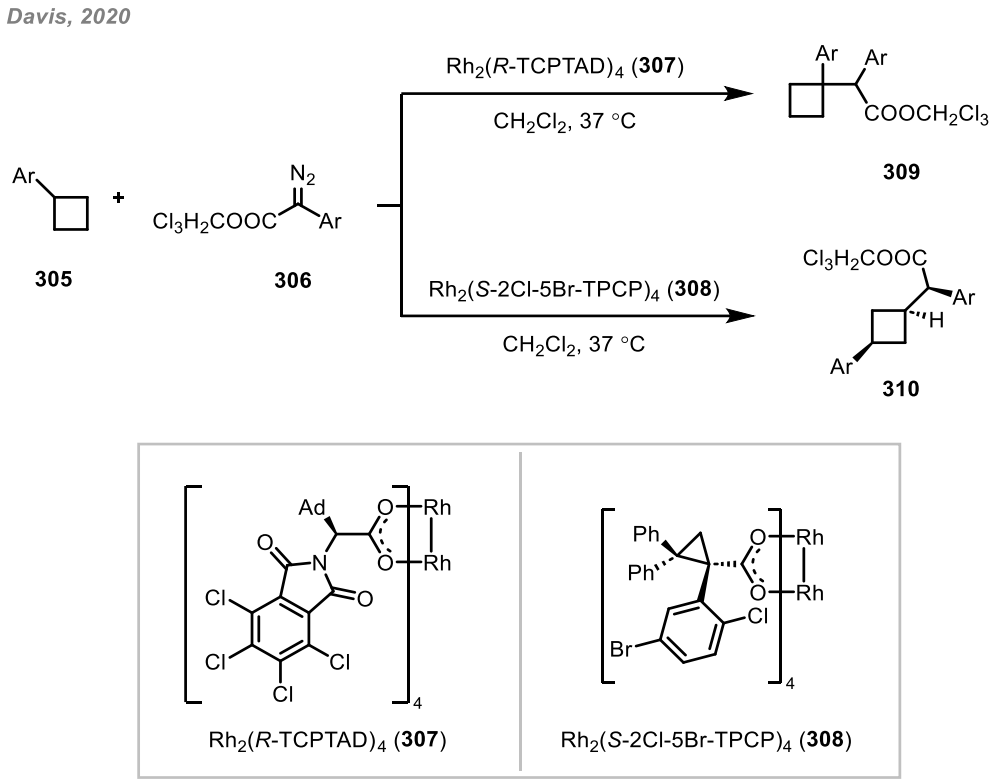
since aromatic groups were also tolerated. In contrast to the previously-reported work, it was unnecessary to add base and oxidant in this transformation.

Xu, 2020



Scheme 51 Ir-catalysed enantioselective C(sp^3)–H borylation of cyclobutanes.

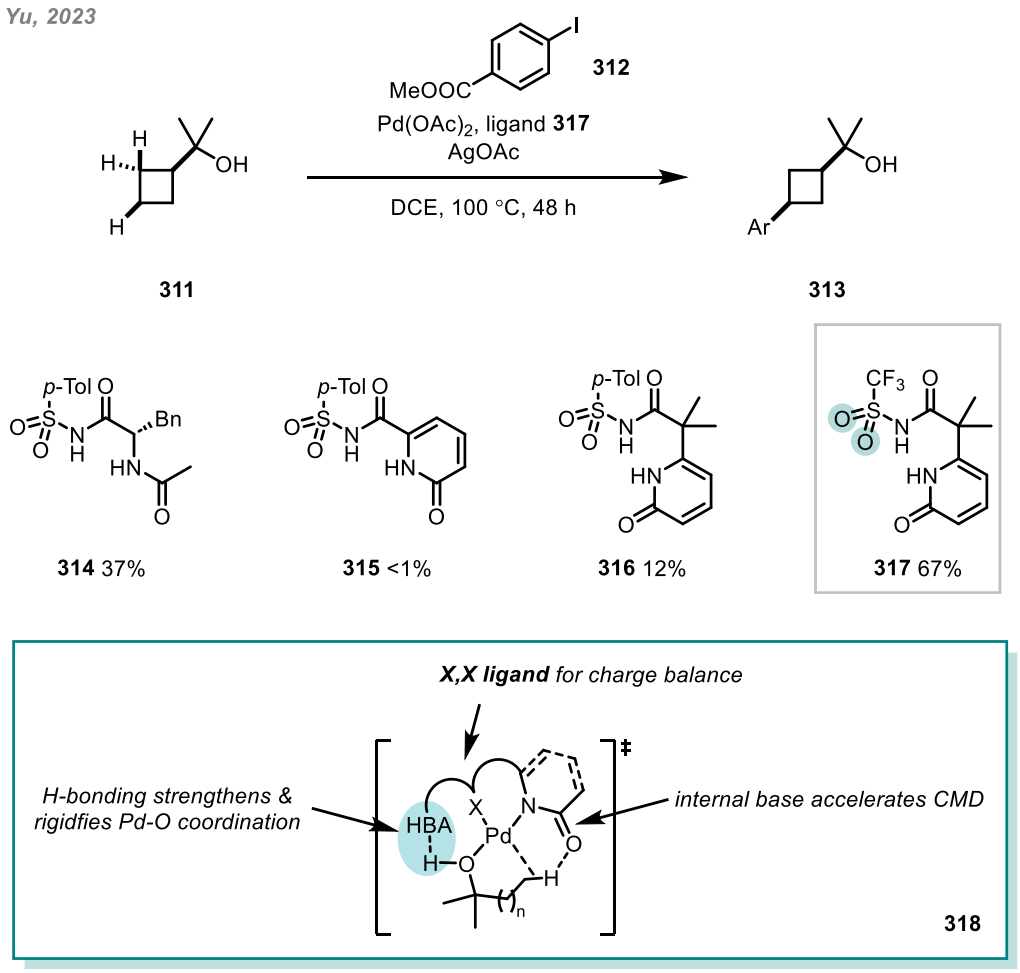
A study reported by the Davis group demonstrated an exquisite regio- and stereoselective dirhodium(II)-catalysed C–H desymmetrisation of arylated cyclobutanes using aryldiazoacetates, which afforded 1,1- or 1,3-disubstituted cyclobutanes (**309** or **310**) (**Scheme 52**).[138] Good levels of enantio- and diastereoselectivity were achievable; however, the analogous asymmetric transformation, which would generate 1,2-substituted cyclobutanes, could not be obtained using this unique catalytic system.



Scheme 52 Dirhodium(II)-catalysed C(sp^3)–H functionalisation of cyclobutanes.

Alcohols are one of the most common functional groups in nature,[139] however, until recently, there remained no practical solution for using a hydroxyl group as the directing group to assist the C−H activation on cyclobutanes, primarily because of its low affinity for the transition-metal catalysts.[140, 141] To overcome this longstanding challenge, Yu and coworkers developed an "L-type" hydroxyl group directed C(sp^3)−H arylation of cyclobutane **311** selectively at the C3 position (**Scheme 53**).[142] In previous work, most monoanionic L,X chelates such MPAA ligands and their analogues mentioned above, were designed for anionic DGs.[143, 144] In contrast, when employing L,X ligands with neutral DGs, the resulting agostic complex is likely to be destabilized due to the absence of charge balance at the metal center. Despite the fact that the neutral alcohol-DG could be more affined to the metal centre by deprotonation and provided charge balance with L,X ligand, Pd-alkoxides were found to lead to multiple undesired side reactions such as μ-alkoxo-bridged dimer formation,[145]

oxidation,[146] and fragmentation.[147, 148] Here, a type of bisanionic X,X ligand pyridone-triflamide ligand **317** was found to promote the efficient coordination of the substrate hydroxyl group with the palladium(II) catalyst. The oxygens from the sulfonamide moiety on the ligand served as the hydrogen bond acceptor with the Pd-bound hydroxyl group, which helped strengthen and rigidify the coordination of the pyridone directing group to the metal.



Scheme 53 Free-alcohol-directed C(sp^3)–H arylation of cyclobutane enabled by secondary interactions.

As exemplified by the modern methods mentioned above, commonly-used weakly-coordinating directing group (such as carboxylic acids and amides), as well as imine-based transient directing groups, have been employed to achieve direct C(sp^3)–H functionalisation

reactions on cyclobutanes (although these transformations are limited to arylation, vinylation and borylation) catalysed by palladium/iridium/dirhodium catalysts. In contrast, strongly coordinating directing groups such as pyridine, pyrimidine, and 8-aminoquinoline, which have proved as useful DGs for C–H activation reactions (most of them were based on C(sp^2)−H bond activation), have never been applied to such enantioselective C(sp^3)−H activation of cyclobutanes (the potential challenges have been described in chapter 1). Additionally, the control of enantioselectivity during this transformation remains intractable, which is valuable to further explore.

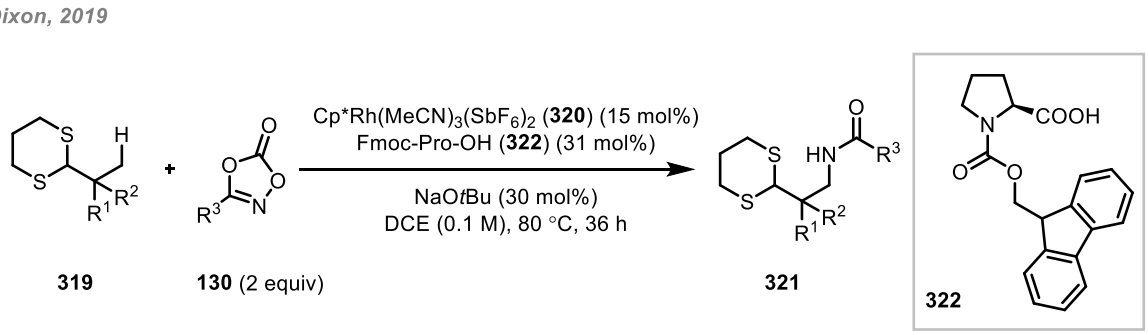
2.5 Project Aims

The aims of this project were to develop Cp*Rh(III)-catalysed enantioselective C(sp^3)−H functionalisation reactions, involving the discovery of new C(sp^3)−H activation reaction catalysed by the achiral Cp*Rh(III) complex, and to develop new chiral ligands to confer the desired enantioselectivity. Building upon our previous use of the Cp*Rh(III) catalytic system in the Dixon group for the amidation of C(sp^3)–H bonds with dioxazolones, and recognizing the absence of the approaches for the asymmetric C−H functionalisation of cyclobutanes,[149] we focused on developing new methodologies for the C(sp^3)–H amidation of cyclobutanes catalysed by Cp*Rh(III), utilising strongly coordinating directing groups which haven't been achieved so far.

2.6 Initial Preliminary Studies

2.6.1 Proposal for the development of enantioselective Cp*Rh-catalysed C(sp^3)–H amidation of cyclobutanes

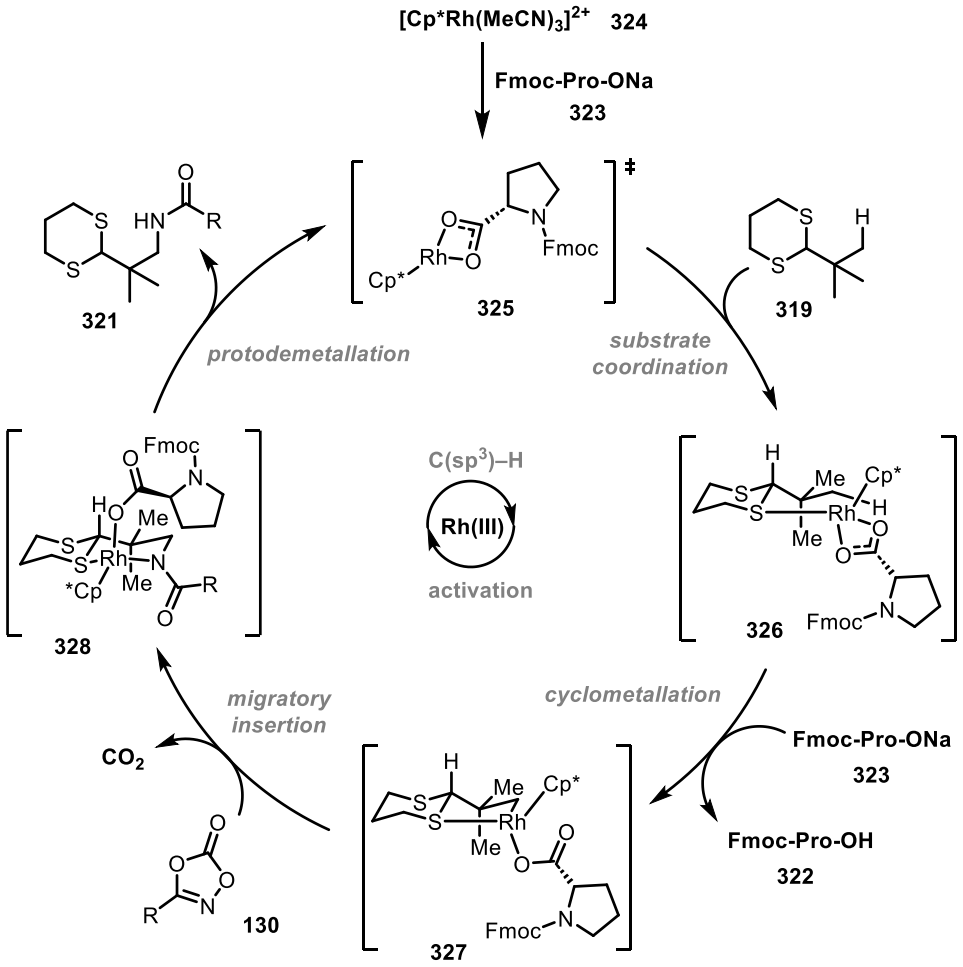
In 2019, the Dixon group reported a dithiane-directed Cp*Rh(III)-catalysed amidation of unactivated C(sp^3)−H bond (**Scheme 54**).[149] In this novel catalytic system, the Fmoc-protected sodium prolinate (Fmoc-Pro-ONa) (**323**) was found to be the optimal ligand which was generated in situ from carboxylic acid **322** and sodium *tert*-butoxide, and subsequently allowed the efficient coordination of readily available Cp*Rh(MeCN)$_3$(SbF$_6$)$_2$ (**320**) and dioxazolones **130** assisted by the dithiane directing group.



Scheme 54 Dithiane-directed Cp*Rh(III)-catalysed amidation of unactivated C(sp^3)–H bonds.

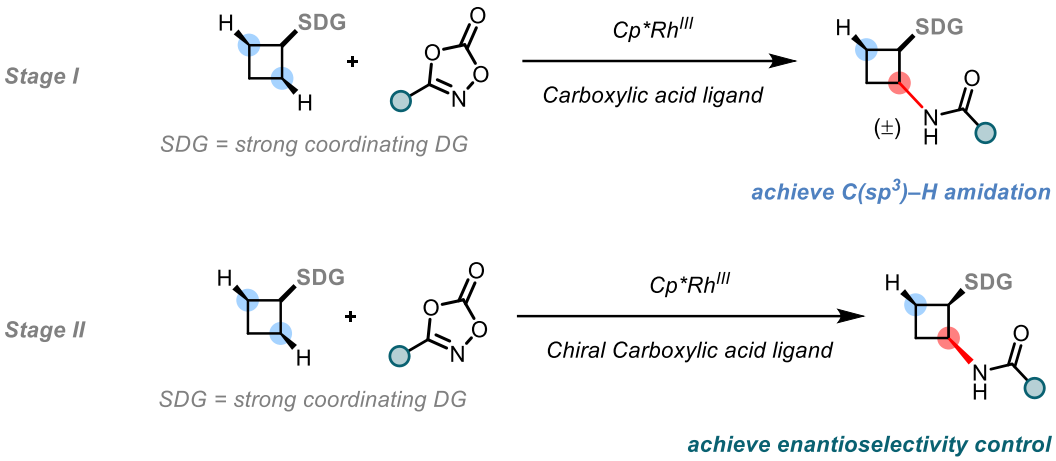
A plausible reaction mechanism suggested that the three acetonitrile ligands in Cp*Rh(III) catalyst dissociated first and were replaced with the Fmoc-Pro-ONa (**323**) additive to give the intermediate **325** (**Scheme 55**). Next, the sulfide groups on the dithiane occupied the empty site of the metal centre producing complex **326**, followed by the carboxylate mediated CMD process leading to the intermediate **327**. Following migratory insertion, coordination of the Rh−C bond into the N−O bond of the dioxazolone **130** generated spieces **328** and

released a molecule of CO_2. Finally, the amidated product **321** was formed *via* protodemetallation.



Scheme 55 Postulated reaction mechanism of dithiane-directed Cp*Rh(III)-catalysed amidation of unactivated C(sp^3)–H bonds.

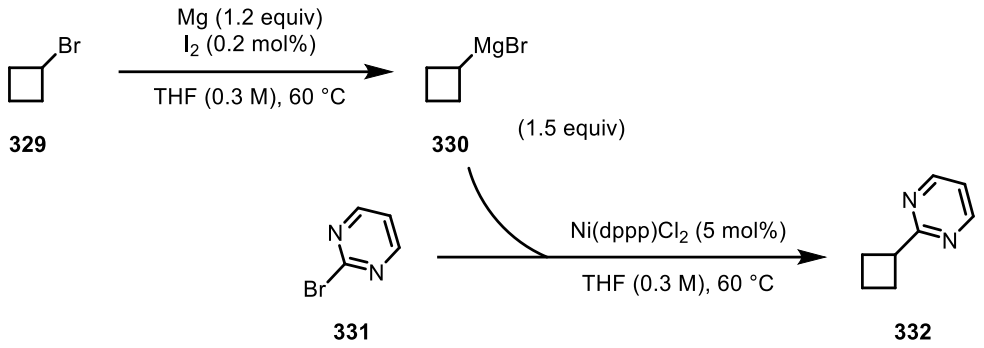
Based on this concept, in **stage I**, we proposed to utilise a strongly coordinating directing group to direct a diastereoselective Cp*Rh(III)-catalysed amidation of C(sp^3)−H bonds on cyclobutane rings in the presence of dioxazolone reagents (**Scheme 56**). Different carboxylic acids would first be introduced as the ligand to promote the C−H bond amidation transformation based on our previous work. In **stage II**, extensive enantiocontrol will be identified by exploring chiral carboxylic acids to establish the ideal chiral environment.



Scheme 56 Proposal for the development of enantioselective Cp*Rh-catalysed C(sp^3)–H amidation of cyclobutanes.

2.6.2 Synthesis of model substrate 2-cyclobutylpyrimidine

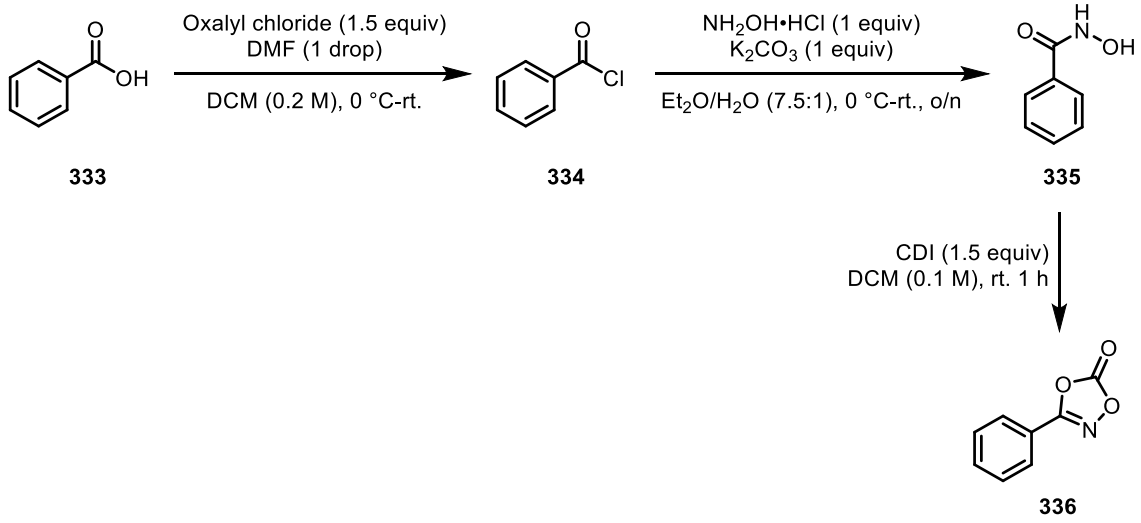
Considering the challenge of introducing heteroaromatic group such as pyrimidines directly *via* C−H activation strategies, or the difficulty of modifying pyrimidines with decent regioselectivity,[150] in combination with the exceedingly high value of those heteroaromatic group in many drug molecules,[151] the simple 2-cyclobutylpyrimidine **332** was initially chosen as the model C−H amidation substrate, which was synthesised from commercially available cyclobutyl bromide **329**. The cyclobutylmagnesium bromide Grignard solution **330** was prepared first. Subsequently, the 2-cyclobutylpyrimidine **332** was readily afforded through a Kumada cross coupling reaction with the 2-bromopyrimidine **331** catalysed by the bench-stable Ni(dppp)Cl_2 catalyst (**Scheme 57**).[152]



Scheme 57 Synthesis of model substrate 2-cyclobutylpyrimidine.

2.6.3 Preparation of starting material 3-phenyl-1,4,2-dioxazol-5-one

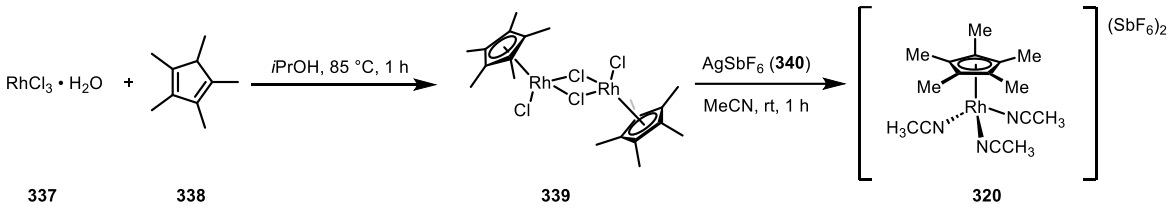
The amide source 3-phenyl-1,4,2-dioxazol-5-one **336** was prepared starting from simple benzoic acid **333**. The benzoic acid chloride **334** was generated to further synthesize hydroxamic acid **335** by a reaction with hydroxylamine hydrochloride salt.[153, 154] Finally, the starting material dioxazolones **336** was obtained by treating with carbonyldiimidazole (CDI) (**Scheme 58**).[155]



Scheme 58 Preparation of starting material dioxazolones.

2.6.4 Preparation of Cp*Rh(III) complex

Based on the previous study in our lab, the bench-stable achiral $[Cp^*Rh(MeCN)_3](SbF_6)_2$ complex (**320**) was first chosen as the metal catalyst in this project. It was the cationic form derived from its neutral form $[Cp^*RhCl_2]_2$ (**339**) which was prepared by the complexation of pentamethylcyclopentadiene (Cp*) (**338**) and $RhCl_3 \cdot H_2O$ (**337**).[156] Finally, the complex (**339**) was treated with $AgSbF_6$ salt (**340**) in acetonitrile to facilitate the ligand exchange on the rhodium metal centre and attain the $[Cp^*Rh(MeCN)_3](SbF_6)_2$ catalyst (**320**) (**Scheme 59**).



Scheme 59 Preparation of Cp*Rh(III) complex.

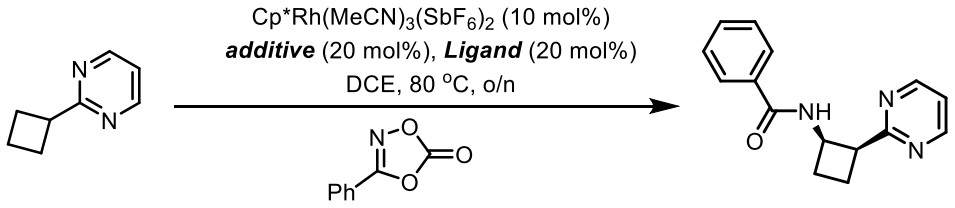
2.6.5 Preliminary experiments of Cp*Rh(III)-catalysed C(sp^3)–H activation reaction

Motivated by previous work on Cp*Rh(III)-catalysed C(sp^3)–H amidation reaction in the Dixon group,[149] our initial study focused on achieving the C−H amidation of cyclobutanes directed by strongly coordinating directing group (**Table 1**). A readily available 2-cyclobutylpyrimidine (**332**) was selected as a model substrate, since the strongly coordinating pyrimidyl group has been shown to be a powerful directing group in various C–H activation systems.[157] With 2 equivalents of dioxazolone **336** as the nitrene precursor

and amide source, a catalytic amount of achiral [Cp*Rh(MeCN)$_3$](SbF$_6$)$_2$ (10 mol%) and Fmoc-protected prolinate (Fmoc-Pro-OH (**322**) and NaO^{t}Bu as additive) serving as the ligand, were first tested in 0.1 M of 1,2-dichloroethane (DCE) at 80 °C (**Table 1, entry 3**). It was pleasing to find that this very initial system easily gave the target amidated cyclobutane product **341** in 48% NMR yield, and pleasingly, in small but significant enantiomeric ratio (55:45 er) (**Table 1, entry 3**). Next, the same conditions but without additives or with silver acetate (AgOAc) as additive were also tested (**Table 1, entry 1 & 2**). However, both of them provided racemic mixtures, while the former one showed only trace yield and the latter one gave 46% NMR yield. It indicated that NaO^{t}Bu was the favoured additive in such catalytic systems. Subsequently, a series of commercial ligands were screened in the presence of NaO^{t}Bu additive under the standard condition (**Table 1, entry 4-11**). Using the bulkier *N*-(*tert*-Butoxycarbonyl)-L-proline (Boc-Pro-OH) (**342**) and *N*-alpha-Fmoc-*N*-epsilon-Boc-L-lysine (Fmoc-Lys(Boc)-OH) (**347**) as ligands, it obtained 63% NMR yield, but neither of them provided ideal enantioselectivity (**Table 1, entry 4 & 9**). Very pleasingly, only mono-amidated product was generated, with no bis-amidated product being observed after all the substrate **332** was consumed the reaction.

The initial study demonstrated that in such Cp*Rh(III)-catalysed systems, the C−H amidation transformation was promising to simply achieve by the use of carboxylate ligands under the initially standard condition, however, it was still necessary to find a superior carboxylic acid ligand to reach high stereoinduction, which is generally accomplished by the formation of a well-defined chiral environment coordinating with Cp^{x}M(III) during the stereo-determining step.

Table 1 Initial investigation of reaction conditions.[a]



332 **336** (2 equiv) **341**

Entry	Ligand	Additives	Yield (%)	er
1	Fmoc-Pro-OH **322**	-	trace	-
2	Fmoc-Pro-OH **322**	AgOAc	46	-
3	Fmoc-Pro-OH **322**	NaO*t*Bu	48	55:45
4	Boc-Pro-OH **342**	NaO*t*Bu	63	52.5:47.5
5	Fmoc-Thr(trt)-OH **343**	NaO*t*Bu	32	54:46
6	Boc-Thr-OH **344**	NaO*t*Bu	48	53.5:46.5
7	Fmoc-His(trt)-OH **345**	NaOtBu	0	-
8	Fmoc-Asn(trt)-OH **346**	NaOtBu	12	54:46
9	Fmoc-Lys(Boc)-OH **347**	NaO*t*Bu	63	51:49
10	Fmoc-Ile-OH **348**	NaO*t*Bu	29	53.5:46.5
11	Fmoc-Trp(Boc)-OH **349**	NaO*t*Bu	39	-

[a] Reaction condition: **332** (0.05 mmol), **336** (0.1 mmol, 2 equiv), $[Cp^*Rh(MeCN)_3][(SbF_6)_2]$ (10 mol%), Ligand (20 mol%), additives (20 mol%), DCE (0.1 M, 0.5 mL), 80 °C, overnight, under argon, all with variations as noted above; All ^1H NMR yield; The er values were determined by chiral HPLC on a chiral stationary phase.

2.7 Investigation

2.7.1 Initial investigation of chiral carboxylic acid ligands in enantioselective C(sp^3)–H functionalisation of cyclobutanes

Despite of the fact that the enantioselectivity control during the initial study above was not ideal, it displayed the promising viability of the ***stage 1*** – C(sp^3)–H functionalisation of cyclobutanes, and it also implied that the carboxylic ligand could bring decent influences on the enantioselectivity control. Hence, we next aimed to the ***stage 2*** – enantioselectivity control. In this section some chiral carboxylic acids were designed and tested to explore the backbone of various chiral ligands for performance. Additionally, an initial optimisation with the best ligand selected was performed to understand the viability of the enantioselectivity control in this project.

2.7.2 Synthesis of chiral dicarboxylic acid ligands

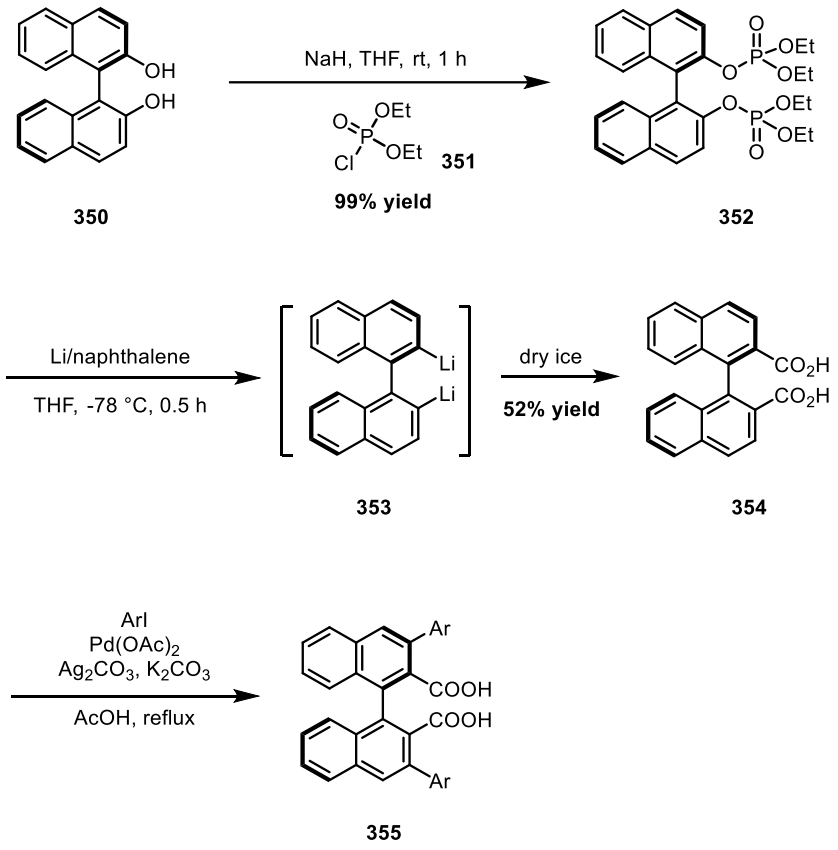
Chiral binaphthyl structure is one of the most privileged and widely studied chiral backbones in asymmetric catalysis, particularly using $Cp^xM(III)$ as catalyst (See chapter one for more details).[76] Since Akiyama and Terada group reported the asymmetric Mukaiyama-aldol reaction[158] and Mannich-type reaction[159] in 2004, respectively, the binaphthol-derived chiral phosphoric acids have been broadly investigated.[160] In 2007, Maruoka and coworkers developed a number of axially chiral dicarboxylic acids with the binaphthyl backbone, which fulfilled the research vacancies in this area.[161] The hydrogen bonding interaction

between the dicarboxylic acids were found to be key for increased acidity and for rigidifying the transition state structure of the ligand efficiently.

Therefore, we initially selected the unsubstituted (*R*)-1,1'-binaphthyl-2,2'-dicarboxylic acid (**354**) as the simplest ligand to investigate the enantioselectivity control, and subsequently a library of binaphthyl-based chiral carboxylic acids modified by multiple aromatic groups were further synthesised and screened under the initial standard condition. We anticipated that an optimal chiral environment could be attained through precise structure tuning.

The (*R*)-1,1'-binaphthyl-2,2'-dicarboxylic acid (**354**) was prepared starting from the phosphorylation of the readily available active (*R*)-BINOL (**350**), following with the reductive lithiation to generate the dilithio species (**353**) in the presence of lithium/naphthalene reagent. Finally, the carboxylic acid product (**355**) was obtained by addition of carbon dioxide (**Scheme 60**). It is worth noting that quickly bubbling the CO_2 gas here afforded the dicarboxylic acid in a very low yield (< 35% on average); however, replacing the CO_2 gas with the addition of solid CO_2 (dry ice) could improve the yield of this step up to 60%.

The modification on the C3 and C3' positions of the (*R*)-1,1'-binaphthyl-2,2'-dicarboxylic acid (**354**) was readily implemented *via* the carboxylate-directed C−H functionalisation strategy catalysed by $Pd(OAc)_2$ to provide variously sterically and electronically modified ligands.[162]



Scheme 60 Synthesis of chiral dicarboxylic acids.

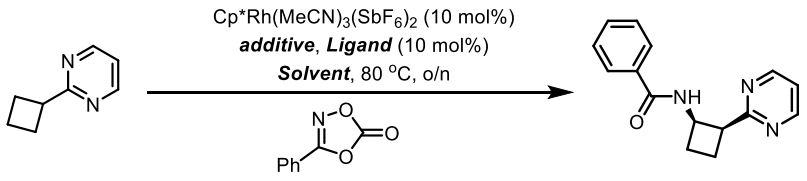
2.7.3 Preliminary screening of the chiral carboxylic acid ligands in enantioselective C(sp^3)–H functionalisation of cyclobutanes

The preliminary ligand investigation commenced with the unsubstituted axially chiral 2,2'-dicarboxylic acid (**354**) (10 mol%), with 10 mol% Cp*Rh(III) catalyst and 20 mol% of NaO^{t}Bu in 0.1 M of DCE at 80 °C overnight (**Table 2, entry 1**). The corresponding mono amidated product (**341**) was observed in 60% NMR yield, while disappointingly, it only resulted in poor enantioselectivity (56:44 er).

Because of the symmetrical characteristics of the cyclobutane substrate, we postulated that substituting the ligand (**354**) with CCAs containing different sterically hindered substituents could significantly impact the establishment of an appropriate chiral environment, thereby enhancing enantioselectivity. Successively, we performed experiments with CCA ligands bearing increased steric bulk at the C3 and C3' positions of the binaphthyl skeleton. Ligand (**356**) substituted by 4-tert-butylphenyl group on C3 and C3' positions were added to replace ligand **354** under the standard condition (**Table 2, entry 2**). Despite the sharp decrease in the yield (7%), the enantioselectivity was slightly increased to 63:37 er. At the same time, the CCA **357** possessing a 3,5-dimethyl aryl group provided both higher yield and enantioselectivity (32% yield, 65:35 er) (**Table 2, entry 3**). By replacing the two methyl groups with two *tert*-butyl groups, the enantiomeric ratio was further improved to 68:32 er, though the yield dropped to 15% yield (**Table 2, entry 4**). A brief test of the additives and concentration in the presence of ligand (**358**) was then further studied in the catalysis. It was found that with Ag_2CO_3 as additive in 0.1 M of DCE, the yield was enhanced slightly to 27%, albeit with a drop in enantioselectivity to 62:38 er (**Table 2, entry 5**). Concentrating the solution to 0.25 M afforded a better yield (35%), while improved the enantioselectivity to 68:32 er (**Table 2, entry 6**). Eventually, ligand (**359**) containing a *para* methoxy phenyl group was applied using Ag_2CO_3 as additive in 0.25 M of DCE, which gave similar yield (34%), and the best enantioselectivity 68:32 er at the time (**Table 2, entry 8**). In this context, we envisioned that the 2,6-dimethyl group on the aryl substituent could effectively rigidify the flexibility of the aryl-aryl bond axis possibly augmenting the enantiofacial selectivity. However, both enantioselectivity and yield (11% yield, 62:38 er) were depressed sharply (especially the yield), which was out of expectation (**Table 2, entry 9**). It indicated that further increasing the steric bulk of the 3,3'-bis(4-(*tert*-butyl)-2,6-dimethylphenyl group

would not give significant improvement to the results, but likely would lead to the decrease of reactivity.

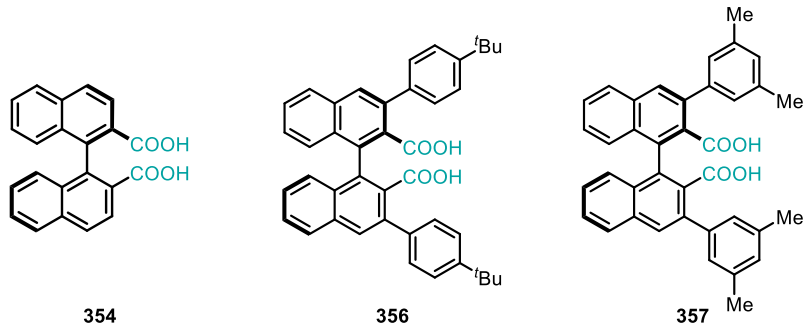
Table 2 Preliminary screening of the chiral carboxylic acid ligands.[a]



332 **336** (2 equiv) **341**

Entry	Ligand	Additives (mol%)	Solvent	Yield (%)	er
1	**354**	NaO*t*Bu (20)	DCE (0.1)	60	56:44
2	**356**	NaO*t*Bu (20)	DCE (0.1)	7	63:37
3	**357**	NaO*t*Bu (20)	DCE (0.1)	32	65:35
4	**358**	NaO*t*Bu (10)	DCE (0.1)	15	68:32
5	**358**	Ag_2CO_3 (10)	DCE (0.1)	27	62:38
6	**358**	Ag_2CO_3 (10)	DCE (0.25)	35	68:32
7	**358**	Ag_2CO_3 (10)	DCE (0.15)	36	62:38
8	**359**	Ag_2CO_3 (10)	DCE (0.25)	34	68:32
9	**360**	Ag_2CO_3 (10)	DCE (0.25)	11	62:38

Ligand



354 **356** **357**

358 **359** **360**

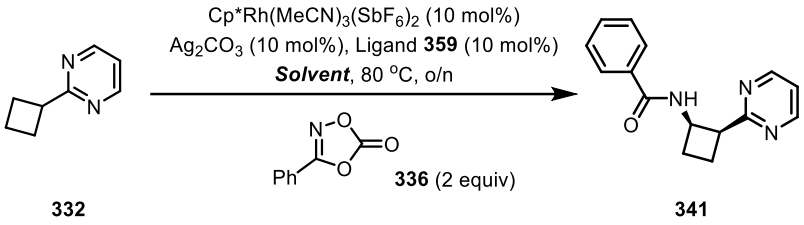
[a] Reaction condition: **332** (0.05 mmol), **336** (0.1 mmol, 2 equiv), [Cp*Rh(MeCN)$_3$][(SbF$_6$)$_2$] (10 mol%), Ligand (10 mol%), additives, 80 °C, overnight, under argon, all with variations as noted above; All ^{1}H NMR yield; The er values were determined by chiral HPLC on a chiral stationary phase.

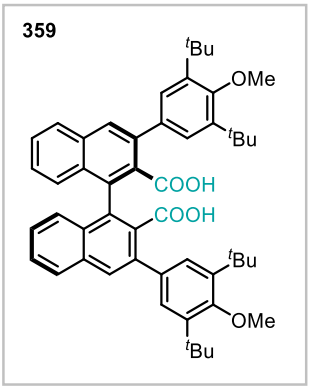
2.7.4 Preliminary optimisation of enantioselective C(sp^3)–H functionalisation of cyclobutanes assisted by CCA 359

Observing the ligand **359** boosted both reactivity and selectivity (**Table 3, entry 9**), it was then chosen to conduct a preliminary optimisation to examine whether the enantioselectivity could be further improved by simply changing the other conditions including solvent, concentration, and ratios of materials (**Table 3**). Firstly, a thorough solvent screen commenced in the presence of 10 mol% of ligand **L5** and 10 mol% of Ag_2CO_3 as additive, 10 mol% of Cp*Rh(MeCN)$_3$(SbF_6)$_2$ catalyst with 2 equivalent of dioxazolones at 80 °C reacting overnight under argon (**Table 3, entry 1-12**). Out of all the solvents, 1,4-dioxane and 1,2-dichlorobenzene (DCB) afforded the best yield both in 40% (**Table 3, entry 4 & 8**), while 1,4-dioxane proved to act the best in terms of a combination of both reactivity and enantioselectivity with 40% yield and 76:24 er (**Table 3, entry 4**). Diethyl ether (DE) furnishing the product in 78:22 er, which was the best enantioselectivity up to this point, however, with a significantly diminished of the yield in only 21% (**Table 3, entry 6**). Both dimethylformamide (DMF) and acetonitrile (MeCN) shut down the reaction (**Table 3, entry 9 & 11**). Moreover, cyclopentyl methyl ether (CPME) afforded product in 44% yield, however with only relatively common enantiomeric ratio (72:28) (**Table 3, entry 10**). Subsequently, using the optimal solvent 1,4-dioxane in our hand so far, double amounts of Cp*Rh(III) catalyst (20 mol%) were added to the reaction based on the original condition, which only lowered both yield and enantioselectivity (26% yield, 66:34 er) (**Table 3, entry 13**). However, further increasing the amounts of Ag_2CO_3 to fix the ratio of Cp*Rh(III) catalyst and Ag_2CO_3 at 1:1, it allowed a better transformation with the yield of 54%, and with 77:23 er (**Table 3, entry 14**). Continue increasing the amount of ligand **359** to 20 mol%, in the presence of 20 mol% of Cp*Rh(III) and 10 mol% of Ag_2CO_3, the product was

furnished in 81% yield with 76:24 er, which was the best result so far on average (**Table 3, entry 15**). Eventually, it was found that increasing the amount of dioxazolones from 2 equivalent to 3 equivalents reduced both reactivity and enantioselectivity (**Table 3, entry 16**).

Table 3 Preliminary optimisation using CCA ligands **359**.[a]





Entry	Solvent (0.25 M)	Yield (%)[c]	er [d]
1	PhCl	34	66:34
2	toluene	31	72:28
3	THF	32	75:25
4	1,4-dioxane	40	76:24
5	DCM	27	70:30
6	DE	21	78:22
7	EA	31	74:26
8	DCB	40	65:35
9	DMF	-	-
10	CPME	44	72:28
11	MeCN	trace	-
12	$CHCl_3$	28	70:30
13[b]	1,4-dioxane	26	66:34
14[c]	1,4-dioxane	54	77:23
15[d]	1,4-dioxane	81	76:24
16[e]	1,4-dioxane	34	65:35

[a] Reaction condition: **332** (0.05 mmol), **336** (0.1 mmol, 2 equiv), Cp*Rh(MeCN)$_3$(SbF$_6$)$_2$ (10 mol%), **359** (10 mol%), Ag_2CO_3 (10 mol%), 80 °C, overnight, under argon; All ^{1}H NMR yield; The er values were determined by chiral HPLC on a chiral stationary phase.

[b] With Cp*Rh(MeCN)$_3$(SbF$_6$)$_2$ (20 mol%).

[c] With Cp*Rh(MeCN)$_3$(SbF$_6$)$_2$ (20 mol%), Ag_2CO_3 (20 mol%).

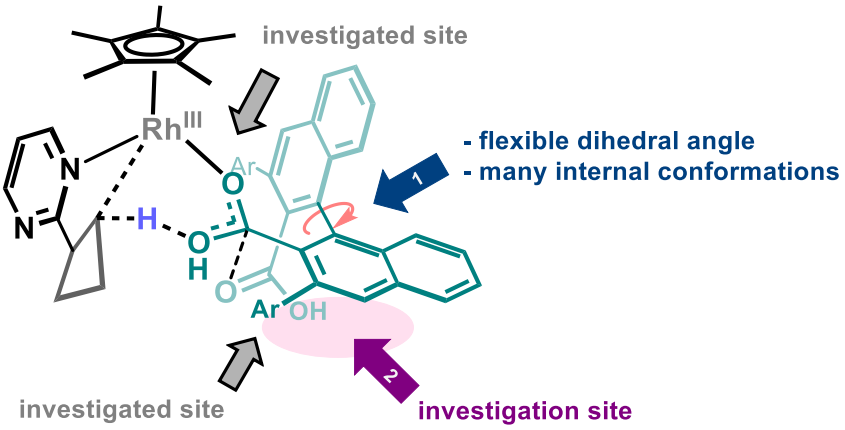
[d] With Cp*Rh(MeCN)$_3$(SbF$_6$)$_2$ (20 mol%), **359** (20 mol%,), Ag_2CO_3 (10 mol%).

[e] With **336** (3 equiv), Cp*Rh(MeCN)$_3$(SbF$_6$)$_2$ (20 mol%), Ag_2CO_3 (20 mol%).

All with variations as noted above.

2.7.5 Design and synthesis of binaphthyl-based CCA ligands

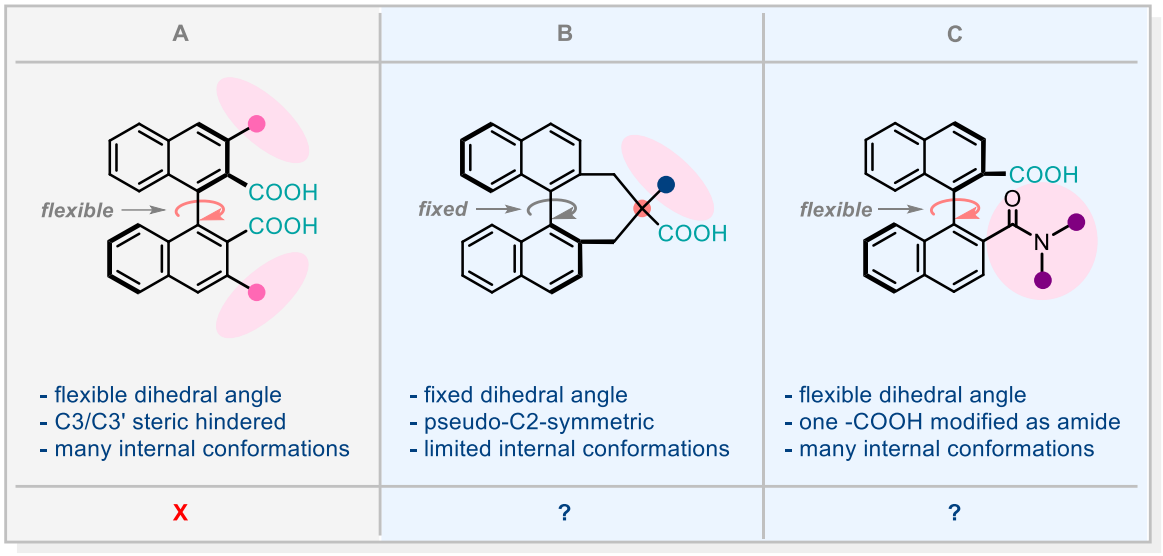
Despite the great potential of C1-symmetric binaphthyl-based axially chiral dicarboxylic acids with bulkier disubstituent in C3 and C3' position, the improvement it brought to the asymmetric catalysis was very limited. Therefore, we next focused on fixing the flexible dihedral angle of the binaphthyl skeleton. It could reduce the internal conformations between ligand, metal and substrate, which likely avoided a large number of unfavourable transition states for C−H activation (**Scheme 61, 1**); at the same time, we also tried to investigate the steric hinderance in the other positions, which could appropriately generate the "wall" to establish the favoured chiral environment (**Scheme 61, 2**).



Scheme 61 Proposed transition state structure.

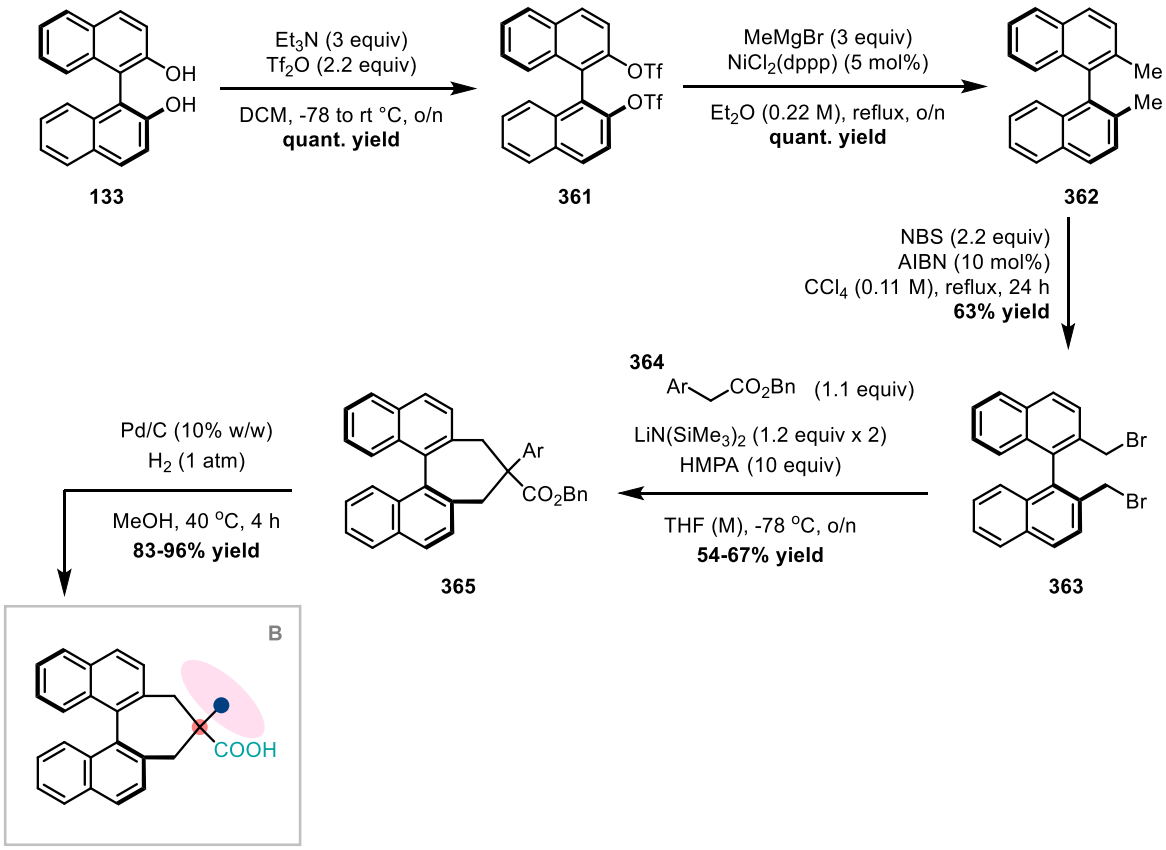
Given the impressive performance of the pseudo-C2-symmetric chiral carboxylic acids for the enantioselective C−H functionalisation demonstrated by Matsunaga group,[66] we decided to start from this type of "fixed" ligands (**Scheme 62, B)** mentioned in their work first (See chapter 1 for details about their work in this area). The C1−C1' bond on the highly tuneable C1-symmetric binaphthyl-based CCAs could flexibly rotate the dihedral angle between the naphthyl rings, which would allow a number of potential reaction conformations (**Scheme**

62, A). Hence, "locking" the rotation of C1−C1' bond by establishing a carbocycle is one of the most straightforward ways to reduce its flexibility (**Scheme 62, B**).



Scheme 62 Ligand design and their characteristics.

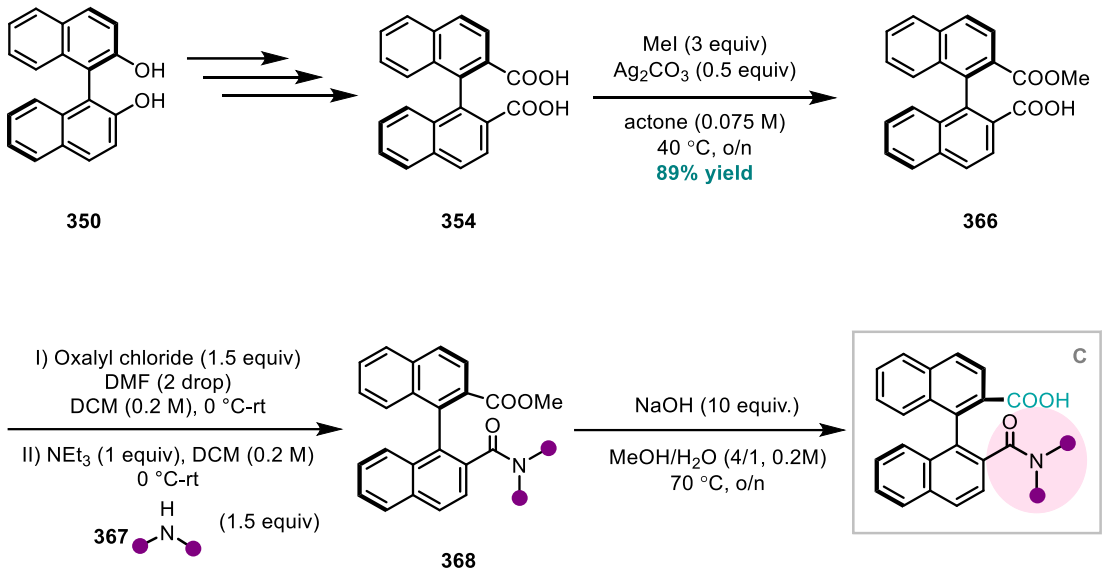
The pseudo-C2 symmetric CCAs could be prepared *via* the double alkylation of the binaphthyl-based alkyl bromides **363** under a basic condition, followed by the Pd/C catalysed hydrogenolysis. The bromides **363** could be easily synthesised from BINOL (**133**) in 3 steps, which was also commercially available (**Scheme 63**).



Scheme 63 Synthesis of pseudo-C2 symmetric CCA.

Apart from investigating the effects of rotation about the binaphthyl axis, we also focused on the potential influence of steric effects surrounding the coordinating site on the ligand. Establishing an appropriate steric hinderance near the acid would rotate the dihedral angle between two naphthyl rings differently than the angle formed by the bulky groups at C3/C3' position. Therefore, we decided to convert one of the carboxylic acids into either an ester group or amide group (**Scheme 62, C**).

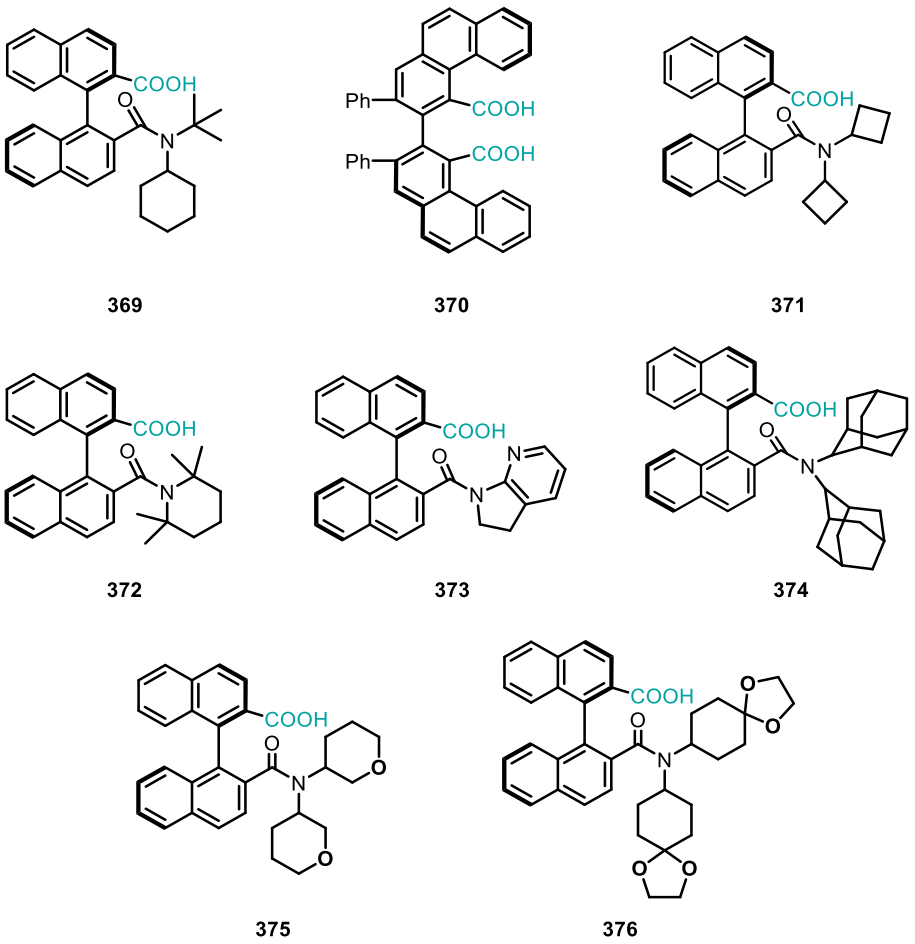
The binaphthyl-based CCA modified with an amide could be easily accessed *via* the amidation reaction of the ester **366** to obtain compound **368**. The ester **366** was prepared from the dicarboxylic acid which was synthesised from BINOL (**350**) as mentioned above (**Scheme 64**).



Scheme 64 Synthesis of binaphthyl amido acid C.

2.7.6 Unsuccessful synthesis of CCAs

Following the procedures mentioned above, the attempted synthesis of several CCAs were failed in the peptide coupling step (**Scheme 65**). Many other commonly used peptides coupling reagents (e.g. HATU, DCC, HOBt, HOAt) were tried as well, although no target amide product observed.



369 370 371

372 373 374

375 376

Scheme 65 Unsuccessful synthesis of CCAs.

2.7.7 Screening of new CCA ligands

Despite these failures, a library of newly-designed binaphthyl-based CCAs were synthesised successfully, and we next started to examine them for performance in the Cp*Rh(III)-catalysed C−H amidation reaction of the azine-linked cyclobutanes under the aforementioned optimal condition in hand (as the reminder, the product was obtained in 81% yield with 76:24 er in our previous best experiment). In the presence of 20 mol% of $Cp^*Rh(MeCN)_3(SbF_6)_2$ catalyst, 10 mol% of Ag_2CO_3 additive, and 2 equivalents of

dioxazolone in 1,4-dioxane (0.25 M), the reaction was performed with 20 mol% of various CCA ligands and warmed up to 80 °C for 20 h under argon (**Table 4**). Firstly, using pseudo-C2 symmetric CCAs **377** containing a 4-fluoro-phenyl group afforded moderate 34 % yield with 76:24 er, while the one containing a 3,4,5-trifluorophenyl group (**380**) gave almost the same result in 34% yield with 77:23 er (**Table 4, entry 1**). Before we started to test the binaphthyl-based amino acids, the spirobiindanyl-based chiral dicarboxylic acid **378**, synthesised from (*R*)-SPINOL was applied to the reaction, and afforded 70:30 er in 69% yield (**Table 4, entry 2**). Subsequently, we performed the simple methyl-esterification of one carboxyl group based on ligand **354** and **378**. Although the spiro-based monoester **379** failed to bring any groundbreaking result (43% yield, 68:32 er) compared with acid **378** (**Table 4, entry 4**), the monoester **366** based on the binaphthyl backbone demonstrated intriguing improvement both yield (40%) and enantioselectivity (61:39 er) in comparison with **354** (60% yield, 56:44 er) (**Table 4, entry 3 & 4**). This result encouraged us to further study a variety of chiral monocarboxylic acids next.

Intriguingly, using the CCA possessing an additional carboxamide group, the enantioselectivity was dramatically increased to 83:17 er and 89:11 er with binaphthyl-based **383** and **385**, respectively (**Table 4, entry 8 & 10**), while also the product was formed in good yields (78% and 70% respectively). According to the results of the reaction using **383** and **385**, we designed **386** with two chiral centres which was slightly steric bulker than **383** and less than **385**. It was found that the steric hinderance of the amide surrounding the coordinating site of the ligand was indeed of importance, as **386** afforded 87:13 er (in 56% yield) which was in between the enantiomeric ratio of **383** and **385** (**Table 4, entry 11**). Interestingly, with ligand **387**, which was the diastereomer of the ligand **386,** the product was obtained in higher yield (77%) and with a marginally lower enantiomeric ratio (85:15)

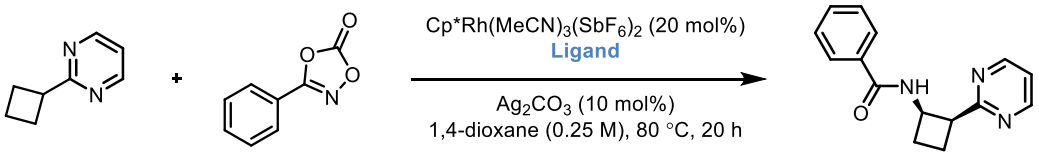
(**Table 4, entry 12**). Slightly expanding the ring size of the substituents on the amide of the ligand **L16** from six-membered to seven-membered, ligand **388** gave similar results (74% yield, 89:11 er) (**Table 4, entry 13**), while the much bulkier ligand **390** improved both the yield (80%) and the enantioselectivity (91:9 er) (**Table 4, entry 15**).

Due to the positive influences caused by the bulky substituents on the amide, the investigation was then followed with a series of even bulkier CCA ligands (**Table 4, entry 14-21**). While the ligand **392** containing twelve-membered rings shut down the reaction completely, the *N*,*N*-4,4-dimethylcyclohexyl analogue (*R*)-**396**, which modified with additional dimethyl groups on the cyclohexyl rings of amide skeleton based on ligand **385**, exhibited remarkable enantioselectivity enhancement resulting in 93% yield with 98:2 er (**Table 4, entry 21**).

Furthermore, two prevalent steric-hindered α-amino (**381** & **382**) in our lab were test as well. Unfortunately, none of them showed impressive results (**Table 4, entry 6 & 7**). It was also found that there was no reaction occuring in the absence of ligand in this catalytic system (**Table 4, entry 22**).

It is worth noting that we observed a very minor amount of benzamide which was generated from the decomposition of the dioxazolone after reaction. In order to check the potential role it played in the catalysis, we replaced the CCAs with 1 equivalent of benzamide. Only <5% of product was yielded (**Table 4, entry 23**). It indicated that a large amount of the byproduct from dioxazolone had a very limited catalytic function on the reaction, while it also demonstrated the benzamide was able to coordinate with the Cp*Rh(III) weakly in this catalytic system. Accordingly, ligand (*R*)-**396** was next selected as the optimal ligand and taken forward for further optimisation studies.

Table 4 Ligand screening.[a]

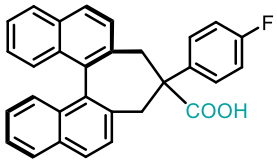


332 **336** (2 equiv) **341**

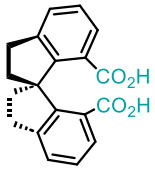
Entry	Ligand (mol%)	Yield (%)	er
1	**377** (20)	34	76:24
2	**378** (20)	69	70:30
3	**366** (20)	40	61:39
4	**379** (20)	43	68:32
5	**380** (20)	34	77:23
6	**381** (20)	15	55:45
7	**382** (20)	18	52:48
8	**383** (20)	78	83:17
9	**384** (20)	44	62:38
10	**385** (20)	70	89:11
11	**386** (20)	56	87:13
12	**387** (20)	77	85:15
13	**388** (20)	74	89:11
14	**389** (20)	81	76:24
15	**390** (20)	80	91:9
16	**391** (20)	62	83:17
17	**392** (20)	-	-
18	**393** (20)	71	82:18
19	**394** (20)	72	91:9
20	**395** (20)	71	92:8
21	**396** (20)	93	98:2
22	**-**	0	-
23	**benzamide (397)** (100)	<5%	-

[a] Reaction condition: **332** (0.05 mmol), **336** (0.1 mmol, 2 equiv), $Cp^*Rh(MeCN)_3(SbF_6)_2$ (20 mol%), Ag_2CO_3 (10 mol%), 1,4-dioxane (0.25 M), 80 °C, 20 h, under argon; All ^1H NMR yield; The er values were determined by chiral HPLC on a chiral stationary phase.

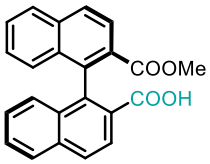
Ligand



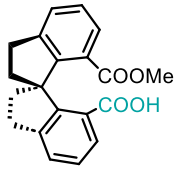
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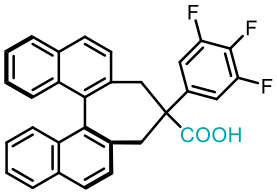
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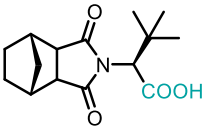
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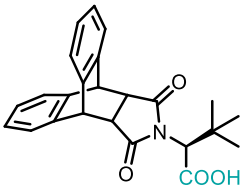
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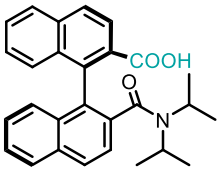
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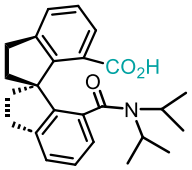
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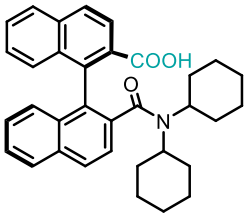
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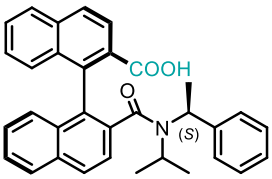
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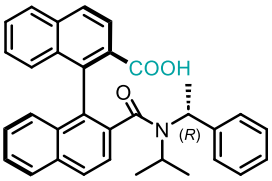
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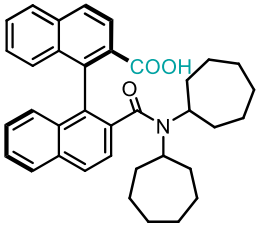
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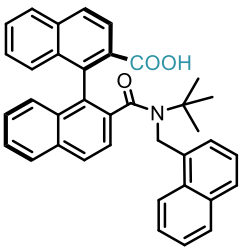
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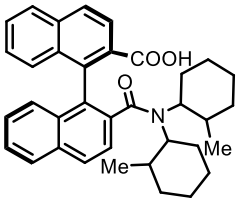
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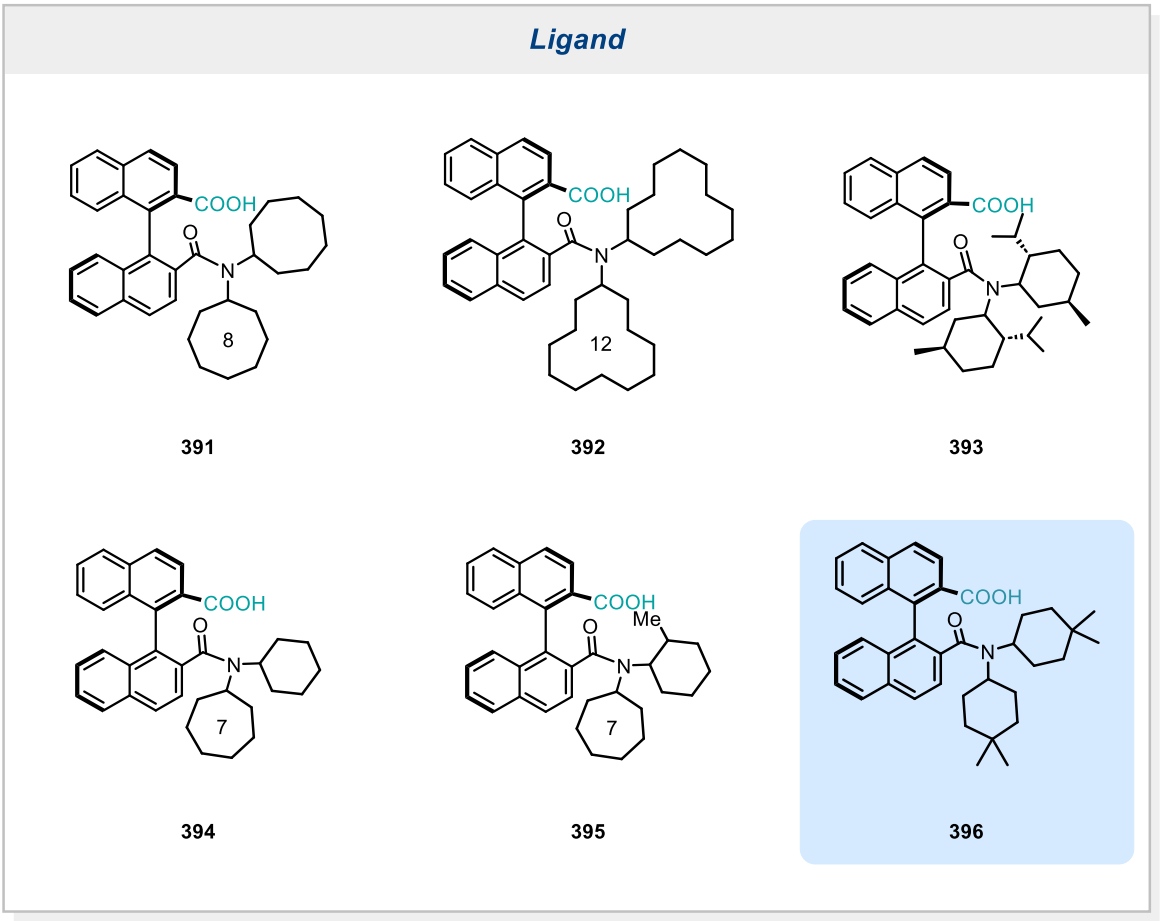
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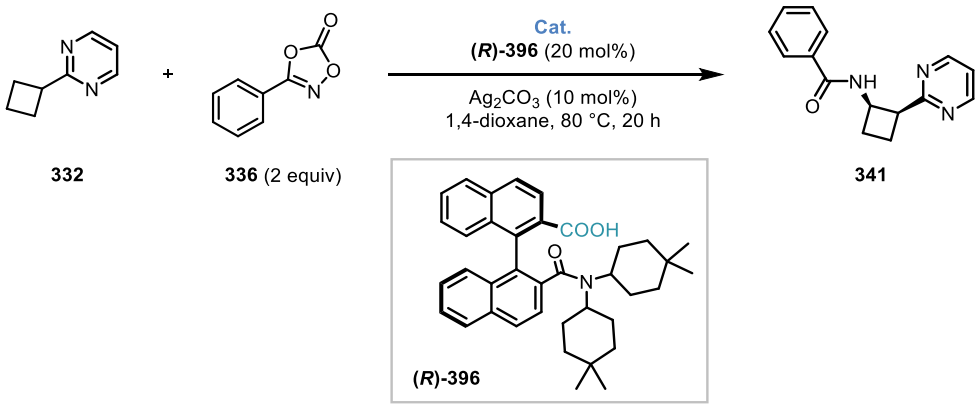
2.7.8 Metal catalyst screening

With the optimal ligand in hand, we proceeded to optimize other conditions, encompassing metal catalysts, the equivalents of dioxazolone, reaction time, additives, and solvents.

Initially, the reaction was attempted under ambient conditions and open to the air. Surprisingly, under argon, the yield decreased from 98% to 93%, but the enantiomeric ratio of 98:2 remained constant (**Table 5, entry 2**). Subsequently, efforts were made to reduce the metal catalyst loadings down to 10 mol%, 5 mol%, and 3 mol%, respectively (**Table 5, entries 3-5**). However, as the catalyst loading decreased, both yield and enantioselectivity

gradually diminished. Using 5 mol% of the Cp*Rh(III) catalyst gave only 40% yield product with a 92:8 er (**Table 5, entries 3-5**). Extending the reaction time to 48 hours produced the same result (**Table 5, entry 6**), while further reduction in ligand loading deteriorated reactivity (**Table 5, entry 7**). The $Cp^*Co(MeCN)_3(SbF_6)_2$ catalyst was applied to the reaction but did not yield the target product (**Table 5, entry 8**). There was also no reaction in the absence of the Cp*Rh(III) catalyst (**Table 5, entry 9**).

Table 5 Metal catalyst screening.[a]



Entry	Cat. (mol%)	NMR yield (%)	er
1[b]	Cp*Rh (20)	93	98:2
2	Cp*Rh (20)	98	98:2
3	Cp*Rh (10)	83	96:4
4	Cp*Rh (5)	40	92:8
5	Cp*Rh (3)	30	92:8
6[c]	Cp*Rh (5)	40	93:7
7[d]	Cp*Rh (5)	22	91:9
8	Cp*Co (20)	-	-
9	-	-	-

[a] Reaction condition: **332** (0.05 mmol), **336** (0.1 mmol, 2 equiv), **(*R*)-396** (20 mol%), Ag_2CO_3 (10 mol%), 1,4-dioxane (0.25 M), 80 °C, 20 h, under air; All ^1H NMR yield; The er values were determined by chiral HPLC on a chiral stationary phase. Cp*Rh = $Cp^*Rh(MeCN)_3(SbF_6)_2$, Cp*Co = $Cp^*Co(MeCN)_3(SbF_6)_2$

[b] under argon;

[c] 48 h;

[d] **(*R*)-396** (5 mol%), 48 h.

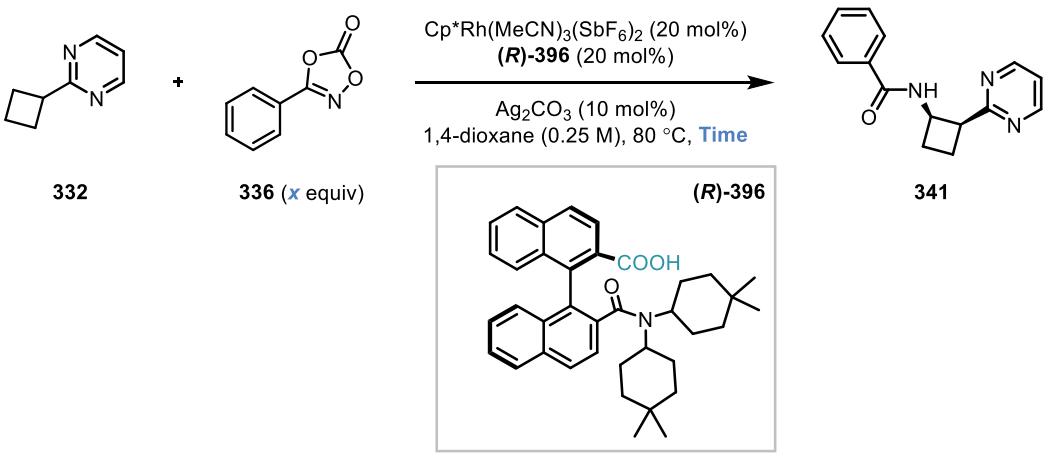
2.7.9 Equivalent of dioxazolone and reaction time screening

Based on the aforementioned investigation, it was evident that the metal catalyst loading could not be reduced directly without compromising yield. Consequently, our focus shifted to optimising other conditions in the hope of improving efficiency. The addition of 1.2 or 1.5 equivalents of dioxazolone **336** resulted in lower reactivity and slightly reduced enantioselectivity (78% yield, 94:6 er, and 91% yield, 97:3 er) (**Table 6, entries 2 & 3**). In contrast, the use of 1.7 equivalents of dioxazolone **336** yielded the same favorable results as before (98% yield, 98:2 er) (**Table 6, entry 4**).

It was observed that both yield and enantiomeric ratio slightly increased after 7 hours (92% yield, 97:3 er) (**Table 6, entry 5**). Further shortening the reaction time to 5 h prematurely interrupted the catalytic turnover, leading to an 82% lower yield with a 95:5 er (**Table 6, entry 6**). A comparison of entries **4**, **5**, and **6** revealed an unusual slight decrease in the er values (from 98:2 to 95:5). While experimental errors could be a factor, this was likely due to an undesirable competition between the optimal CCA and a minor amount of benzamide formed from the decomposition of dioxazolone at the beginning of the reaction. However, since these conditions did not yield optimal results, they were not further investigated.

Additionally, using half the amount of acid ligand resulted in the product with only 76% yield, without altering the enantioselectivity (**Table 6, entry 7**). In conclusion, in this section, the stoichiometry of dioxazolone was successfully reduced to 1.7 equivalents.

Table 6 Equivalent of dioxazolone and reaction time screening.[a]



Entry	336 (eq.)	Time (h)	Yield (%)[c]	er[d]
1	2	20	98	98:2
2	1.2	20	78	94:6
3	1.5	20	91	97:3
4	1.7	20	98	98:2
5	1.7	7	92	97:3
6	1.7	5	82	95:5
7[b]	1.7	20	76	95:5
8[c]	1.7	20	83	95:5

[a] Reaction condition: **332** (0.05 mmol), $Cp^*Rh(MeCN)_3(SbF_6)_2$ (20 mol%), **(*R*)-396** (20 mol%), Ag_2CO_3 (10 mol%), 1,4-dioxane (0.25 M), 80 °C, under air; All ^1H NMR yield; The er values were determined by chiral HPLC on a chiral stationary phase.

[b] **(*R*)-396** (10 mol%).

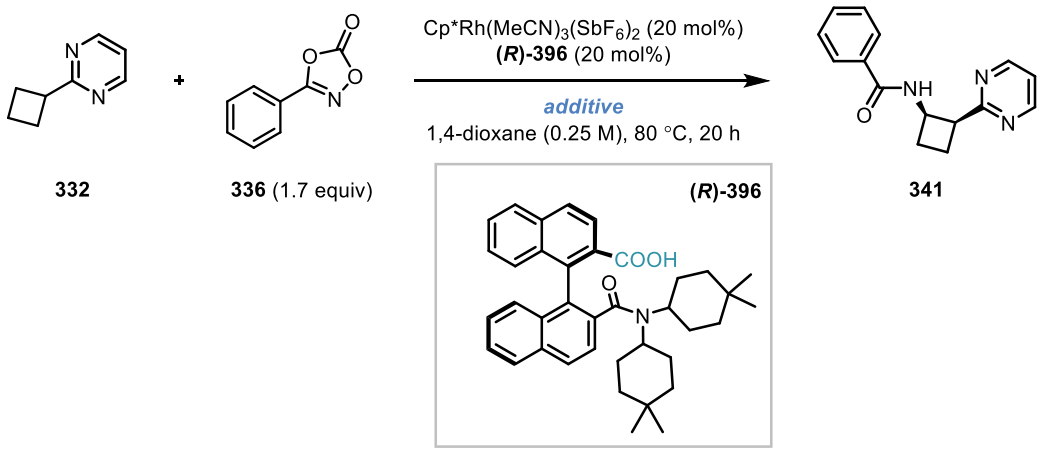
[c] $Cp^*Rh(MeCN)_3(SbF_6)_2$ (10 mol%), **(*R*)-396** (60 mol%).

2.7.10 Additives screening

At the same time, we were interested to see if the additives in the above optimal condition would further improve reactivity or enantioselectivity. Therefore, a number of additives were subsequently examined in the presence of 1.7 equivalents of dioxazolone **336**. 10 mol%

of silver salts, including AgOAc, $AgNO_3$, AgF, and Ag_3PO_4, were separately added to the reaction; however, none of them yielded better results compared to Ag_2CO_3 (**Table 7, entries 3-6**). Without any additive, reactivity sharply dropped, while K_3PO_4 also provided only moderate results (**Table 7, entries 2 & 7**). Overall, this indicates that Ag_2CO_3 played a significant role in improving/maintaining reactivity.

Table 7 Additives screening.[a]



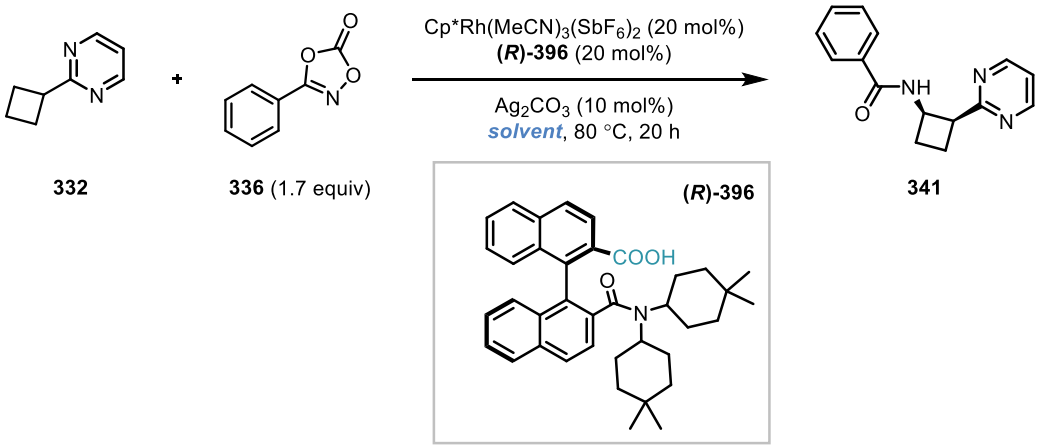
Entry	Additive (mol%)	Yield (%)[c]	er[d]
1	Ag_2CO_3 (10)	98	98:2
2	-	83	97:3
3	AgOAc (10)	93	97:3
4	$AgNO_3$ (10)	60	96:4
5	AgF (10)	94	97:3
6	Ag_3PO_4 (10)	91	97:3
7	K_3PO_4 (10)	86	96:4

[a] Reaction condition: **332** (0.05 mmol), **336** (1.7 equiv), $Cp^*Rh(MeCN)_3(SbF_6)_2$ (20 mol%), **(*R*)-396** (20 mol%), 1,4-dioxane (0.25 M), 80 °C, 20 h, under air; All ^1H NMR yield; The er values were determined by chiral HPLC on a chiral stationary phase.

2.7.11 Solvent screening

Solvent is arguably always considered as an important factor in influencing enantioselectivity control. Although a preliminary screening of solvents was conducted in the early stages of reaction discovery, it became necessary to re-examine the solvent based on our latest optimal conditions to identify the best solvent and concentration for the system. Firstly, by increasing the concentration of the solution to 0.5 M, the reaction was stirred in 1,4-dioxane for 20 h. Delightfully, both reactivity and enantioselectivity improved to a remarkable level (98% yield, 99:1 er) (**Table 8, entry 2**). Additionally, chlorobenzene (PhCl) and ethyl acetate (EA) also exhibited excellent enantioselectivity, reaching up to 98.5:1.5 er (**Table 8, entry 4 & 9**). Furthermore, 0.5 equivalents of 1,2-dichloroethane (DCE), toluene, tetrahydrofuran (THF), diethyl ether (DE), cyclopentyl methyl ether (CPME), and methyl *tert*-butyl ether (TBME) were tested in the reaction, each providing ideal but not optimal results (**Table 8, entry 3, 5, 6, 8, 11, 13**). Interestingly, using the polar solvents dimethylformamide (DMF) or hexafluoroisopropanol (HFIP), no product was detected after 20 h (**Table 8, entry 10 & 14**).

Table 8 Solvent screening.[a]



Entry	Solvent (M)	Yield (%)[c]	er[d]
1	1,4-dioxane (0.25)	97	98:2
2	1,4-dioxane (0.5)	98	99:1
3	DCE (0.5)	94	96:4
4	PhCl (0.5)	93	98:2
5	Toluene (0.5)	85	97:3
6	THF (0.5)	93	97:3
7	DCM(0.5)	96	95:5
8	DE (0.5)	77	97:3
9	EA (0.5)	98	98.5:1.5
10	DMF (0.5)	-	-
11	CPME (0.5)	81	97:3
12	MeCN (0.5)	21	90:10
13	TBME (0.5)	83	97:3
14	HFIP (0.5)	trace	-

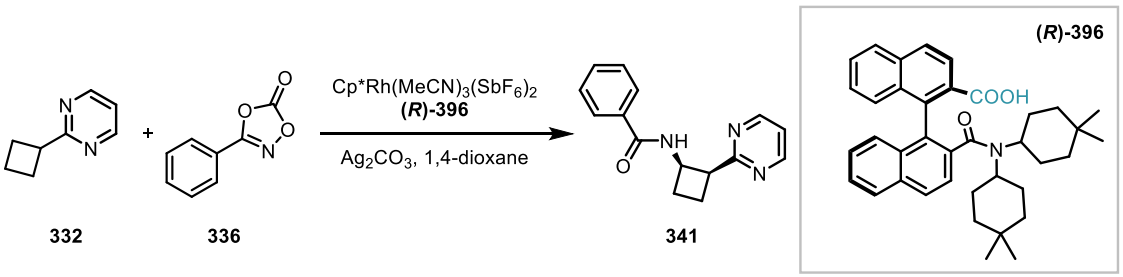
[a] Reaction condition: **332** (0.05 mmol), **336** (1.7 equiv), Cp*Rh(MeCN)$_3$(SbF$_6$)$_2$ (20 mol%), **(*R*)-396** (20 mol%), Ag_2CO_3 (10 mol%), 80 °C, 20 h, under air; All ^{1}H NMR yield; The er values were determined by chiral HPLC on a chiral stationary phase.

2.7.12 Optimisation endgame – catalyst loading

Eventually, we redirected our focus to lowering the Cp*Rh(III) catalyst loading by comprehensively tuning the conditions. Simply reducing the Cp*Rh(III) catalyst loading to 15 mol%, 10 mol%, and 8 mol% only resulted in a decrease in both reactivity and enantioselectivity. Additionally, extending the reaction time and heating up the reaction proved ineffective in improving the results.

Subsequently, it was discovered that using a 1:1 ratio of Cp*Rh(III) catalyst (10 mol%) and Ag_2CO_3 (10 mol%) consistently yielded similar results, even with different concentrations and reaction times (**Table 9, entries 9, 12, 13, 15 & 16**). However, incorporating Cp*Rh(III) and Ag_2CO_3 in a ratio of 2:1 (10 mol% and 5 mol%, respectively) achieved a balanced result in both yield and enantiomeric ratio (90% yield, 97:3 er) (**Table 9, entry 20**). It's noteworthy that slightly scaling up the reaction to 0.15 mol obtained the product in a 90% yield with a 99:1 er, which was chosen as the optimised condition for the subsequent investigation of the reaction scope (**Table 9, entry 21**).

Table 9 Endgame – increase the catalyst loading.[a]



332 336 341

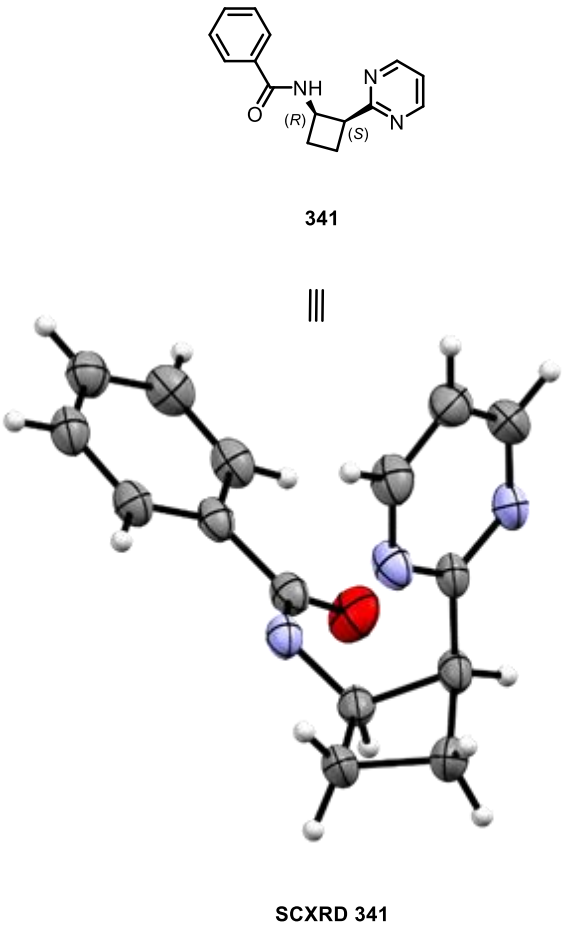
Entry	336 (eq.)	Cat. (mol%)	Additive (mol%)	Solvent (M)	T (°C)	Time (h)	Yield (%)[c]	er[d]
1	1.7	Cp*Rh (5)	Ag_2CO_3 (10)	1,4-dioxane (0.1)	100	20	57	91:9
2	1.2	Cp*Rh (5)	Ag_2CO_3 (10)	1,4-dioxane (0.1)	100	20	60	92:8
3	1.2	Cp*Rh (5)	Ag_2CO_3 (10)	1,4-dioxane (0.5)	100	5	45	91:9
4	1.2	Cp*Rh (5)	Ag_2CO_3 (10)	1,4-dioxane (1)	100	5	51	93:7
5	1.2	Cp*Rh (5)	Ag_2CO_3 (10)	1,4-dioxane (0.1)	100	5	61	91:9
6	1.2	Cp*Rh (8)	Ag_2CO_3 (10)	1,4-dioxane (0.1)	100	20	62	92:8
7	3.4	Cp*Rh (5)	Ag_2CO_3 (10)	1,4-dioxane (0.25)	100	5	35	90:10
8	1.2	Cp*Rh (10)	Ag_2CO_3 (10)	1,4-dioxane (0.1)	100	60	55	90:10
9	1.7	Cp*Rh (10)	Ag_2CO_3 (10)	1,4-dioxane (0.1)	80	60	90	97:3
10	1.2	Cp*Rh (15)	Ag_2CO_3 (10)	1,4-dioxane (0.1)	100	20	88	90:10
11	1.7	Cp*Rh (15)	Ag_2CO_3 (10)	1,4-dioxane (0.1)	80	20	62	95:5
12	1.7	Cp*Rh (10)	Ag_2CO_3 (10)	1,4-dioxane (0.25)	80	60	91	95:5
13	1.7	Cp*Rh (10)	Ag_2CO_3 (10)	1,4-dioxane (0.5)	80	60	80	96:4
14	1.7	Cp*Rh (8)	Ag_2CO_3 (10)	1,4-dioxane (0.5)	80	60	78	95:5
15	1.7	Cp*Rh (10)	Ag_2CO_3 (10)	1,4-dioxane (0.1)	80	48	88	96:4
16	1.7	Cp*Rh (10)	Ag_2CO_3 (10)	1,4-dioxane (0.25)	80	48	88	96:4
17	1.7	Cp*Rh (10)	-	1,4-dioxane (0.5)	80	20	76	95:5
18	1.7	Cp*Rh (5)	-	1,4-dioxane (0.5)	80	20	51	93:7
19	1.7	Cp*Rh (10)	-	1,4-dioxane (0.25)	80	20	82	97:3
20	1.7	Cp*Rh (10)	Ag_2CO_3 (5)	1,4-dioxane (0.5)	80	20	90	97:3
21[b]	1.7	Cp*Rh (10)	Ag_2CO_3 (5)	1,4-dioxane (0.5)	80	20	90	99:1
22	1.7	Cp*Rh (5)	Ag_2CO_3 (2.5)	1,4-dioxane (0.5)	80	52	76	94:6
23	1.7	Cp*Rh (10)	Ag_2CO_3 (5)	1,4-dioxane (0.5)	80	8	66	93:7
24	1.7	Cp*Rh (10)	Ag_2CO_3 (2.5)	1,4-dioxane (0.5)	80	8	69	93:7

[a] Reaction condition: **332** (0.05 mmol); under air; All ^{1}H NMR yield; The er values were determined by chiral HPLC on a chiral stationary phase.

[b] **332** (0.15 mmol);

2.7.13 Single Crystal X-Ray diffraction analysis

In an attempt to establish the absolute and relative stereochemical configuration of the amidated cyclobutane product **341**, a single crystal material was prepared and analysed by single-crystal X-ray diffraction (SCXRD). The enantiopure material was readily crystallised by slowly evaporing the EtOAc solvent from the solution of product (> 99:1 er). The absolute stereochemical configuration of the product **341** was confirmed as (1*R*,2*S*) (**Scheme 66**).



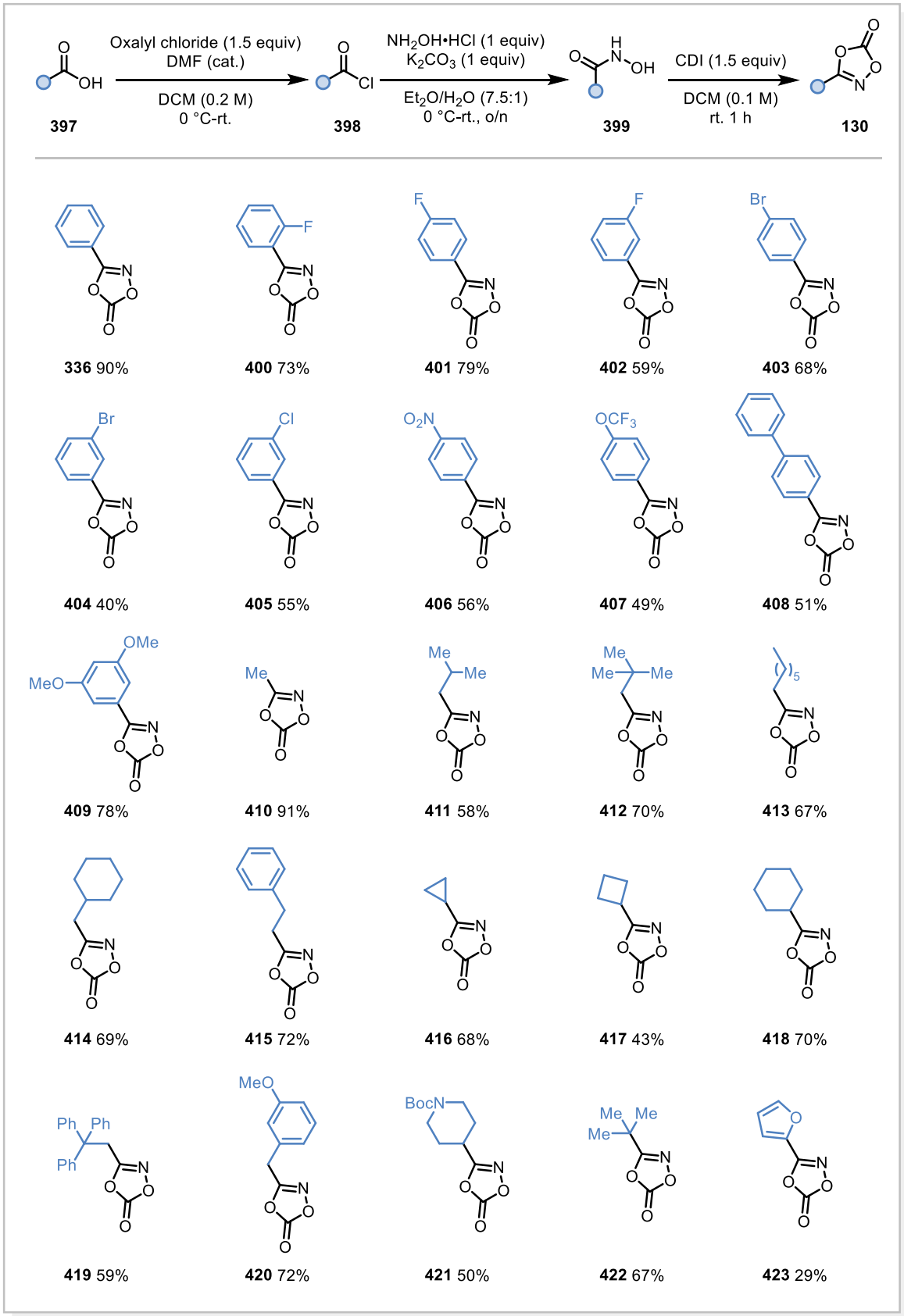
Scheme 66 Single crystal X-ray diffraction of enantiopure *cis*-configured amido-cyclobutane.

2.8 Reaction Scope

2.8.1 Synthesis of starting materials

2.8.1.1 Dioxazolones

Building upon the aforementioned synthetic route in **Scheme 58**, a diverse array of dioxazolones bearing aryl, alkyl, and heteroaromatic groups was subsequently prepared (**Scheme 67**). The dioxazolone amide source **130** was derived from the simple benzoic acid **397**. First, benzoic acid **397** was converted to the corresponding acid chloride **398**, which was then reacted with hydroxylamine salts to yield the hydroxamic acid intermediate **399**.[153, 154] In the final step, treatment of **399** with carbonyldiimidazole (CDI) furnished the desired dioxazolone **130** in moderate to good yields.[155]



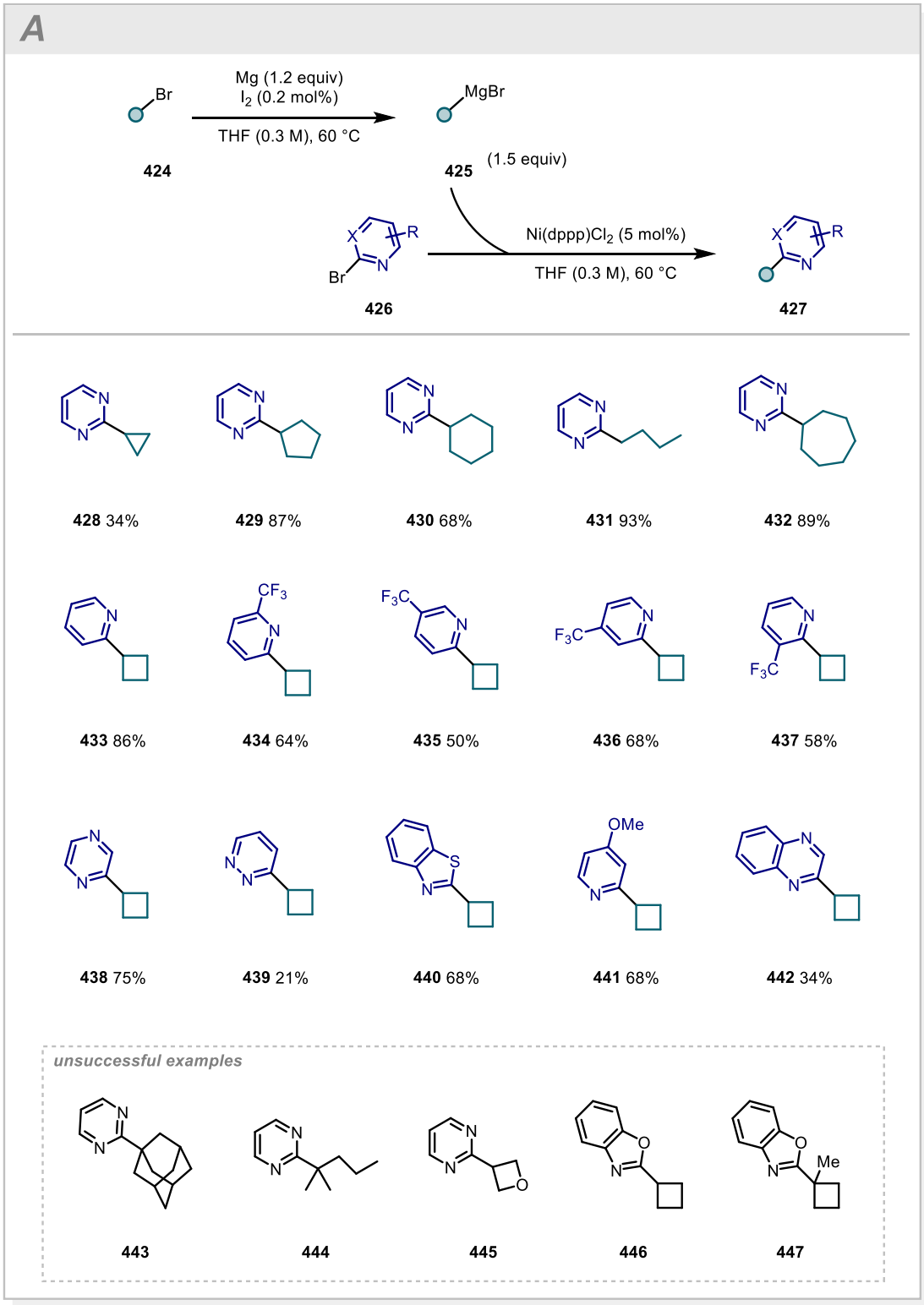
Scheme 67 Dioxazolone examples.

2.8.1.2 Azine-linked (cyclo)alkanes

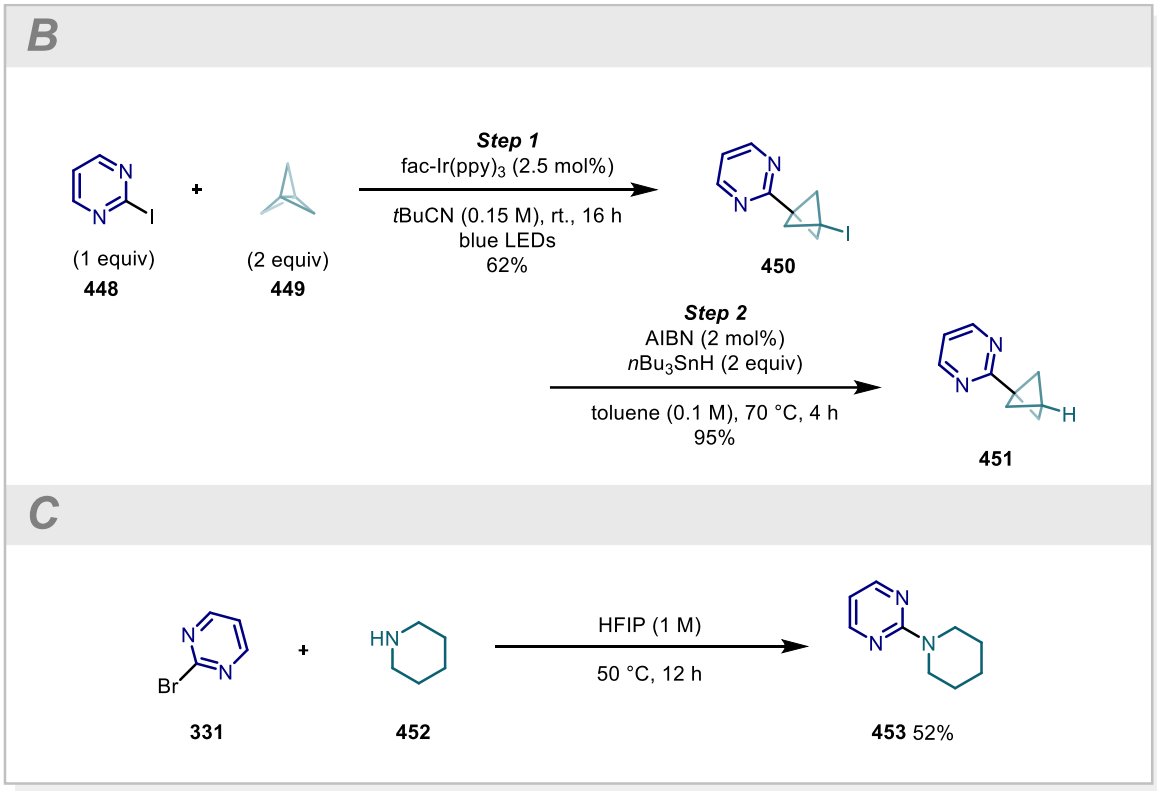
A variety of azine-linked (cyclo)alkanes **427** were subsequently synthesised from commercially available (cyclo)alkyl bromide **424**. The (cyclo)alkylmagnesium bromide Grignard solution **425** was prepared first. Subsequently, the azine-linked (cyclo)alkanes **427** was readily afforded through a Kumada cross coupling reaction with the 2-bromo-heterocyclic compound **426** catalysed by the bench-stable Ni(dppp)Cl_2 (**Scheme 68, A**).[152] Simply by adding the fresh prepared Grignard solution **425** to the solution of 2-bromopyrimidine and Ni(dppp)Cl_2 catalyst slowly and stirring it at 60 °C, the cycloalkylpyrimidines including 2-cyclopropylpyrimidine (**428**), 2-cyclopentylpyrimidine (**429**), 2-cyclohexylpyrimidine (**430**), and 2-cycloheptylpyrimidine (**432**) were successfully prepared in good to excellent yields, followed by the synthesis of diverse cyclobutanes bearing different directing groups (**Scheme 68, 433-442**). However, the bulkier bromo-(cyclo)alkanes such as 2-bromo-2-methylpentane and 1-bromoadamantane were failed to undergo the coupling reaction under these conditions (**Scheme 68, 443, 444, 446**). We also tried to synthesize 2-(oxetan-3-yl)pyrimidine following this route, unfortunately, no target product was generated (**Scheme 68, 445**), while the *α*-methyl substituted cyclobutane was also not accessible using this approach (**Scheme 68, 447**).

We were also interested to investigate whether this C−H amidation reaction could be applied to the bicyclic compounds. Therefore, the 2-(bicyclo[1.1.1]pentan-1-yl)pyrimidine **451** was synthesised from [1.1.1]-propellane **449** and 2-iodopyrimidine **448** catalysed by fac-Ir(ppy)$_3$ under blue light irradiation to form the 2-(3-iodobicyclo[1.1.1]pentan-1-yl)pyrimidine **450**, followed by de-iogenation in the presence of AIBN and *n*-Bu_3SnH to generate the product **451** (**Scheme 69, B**). Moreover, the 2-(piperidin-1-yl)pyrimidine **453**

was also prepared to test whether the heterocyclic pyrimidine is compatible with this C−H amidation transformation (**Scheme 69, C**).



Scheme 68 Azine-linked (cyclo)alkane examples.



Scheme 69 Azine-linked (cyclo)alkane and heterocyclic examples.

2.8.2 Scope of the enantioselective C−H amidation with dioxazolones

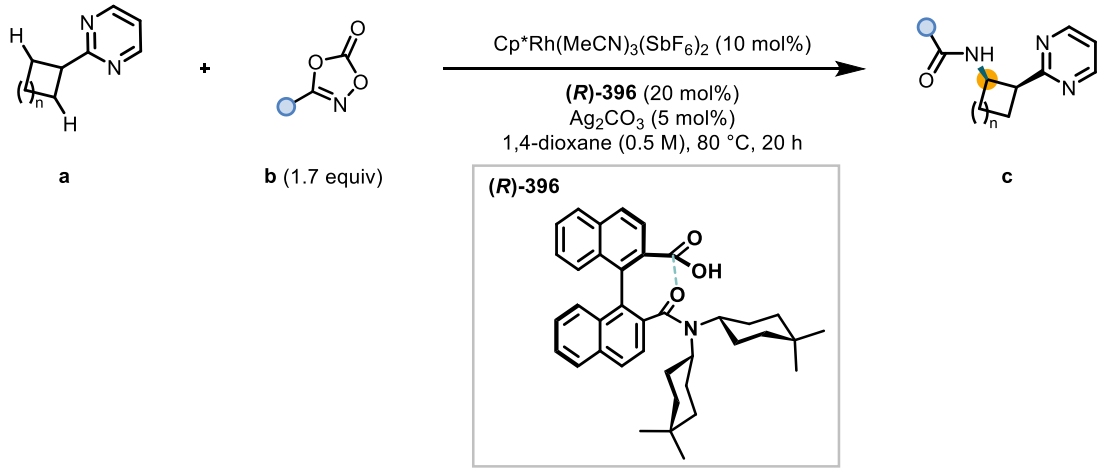
With the optimal reaction conditions and freshly prepared starting materials in hand, we commenced to explore the substrate scope with respect to the dioxazolone coupling partner in the presence of 2-cyclobutylpyrimidine (**a**) (**Scheme 70**). Firstly, dioxazolones bearing a variety of aromatic rings were examined (**341, 453-463**). It was found that with *ortho*-, *para*-, and *meta*-F substituents on the aromatic ring, the corresponding amidated products were afforded in good to excellent yields and enantioselectivities (**454**, **455**: 79-94% yield, 90:10-97:3 er). Aromatic dioxazolones containing other halogen atoms (**457-459**) were also tolerated well, obtaining amidated products in satisfactory yields and enantioselectivities.

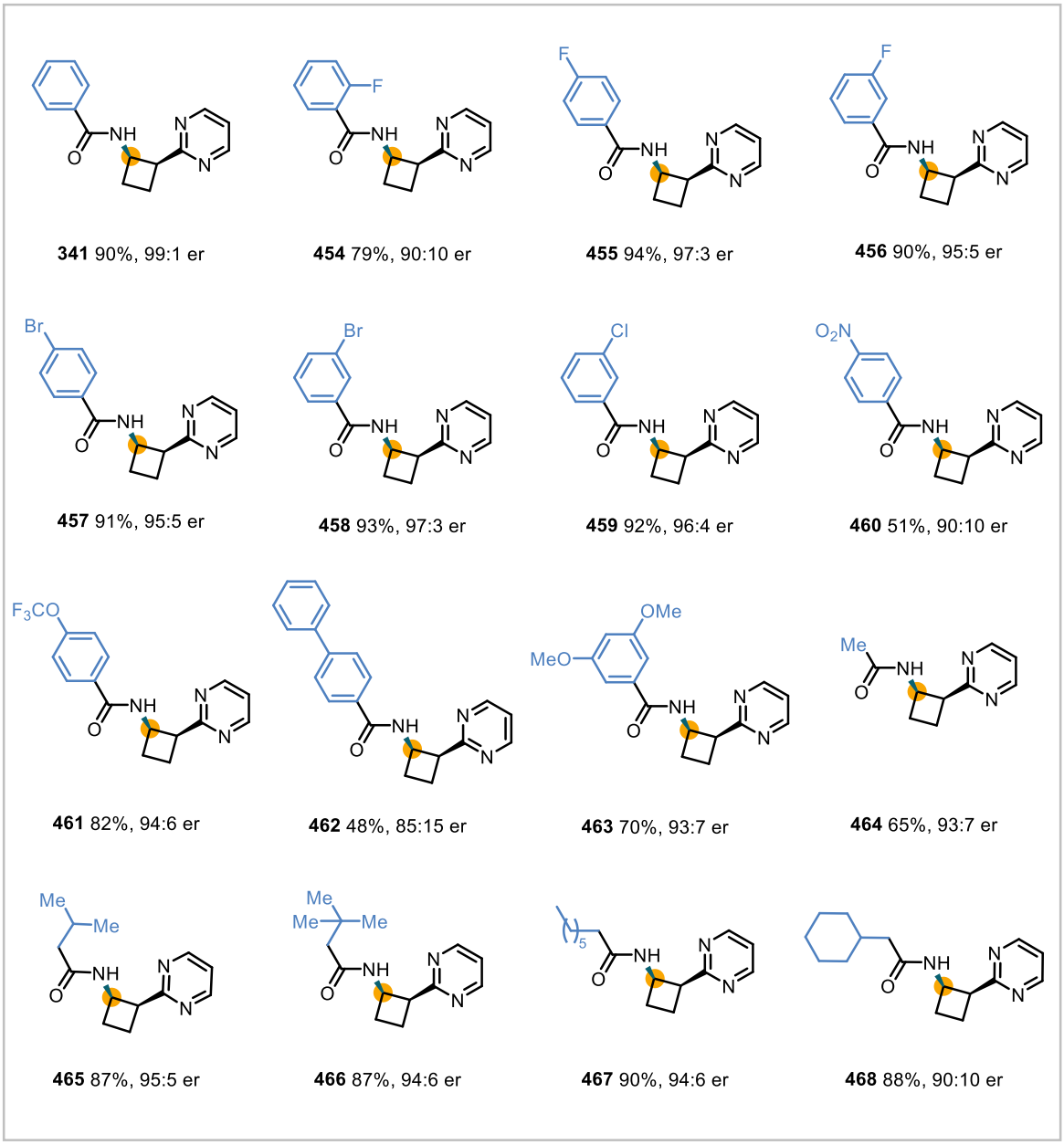
Other substituted functional groups involving an electron-withdrawing nitro group (**460**) as well as weakly electron-donating trifluoromethoxy group (**461**) in the *para*-position of the aryl ring were compatible with our catalytic system, which afforded the desired amidated products in good to excellent yields and enantioselectivities (51% yield, 90:10 er & 82% yield, 94:6 er, respectively). Dioxazolone bearing a biphenyl group afforded **462** in 45% yield and 85:15 er, while bis-3,5-methoxy substituted phenyl dioxazolone furnished **463** in 70% yield with 93:7 er.

Following on, multiple acyclic alkyl-substituted dioxazolones were examined and found to be compatible with the methodology (**464**-**476**). Simple methyl-derived dioxazolone **410** obtained the desired product **463** in 65% yield and 93:7 er, while dioxazolone possessing a longer *n*-heptyl chain **413** gave similar enantioselectivity (94:6 er) in higher isolated yield (90%) (**467**). Importantly, the branched sp^3-rich scope examples demonstrated good compatibility giving **465** and **466** in similar results, however, *tert*-butyl substituted carboxamide **476** was afforded in a slightly lower, 78% yield with 88:12 er. Dioxazolone possessing a bulkier triphenylethyl group was then evaluated to give a 93% yield with a diminished 89:11 er (**473**). Furthermore, examples containing small ring systems of potential medicinal value, were tested next. Cyclobutyl-substituted dioxazolone provided the corresponding product **471** in 69% yield and 92:8 er. It was worth noting that the cyclopropyl-substituted example did not suffer the competitive C−C bond insertion by rhodium as we were initially concerned,[163] and instead, the corresponding product **470** was afforded in 80% yield and 92:8 er. Additionally, the introduction of a furan moiety was achieved successfully, yielding corresponding product in 51% yield and 92:8 er (**477**).

During our investigation of the reaction, we observed that a fraction of the dioxazolones underwent noticeable decomposition to their corresponding amide (which was detected within the reaction mixture).

Scheme 70 Dioxazolone scope.





341 90%, 99:1 er

454 79%, 90:10 er

455 94%, 97:3 er

456 90%, 95:5 er

457 91%, 95:5 er

458 93%, 97:3 er

459 92%, 96:4 er

460 51%, 90:10 er

461 82%, 94:6 er

462 48%, 85:15 er

463 70%, 93:7 er

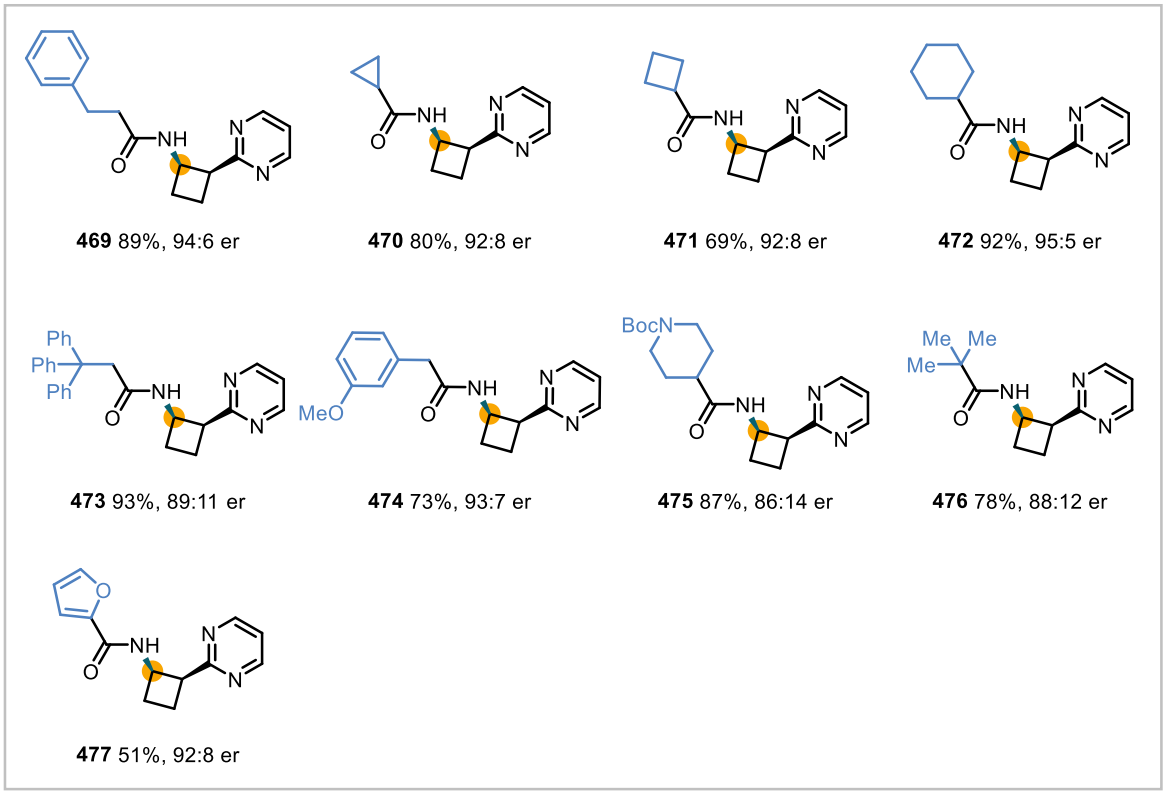
464 65%, 93:7 er

465 87%, 95:5 er

466 87%, 94:6 er

467 90%, 94:6 er

468 88%, 90:10 er



469 89%, 94:6 er

470 80%, 92:8 er

471 69%, 92:8 er

472 92%, 95:5 er

473 93%, 89:11 er

474 73%, 93:7 er

475 87%, 86:14 er

476 78%, 88:12 er

477 51%, 92:8 er

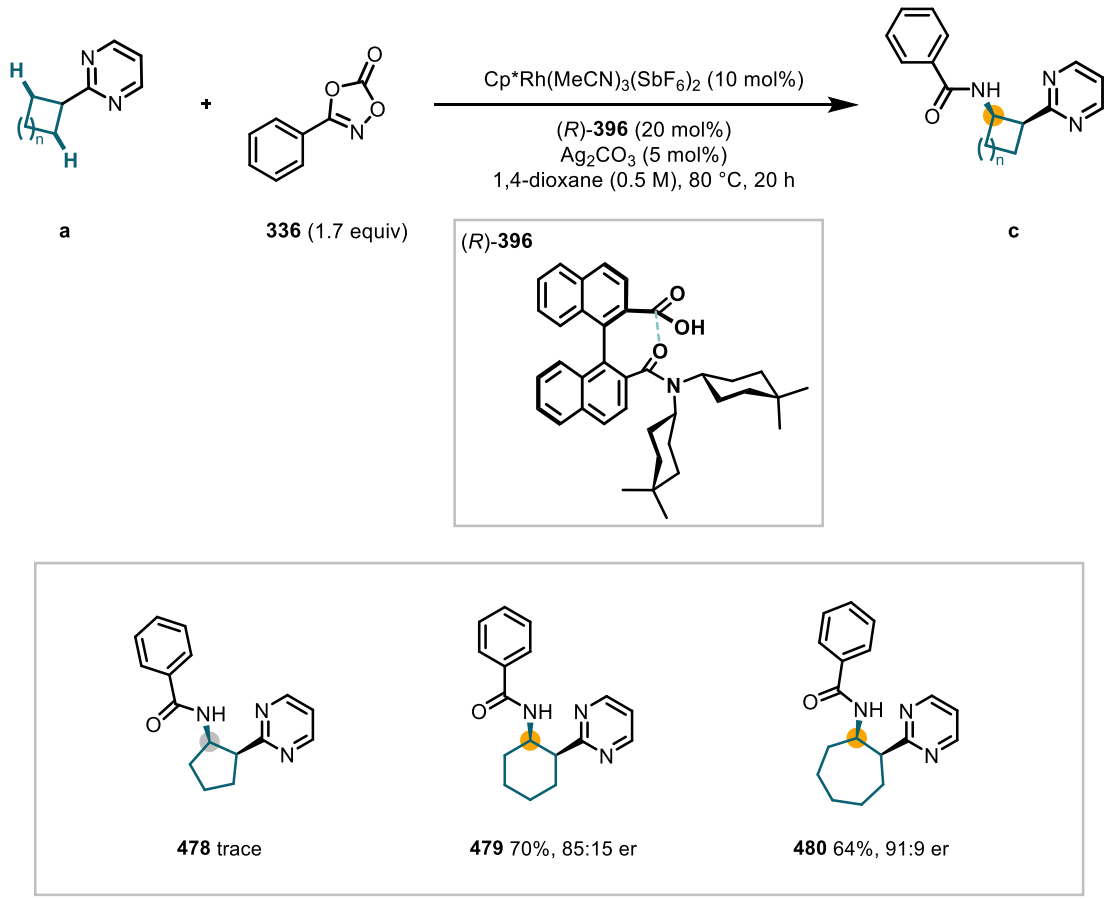
[a] Reaction conditions: **a** (0.15 mmol), **b** (0.26 mmol, 1.7 equiv), $[Cp^*Rh(MeCN)_3][(SbF_6)_2]$ (10 mol%), (*R*)-**396** (20 mol%), Ag_2CO_3 (5 mol%), 1,4-dioxane (0.5 M), 80 °C, 20 h; Isolated yields; the er values were determined by chiral HPLC.

The amides were likely able to bind to the rhodium catalyst as well, serving as ligands to continue the catalytic circle (see details in Chapter 2, **2.7.7**). This process introduced the possible of a competitive dynamic exchange process with ligand (*R*)-**396** during the reaction and thus a competitive non-enantioselective pathway. This suggests that the distinct enantioselectivities in different amidated products were a consequence of the differences in the decomposition rates of the diverse dioxazolones.

2.8.3 Azine-linked (cyclo)alkane scope

Surprisingly, it was subsequently revealed that this methodology could also be directly applied to other cycloalkylpyrimidines in the presence of dioxazolone **336 (Scheme 71)**. Notably, under the standard reaction condition, both 2-cyclohexylpyrimidine and 2-cycloheptylpyrimidine yielded the target product in moderate to good yields and enantioselectivities, respectively (70% yield with 85:15 er (**479**) and 64% yield with 91:9 er (**480**)). However, under the standard conditions 2-cyclopentylpyrimidine (**430**) afforded only traces of product **478**, and the anticipated product derived from 2-cyclopropylpyrimidine (**428**) was entirely undetectable following subjection of xx to the standard reaction.

Scheme 71 Azine-linked (cyclo)alkane scope.[a]



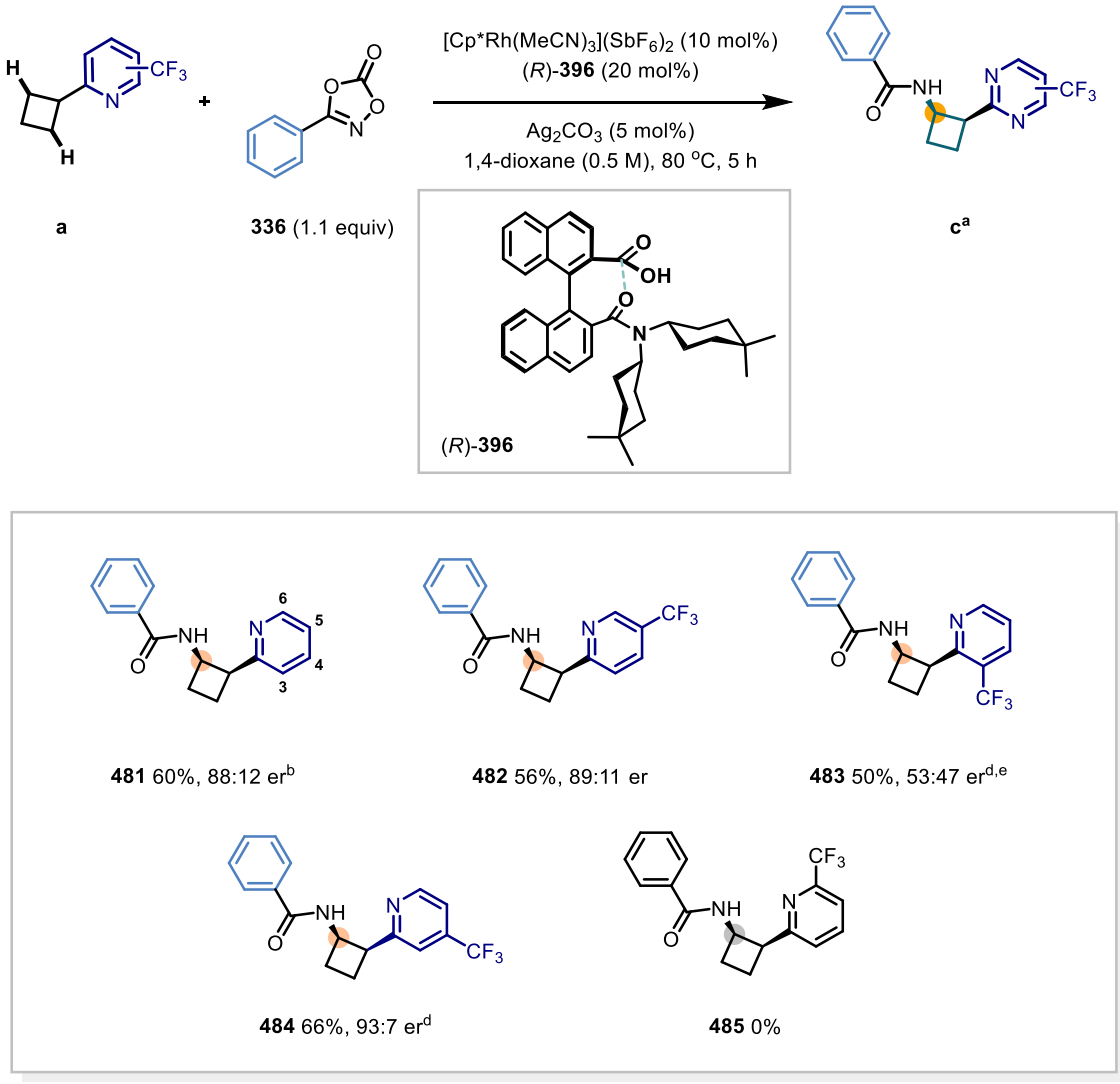
[a] Reaction conditions: **a** (0.15 mmol), **336** (0.26 mmol, 1.7 equiv), $[Cp^*Rh(MeCN)_3][(SbF_6)_2]$ (10 mol%), (*R*)-**396** (20 mol%), Ag_2CO_3 (5 mol%), 1,4-dioxane (0.5 M), 80 °C, 20 h; Isolated yields; the er values were determined by chiral HPLC.

2.8.4 Investigation of various cyclobutanes bearing other DGs

As well as evaluating different (cyclo)alkanes utilising pyrimidine as the directing group, we also directed our attention to other *N*-containing DGs (**Scheme 72**). We observed that the pyridyl cyclobutane (**433**) furnished the corresponding mono-amidated product **481** in 60% yield with an enantiomeric ratio of 88:12 within a mere 2 h, which indicated the higher

reactivity of the pyridine DG in comparison to the pyrimidine DG. However, in contrast to the utilisation of pyrimidine as the DG, when pyridine was employed, significant quantities of bis-amidated products were observed after the reaction time exceeded 2 h. To have a better comprehension of the influence of the electronic and steric effects arising from DGs, a trifluoromethyl group was introduced at different positions on the pyridine ring. A CF_3 group attached at the C5 position of the pyridine ring delivered a similar result to **433** after 5 h, while cyclobutane **435** with the -CF_3 in the C6 position exhibited no conversion. We hypothesized that the -CF_3 in the C6 position hindered the necessary binding of the pyridyl nitrogen with rhodium. When the reaction time was shortened to 1 hour, the mono-amidated product **483** was obtained as the main product in 50% yield and an extremely low enantioselectivity (53:47 er). The C4-CF_3-substituted pyridinyl-cyclobutane (**436**) illustrated an increase in reactivity with full conversion after 1.5 h, transforming to 18% bis-amidated cyclobutane product **495** and the corresponding mono-amidated product **484**. Notably, merely restricting the reaction time to 1 h enabled the compound **436** to predominantly transform into the corresponding mono-amidated product **484** in 66% yield with an enantiomeric ratio of 93:7 (however, if the reaction time was shortened to 0.5 h, a substantial amount of the starting material remained unconverted).

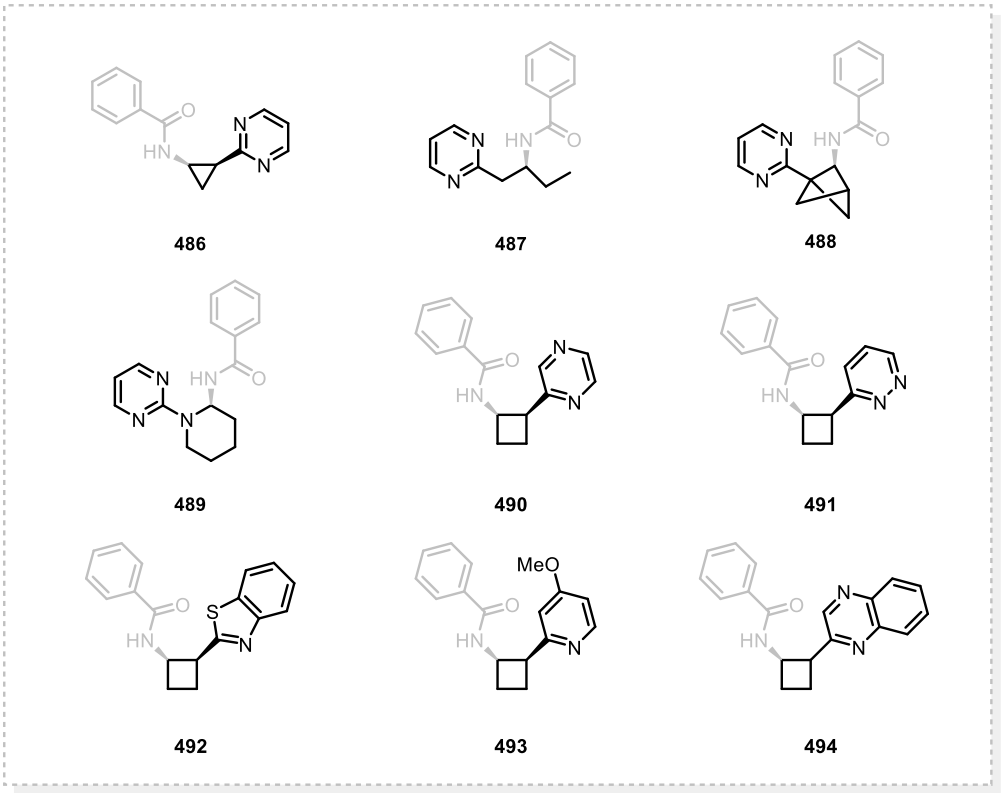
Scheme 72 Investigation of various cyclobutanes bearing other DGs.



[a] Standard reaction conditions: **a** (0.15 mmol), **336** (0.17 mmol, 1.1 equiv), $[Cp^*Rh(MeCN)_3](SbF_6)_2$ (10 mol%), (*R*)-**396** (20 mol%), Ag_2CO_3 (5 mol%), 1,4-dioxane (0.5 M), 80 °C, 5 h; Isolated yields; the er values were determined by chiral HPLC; [b] Reaction time: 2 h; [c] Reaction time: 1.5 h; [d] Reaction time: 1 h; [e] Reaction time: 0.5 h.

2.8.5 Unsuccessful examples

However, not all the substrates we evaluated furnished the anticipated amidated products (**Scheme 73**). Some other alkanes bearing a pyrimidine as the DG, such as 2-cyclopropylpyrimidine (**428**), acyclic 2-butylpyrimidine (**431**), and bicyclic 2-(bicyclo[1.1.1]pentan-1-yl)pyrimidine (**451**), did not yield the desired products. Under the standard reaction conditions, the smaller ring-sized 2-cyclopropylpyrimidine (**428**) was found to have decomposed completely after a 20 h reaction time, while both acyclic 2-butylpyrimidine (**431**) and bicyclic 2-(bicyclo[1.1.1]pentan-1-yl)pyrimidine (**451**) did not undergo the amidation reaction without any decomposition. Additionally, the heterocyclic 2-(piperidin-1-yl)pyrimidine (**453**) failed to undergo the desired transformation as well.



Scheme 73 Unsuccessful examples.

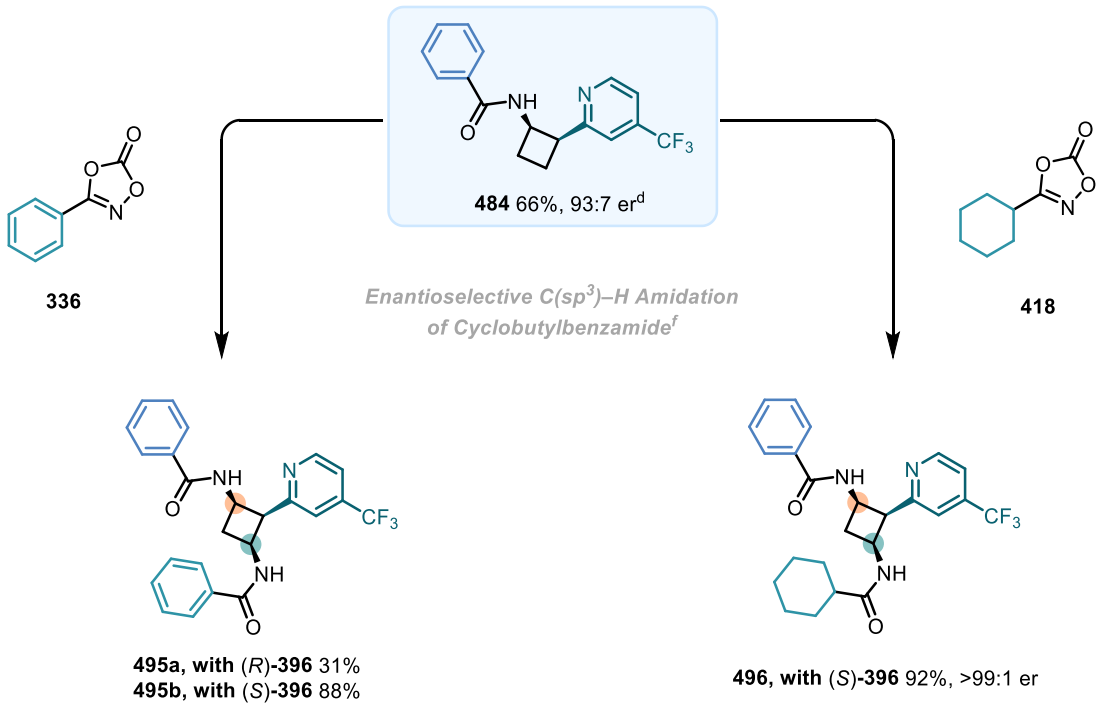
Despite the fact that pyridines exhibited greater reactivity in this transformation, unfortunately, cyclobutanes bearing other DGs (**Scheme 73**, **490-494**) were not compatible with the catalytic system.

2.9 Synthesis of cyclobutane containing three contiguous stereogenic centres

Based on the aforementioned outcomes, we envisaged the prospect of achieving a highly selective secondary amidation of cyclobutylbenzamide to establish the four-member ring containing three contiguous stereogenic centres within the same methodology (**Scheme 74**). Encouragingly, in the presence of 1.7 equivalents of dioxazolones **336**, we successfully obtained the desired bis-amidated product **495** from the mono-amidated cyclobutylpyrimidine **484**, albeit in a modest 31% yield after two amidation steps, only employing (*R*)-**396** as the ligand.

Interestingly, we found that replacing (*R*)-**396** with (*S*)-**396** in the second amidation process led to an 88% yield of the same symmetrical product after two steps. Similarly, by employing the favored (*R*)-**396** in the first amidation step and (*S*)-**396** in the second amidation step but using dioxazolone **418**, the asymmetrically disubstituted product **496** was readily synthesised with exceptional efficiency, furnishing a remarkable yield of 92% and an outstanding enantiomeric ratio of up to 99:1. These results demonstrated that the particularly impressive effectiveness and preciseness of the enantioselective control could be attributed to the chiral ligand within this catalytic system.

Scheme 74 Synthesis of cyclobutane containing three contiguous chiral centres.



[a] Standard reaction conditions: **484** (0.15 mmol), **b** (0.26 mmol, 1.7 equiv), $[Cp^*Rh(MeCN)_3](SbF_6)_2$ (10 mol%), (*R*)-**396**/(*S*)-**396** (20 mol%), Ag_2CO_3 (5 mol%), 1,4-dioxane (0.5 M), 80 °C, 5 h; Isolated yields; the er values were determined by chiral HPLC;

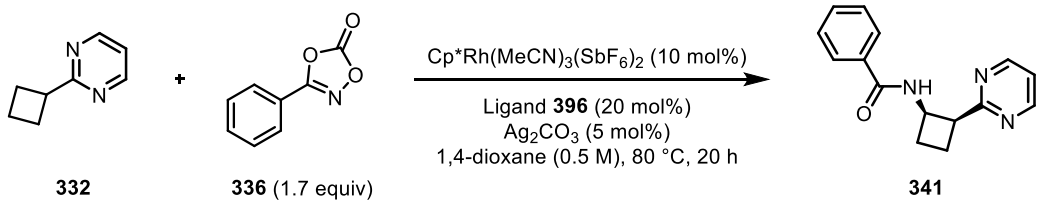
2.10 Mechanistic investigation

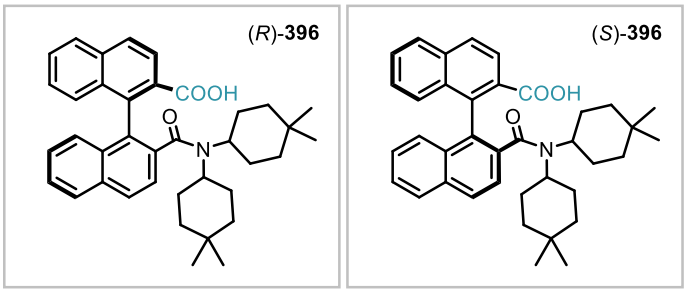
2.10.1 Non-linear effects

In order to elucidate the origin of enantioselectivity, a study was conducted to detect the relationship between the enantiomeric purities of the chiral carboxylic acid (CCA) and the obtained product (**Table 10**). Seven small vials were respectively charged with 2-cyclobutylpyrimidine **332** (0.15 mmol, 20.13 mg), dioxazolone **336** (0.26 mmol, 42.41 mg), (*R*)-**396** of different enantiomeric ratios (totally 16.75 mg, 0.2 equiv; a mixture of (*R*)-**396**

/(*S*)-**396** = 1/1; 3/2; 7/3; 3/1; 4/1; 9/1; 1/0), Ag_2CO_3 (2.06 mg, 0.05 equiv), $Cp^*Rh(MeCN)_3(SbF_6)_2$ (12.41 mg, 0.1 equiv), and 1,4-dioxane (0.3 mL, 0.5 M) under an air atmosphere. The resultant mixtures were subsequently stirred at 80 °C for 20 hours. After cooling to room temperature, the mixtures were concentrated, and the desired product **341** was obtained in different enantiomeric ratios after purification by silica gel column chromatography (neat pentane to pentane/EtOAc = 1/9 to neat EtOAc).

Table 10 Investigation into non-linear effects.



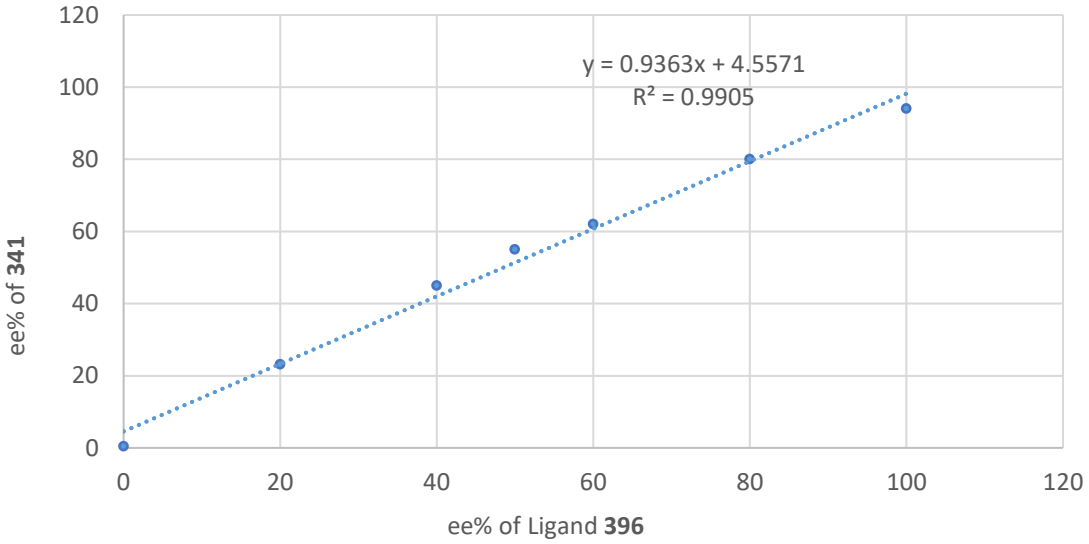


Entry	Ligand **396** ee%	**341** ee%
1	0	0
2	20	23
3	40	45
4	50	55
5	60	62
6	80	80
7	100	94

[a] Reaction condition: **332** (0.05 mmol), **336** (1.7 equiv), $Cp^*Rh(MeCN)_3(SbF_6)_2$ (20 mol%), Ligand **396** (20 mol%), 1,4-dioxane (0.25 M), 80 °C, 20 h, under air; All ^1H NMR yield; The er values were determined by chiral HPLC on a chiral stationary phase.

It was observed that as the proportion of enantiopure (*R*)-**396** increased in the added racemic mixture of the ligand, the enantioselectivity exhibited a proportional increase (**Table 10**).

A distinct linear correlation was discerned between the enantiomeric ratios of the product (*R*,*S*)-**341** and (*R*)-**396**, which indicated the absence of higher-order aggregates of the catalyst operating in the enantio-determining step of the reaction (**Scheme 75**).

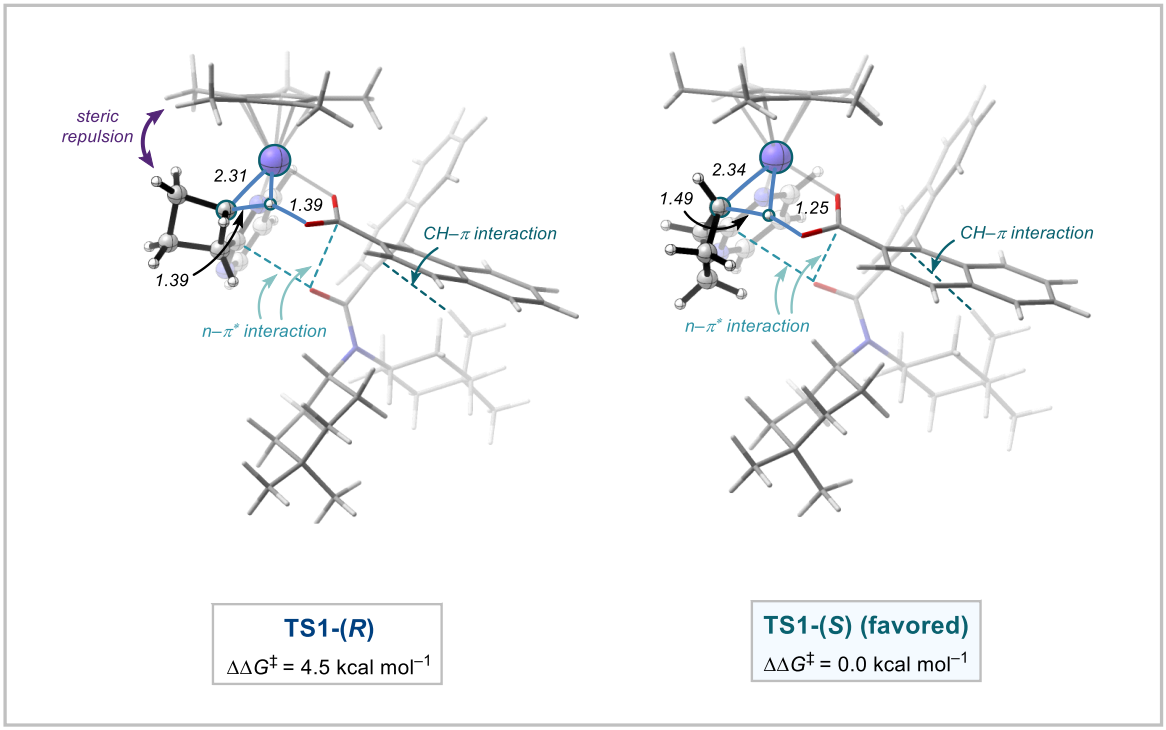


Scheme 75 Non-linear effects - the relationship between the ee of ligand **396** and product **341**.

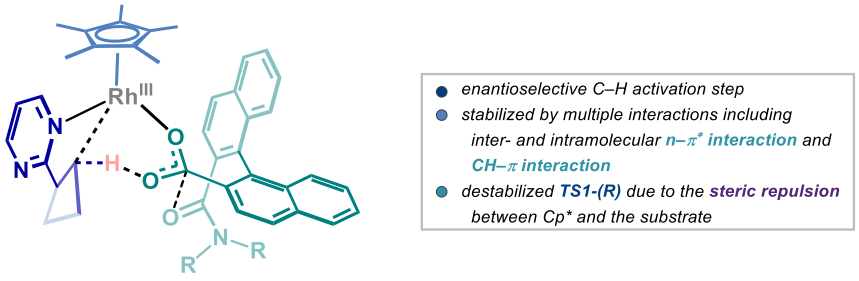
2.10.2 Computational study

To further investigate the role of axially chiral acid ligand for the rhodium(III)-catalysed enantioselective C−H amidation reaction, a density functional theory (DFT) study was performed (**Scheme 76**).[1] The reaction commenced with the coordination of the pyrimidine substrate **332** and the chiral acid co-catalyst (*R*)-**396** to the Cp*Rh(III) moiety, followed by the activation of the adjacent C–H bond on the cyclobutyl ring *via* the ambiphilic metal-ligand activation/concerted metalation deprotonation (AMLA/CMD) mechanism.[25] The computed transition structures (**TS**) for C–H activation led to the formation of the two enantiomeric products **TS1-(*R*)** and **TS1-(*S*)**. The reaction preferably proceeded through **TS1-(*S*)** that formed the *S*-configured product in agreement with the experimentally determined absolute stereochemical outcome of the reaction ($\Delta\Delta G^{\ddagger}$ = 4.5 kcal mol^{-1}).

[1] Computational analysis was performed by Dr. Ken Yamazaki, and data is included for completeness.



[a] (ΔG [kcal mol−1]) computed at the SMD(1,4-dioxane)/B3LYP-D3(BJ)/SDD(Rh)-6-311+G(d,p)//SMD(1,4-dioxane)/B3LYP-D3/LanI2dz(Rh)-6-31G(d) level of theory. Energies (kcal mol−1) and forming bond lengths (Å) of the TS geometries are provided in the insert.



Scheme 76 The key C–H activation transition state structures for the formation of (*R*)-product and (*S*)-product.

An intriguing feature that could be seen in these TSs was that the amide oxygen atom of the ligand contributes to the stabilization of TS conformations by both inter- and intramolecular *n*–π* interaction.[164] The empty π* orbital of the carboxylate group facilitated the acceptance of the lone-pair electron density of the amide nucleophile, resulting in acceleration of the AMLA/CMD process. In addition, the methyl group on cyclohexyl ring interacted with one of the naphthyl rings by an intramolecular CH–π interaction that led to an increased rigidity

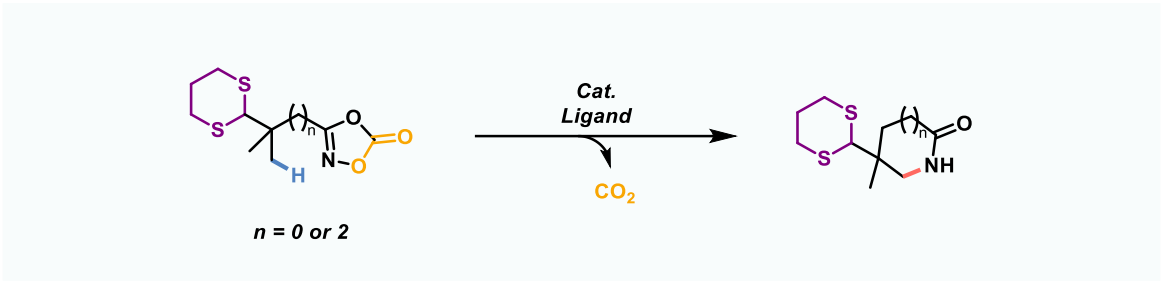
of the axially chiral acid ligand. The origin of the stereoselectivity for this transformation is that the cyclobutane moiety clashes with the Cp* ring in the unfavored transition state **TS1-(*R*)**, and thus the less sterically demanding **TS1-(*S*)** has a lower energy barrier. Therefore, the meticulous adjustment of the catalytic system enables the realization of a high degree of enantioselectivity through multiple stabilizing interactions and steric repulsions between the substrate and the catalyst.

2.11 Conclusions

In summary, we have developed an efficient azine-directed Cp*Rh(III)-catalysed C(sp^3)−H amidation of cyclobutanes. The introduction of a binaphthyl-based chiral carboxylic acid modified with *N*,*N*-4,4-dimethylcyclohexyl amide was demonstrated to be pivotal for the highly enantioselective desymmetrisation process. A wide array of substituted dioxazolones proved amenable to this transformation, furnishing the desired products with moderate to excellent enantioselectivity and yield. Furthermore, various amidated cycloalkylpyrimidines and cyclobutanes bearing other *N*-containing directing groups could also be prepared utilising this catalytic system. Enantioenriched bis-amidated cyclobutanes were rendered accessible under the general conditions. Detailed computational mechanistic studies suggest that the *n*−π interaction with pyrimidine and the amide moiety on the ligand, in conjunction with additional CH−π interactions involving the dimethyl groups on the ligand, contribute to the rigidity of the conformational arrangement. We anticipate that this reaction will serve as an impetus for the development of asymmetric synthesis of enantioenriched four-membered ring-containing drug-like molecules, and the unique chiral carboxylic acid employed herein can be applied to other stereoselective reactions in the future.

Chapter 3 Investigation Into Dithiane-directed Cp*Rh(III)-Catalysed Intramolecular C(sp^3)–H Amidation Reaction

3.1 Chapter Overview



Scheme 77 Dithiane-directed Cp*Rh(III)-catalysed intramolecular C(sp^3)–H lactamisation reaction.

This chapter presents the initial investigation into an intramolecular dithiane-directed C(sp^3)–H amidation reaction utilising a newly designed substrate that incorporates a dioxazolone moiety, an approach not previously explored to generate the lactam compounds (**Scheme 77**). The investigation encompasses two primary aspects: the synthesis of the novel model substrate and the exploration of intramolecular C(sp^3)–H activation methodologies aimed at synthesising the corresponding lactam compounds. Despite the successful preparation of these unique newly designed compounds, which feature both a dithiane group and a dioxazolone ring, the anticipated transformation process to generate cyclic amides did not occur under the many initially tested conditions.

3.2 Introduction

3.2.1 Intramolecular C–H annulation

Intramolecular C–H annulation represents a fascinating and highly efficient strategy in organic chemistry for constructing cyclic compounds through the direct functionalisation of C–H bonds within a molecule. This process is instrumental in synthesising various cyclic structures, which are core components of many biologically active molecules, pharmaceuticals, and natural products. By leveraging the inherent reactivity of C–H bonds in a molecule, intramolecular C–H cyclization enables the formation of rings of varying sizes, including five-membered, six-membered, and larger rings, with remarkable selectivity and efficiency. With the transition metal catalysts, it first facilitates the cleavage of the C–H bond and subsequent formation of a new carbon-carbon (C–C) or carbon-heteroatom (C−X) bond, thus closing the ring.[165, 166] Intramolecular C–H cyclization not only stands out for its ability to streamline synthetic pathways by reducing the number of steps, and avoiding the external reagents or pre-functionalised substrates, but also contributes to the development of sustainable chemical processes, aligning with the principles of green chemistry.

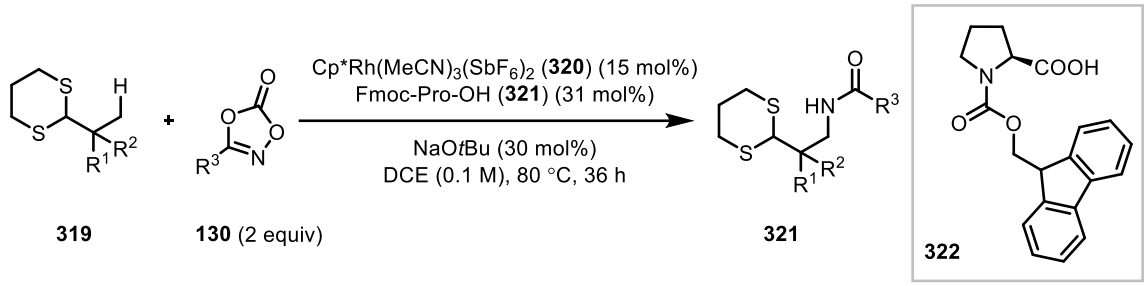
3.2.2 Dithiane-directed C(sp^3)−H functionalisation

Beyond the pyrimidine directing group, which showcases its efficiency in chelation-assisted C−H activation reaction, some other potential DGs, such as the sulfur-containing groups remain to be fully explored.[167, 168] Considering that sulfur in oxidation state 2 features

pronounced Lewis basicity, dithianes stand out for their synthetic flexibility and potential distinctive reactivity. In combination with their straightforward introduction and ease of removal for further functionalisation, dithianes embody the ideal characteristics sought in a directing group for the transition metal-catalysed direct C−H functionalisation reactions.

As mentioned in Chapter 2, the Dixon group reported the first example of the intermolecular Cp*Rh(III)-catalysed amidation of the unactivated C(sp^3)−H bonds utilising the easily installed and removable dithiane as the DG in 2019 (**Scheme 78**).[149] The bench-stable and highly reactive alkyl dioxazolones served as an efficient amide source in this novel catalytic system.[169] Yet, achieving dithiane-directed intramolecular C(sp^3)−H amidation has remained an elusive goal, which is full of potential and challenges.

Dixon, 2019



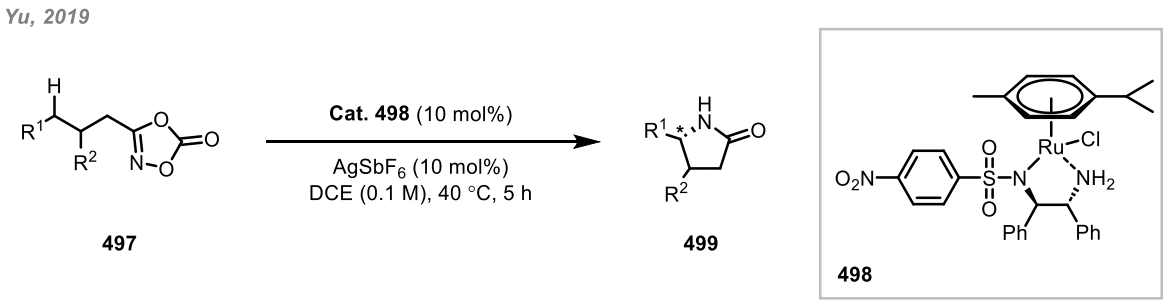
Scheme 78 Previous work on dithiane-directed intermolecular Rh(III)-catalysed C(sp^3)−H amidation.

3.2.3 Catalytic intramolecular C(sp^3)−H amidation to furnish Lactams

Lactams are known as a type of unique and pivotal cyclic amide scaffold considering their bioactivity and extensive use within drug discovery program.[170] Therefore, the development of synthetic approaches to prepare the lactam framework has drawn a significant amount of attention from the organic synthetic community. Given the impressive development of the

C(sp^3)−H activation strategy in organic chemistry, the direct approaches to access cyclic amides *via* transition metal catalysed intramolecular C(sp^3)−H amidation process have been accomplished furnishing a series of lactams from 1,4,2-dioxazol-5-ones.

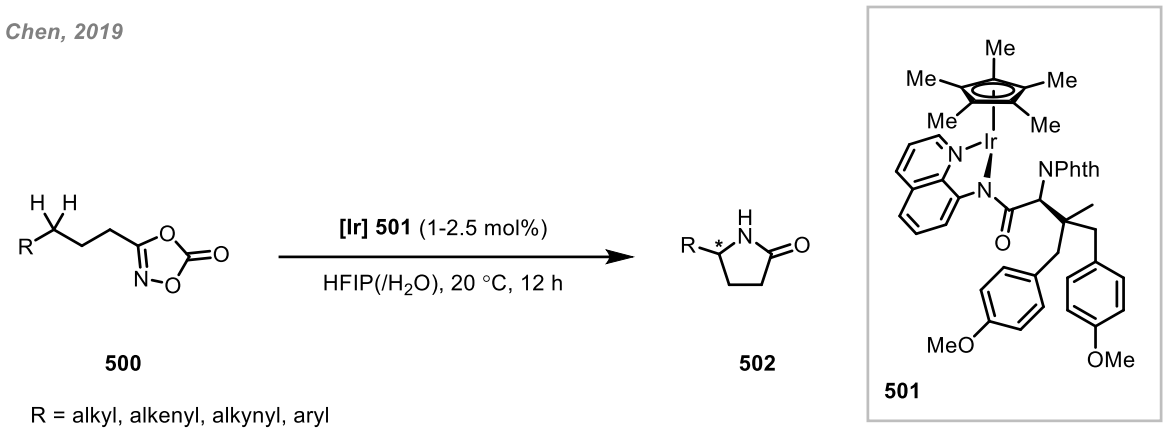
In 2019, Yu *et al.* initially revealed a ruthenium(II)-catalysed enantioselective γ-C(sp^3)−H bond amidation reaction for producing γ-lactams (**499**) from 1,4,2-dioxazol-5-ones derivatives (**497**), achieving yields up to 97% and enantiomeric excesses up to 98% through intramolecular carbonyl nitrene C−H insertion (**Scheme 79**).[171] This method utilised chiral diphenylethylene diamine ligands (**498**) with electron-withdrawing arylsulfonyl substituents, offering high chemo- and enantioselectivities, and suppressing Curtius-type rearrangement which was a common side reaction during this transformation. This enantioselective nitrene insertion process demonstrated broad tolerance to allylic/propargylic C−H bonds.



Scheme 79 Ruthenium(II)-catalysed γ-lactams formation by intramolecular C(sp^3)−H amidation of 1,4,2-dioxazol-5-ones derivate **497**.

In the same year, Chen *et al.* also reported a highly efficient and broadly applicable method for the asymmetric synthesis of γ-lactams *via* Ir(III)-catalysed enantioselective C(sp^3)−H amidation of dioxazolone substrates (**500)** (Scheme **80**).[172] Utilising a novel iridium complex (**501**) equipped with a newly designed α-amino-acid-based chiral ligand, this method proceeded with exceptional efficiency and enantioselectivity (up to 99.6% ee) at room temperature in HFIP/H_2O solvent. The authors reported that the Ir(III) catalyst (**501**)

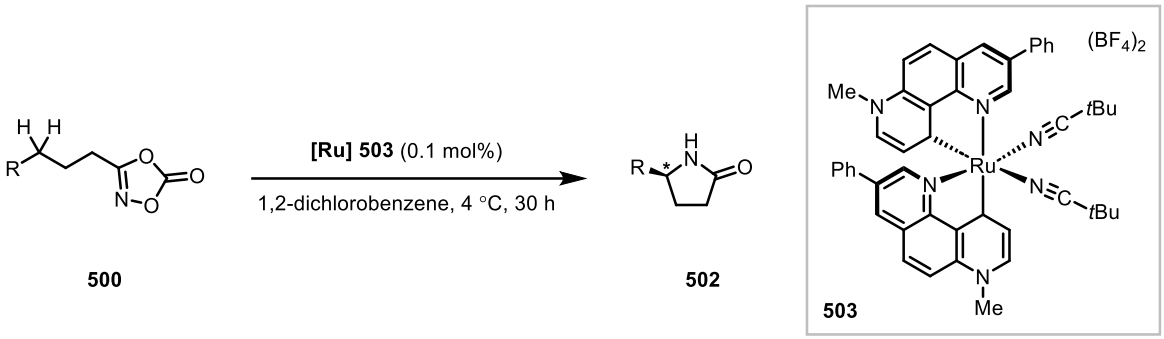
formed a well-defined groove-type chiral pocket around the iridium center, enabling the dioxazolone substrates to bind in various media, including polar or aqueous environments. This approach marks a significant departure from traditional steric repulsion-based methods, instead leveraging multiple attractive noncovalent interactions for enantiocontrol.



Scheme 80 Iridium(III)-catalysed enantioselective C(sp^3)−H amidation of dioxazolone.

Meggers *et al.* introduced a novel class of non-C_2-symmetric ruthenium catalysts (**Scheme 81**),[173] showcasing unprecedented efficiency in enantioselective intramolecular C(sp^3)−H amidation to produce chiral γ-lactams with exceptional enantiomeric ratios (up to 99:1) and extremely low catalyst loadings (down to 0.005 mol %). Interestingly, it was found that during this transformation, the overall chirality was initiated from the stereogenic metal center. When it was employed with a C_2-symmetric diastereomer ruthenium catalyst, the reaction favored an undesired Curtius-type rearrangement process, while the desired lactam products were achieved by using the non-C_2-symmetric ruthenium catalyst.

Meggers, 2019

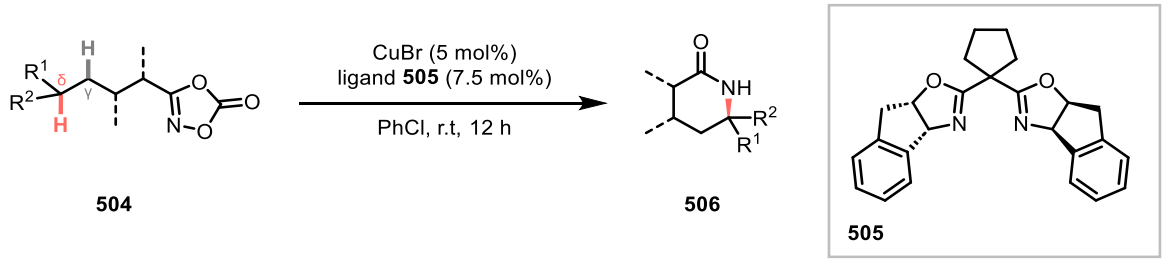


Scheme 81 Ru(III)-catalysed enantioselective C(sp^3)–H amidation of dioxazolone.

Despite the fact that there have been multiple notable achievements in asymmetric γ-lactam production through transition metal-nitrenoid transfers, it still lacks a decent approach to establish six-membered δ-lactams *via* such intramolecular direct δ-C(sp^3)–H amidation strategy. This gap is attributed to two main obstacles: the challenge of regioselectivity, which is exacerbated in molecules with competing γ- and δ-C–H bonds, and the complexities of achieving asymmetric C–N bond formation with existing mechanistic frameworks.[174]

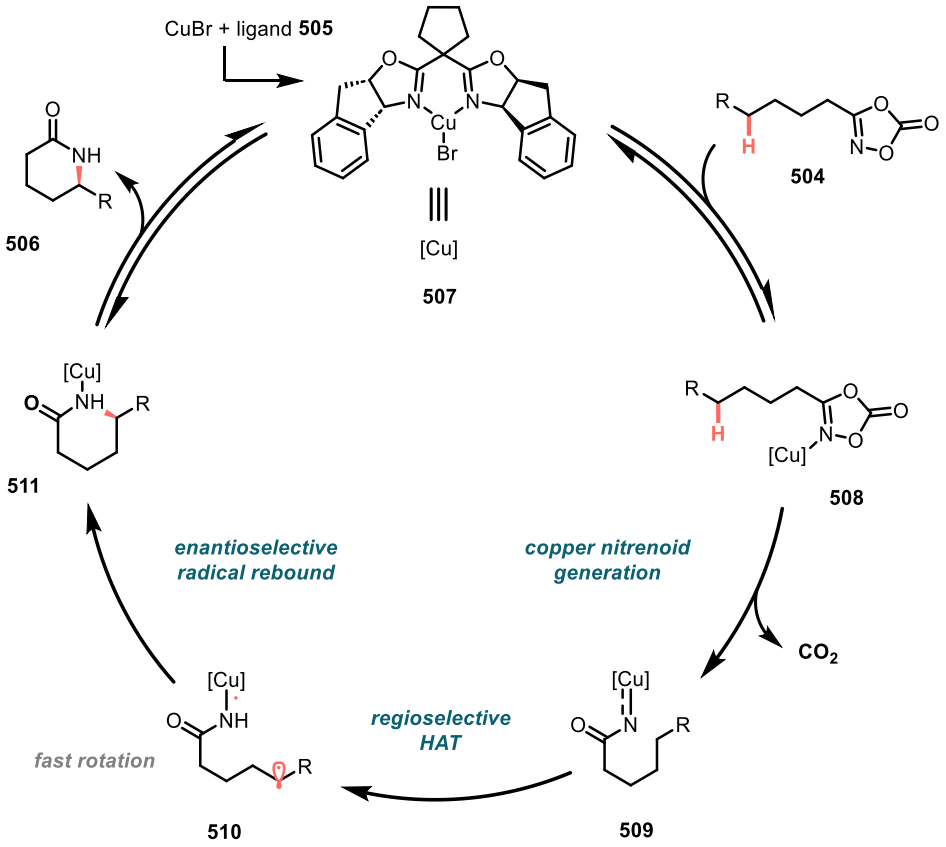
In 2023, the Chang group reported a novel methodology to attain six-membered δ-lactams as the main products through the asymmetric δ-C(sp^3)–H amidation catalysis of dioxazolones, in the presence of a Cu(I) precursor with a chiral bisoxazoline ligand (**505**). The target lactam products were furnished with up to >99:1 er enantioselectivity, while achieving an excellent regioselectivity control (up to >19:1 rr) (**Scheme 82**).[174]

Chang, 2023



Scheme 82 Enantioselective catalytic δ-C–H amidation of dioxazolones enabled by copper-nitrenoid transfer.

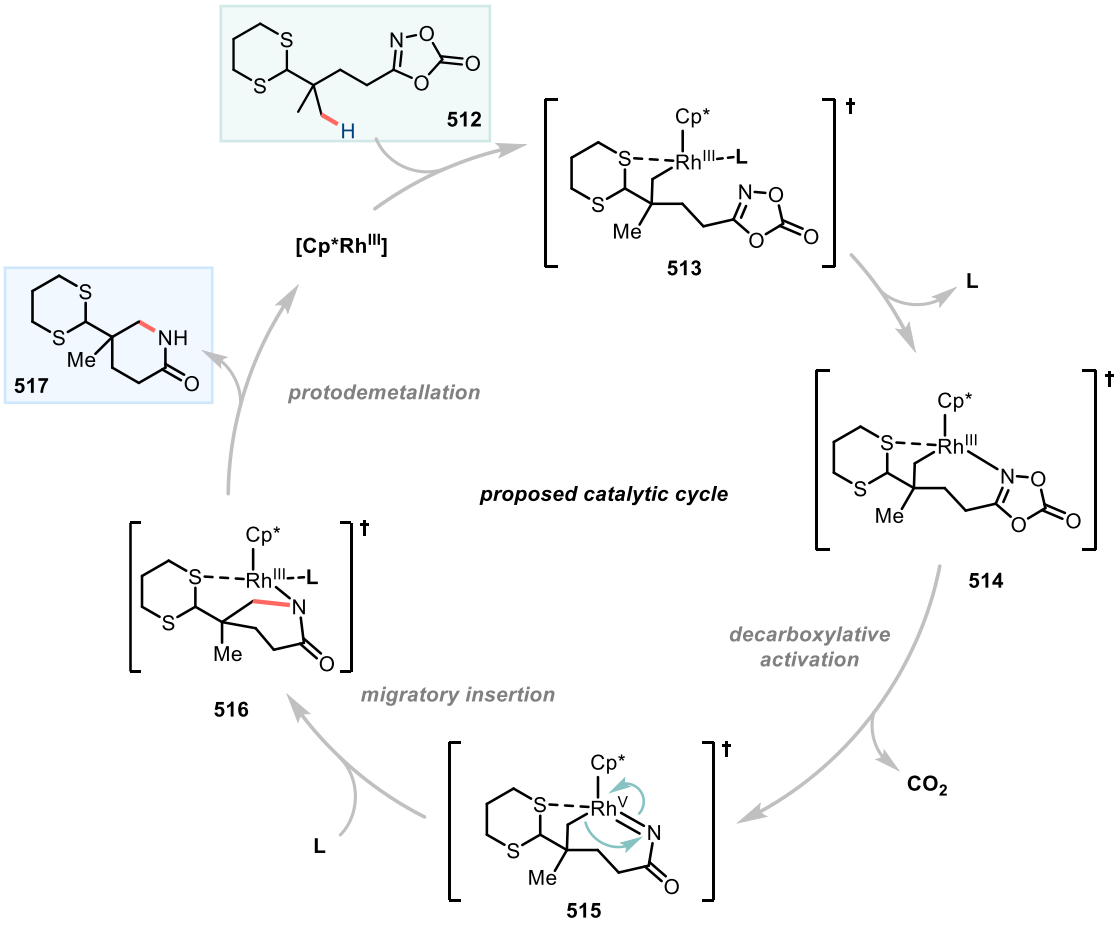
Based on DFT calculations and mechanistic experimental probes, a simplified catalytic cycle for this unique intramolecular δ-C(sp^3)−H amidation reaction is shown in **Scheme 83**. Firstly, a 16-electron species [Cu] was generated in situ through the coordination of CuBr and ligand **505**, which then bound with dioxazolone **504** to form the adduct **508**. Secondly, the species **508** released a CO_2 and generated an open-shell Cu-nitrenoid species **509**, which then proceeded with a regioselective intramolecular hydrogen bond transfer (HAT) leading to a radical species **510**. The C−N bond was then formed to furnish the intermediate **506** *via* a radical rebound which was the enantio-determination step in the overall catalytic cycle. Finally, the target chiral δ-lactam product **506** was released, while regenerating the cooper species to continue the catalytic cycle.



Scheme 83 Proposed catalytic cycle.

3.3 Project Aims

As mentioned above, the regioselective control, which selectively activates the δ-C(sp^3)–H to approach intermolecular lactamisation, remains full of challenges. Inspired by our success on the intermolecular C(sp^3)–H amidation, along with the synthetic versatility of dithianes, we were encouraged to design and synthesize a series of molecules with the potential to undergo intramolecular amidation. Such unique molecules **512** would involve both the dithiane directing group and dioxazolone moiety, which were linked by various carbon chains.



Scheme 84 Proposed catalytic cycle of Cp*Rh(III)-catalysed intramolecular C(sp^3)–H amidation of dioxazolone.

Based on the mechanism of previous intermolecular C−H amidation reaction with the electrophilic dioxazolones, the envisioned intramolecular reaction pathway was proposed in **Scheme 84**, where we anticipated that the dithiane could still first occupy the empty site on the rhodium centre of the Cp*Rh(III) catalyst to form the species **513** which has been revealed as important in our previous catalytic system. Ideally, the newly formed rhodium-dithiane complex **513** would further go through a cyclometallation with the C−H bond from adjacent methyl groups that contain an α-tertiary carbon atom, leading to a reactive cyclometallated intermediate **514**. The dioxazolone in the molecule would complex to the cyclometallated intermediate and subsequently release a carbon dioxide and a Rh(V)−nitrenoid species **515** from the decarboxylative activation process. It might then perform a similar migratory insertion of the Rh−C bond with the Rh(V)−nitrenoid species **515** to generate the intermediate **516**, which successfully occurred in the intermolecular C(sp^3)−H amidation process. Finally, the δ-lactam product would be furnished after protodemetallation.

Given the fact that such a newly planned project has many unknowns, the aim of this project compassed two main parts: i) synthesis of the model substrates, and, ii) investigation of novel intramolecular C(sp^3)−H cyclic amidation reactions (especially for the establishment of δ-lactams).

3.4 Synthesis of the Model Test Substrates

To test the viability of the proposed transformation, the dithianes were synthesised to combine with dioxazolone scaffold, which were bridged by carbon chains of different

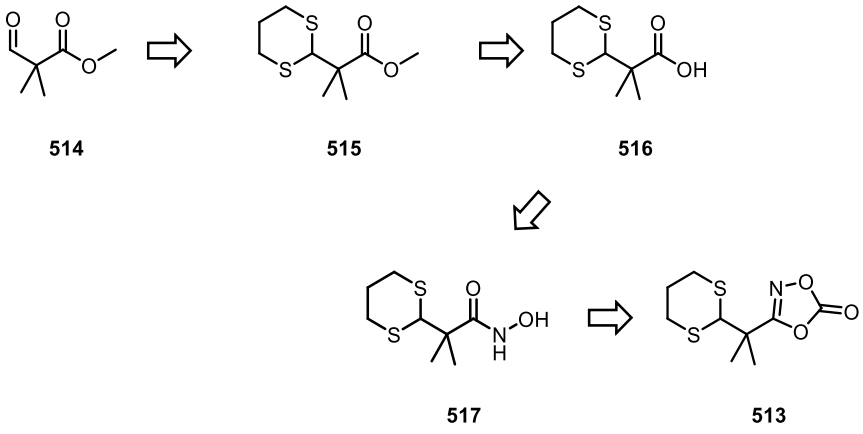
lengths (**Scheme 85**). The simple 3-(2-(1,3-dithian-2-yl)propan-2-yl)-1,4,2-dioxazol-5-one (**513**) and 3-(3-(1,3-dithian-2-yl)-3-methylbutyl)-1,4,2-dioxazol-5-one (**512**) were chosen as the model test substrates (**Scheme 85**), which were anticipated to form β- and δ-lactam, respectively.



513 512

Scheme 85 Model test substrates.

We envisaged that the aldehyde ester **514** could be converted to the corresponding dithiane scaffold **515** with 1,3-propanedithiol, which was a commonly used method to prepare dithiane products in high yields. Next, it required a hydrolysis of the ester to generate the carboxylic acid **516**.[155] Finally, the starting material dioxazolone derived dithiane compound **513** would be afforded by treating with carbonyldiimidazole (CDI) to further transform to its hydroxamic acid (**Scheme 86**).[153, 154]

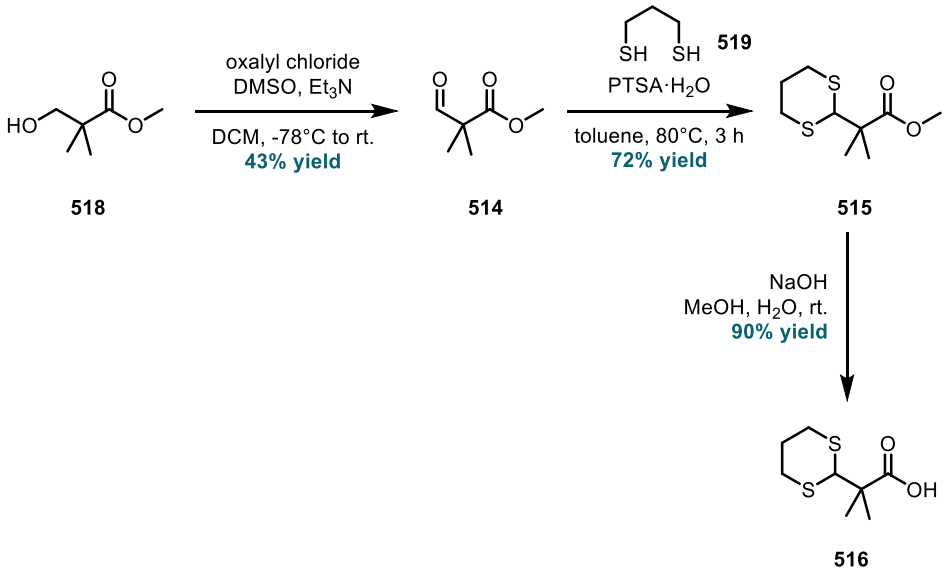


514 515 516 517 513

Scheme 86 Synthesis strategy for modern substrates.

3.4.1 Synthesis of 3-(2-(1,3-dithian-2-yl)propan-2-yl)-1,4,2-dioxazol-5-one

The synthesis of model substrate **513** began with treatment of the commercial methyl 3-hydroxy-2,2-dimethylpropanoate (**518**) with oxalyl chloride, DMSO and triethylamine *via* a Swern oxidation to afford the aldehyde **514** in 43% isolated yield (**Scheme 87**).[175] Next, the 1,3-dithiane **515** was obtained by the protection of aldehyde carbonyl group with dithiol **519** in 72% isolated yield. A hydrolysis of the ester **515** led to the carboxylic acid **516**, poised to undergo the amidation before further cyclisation to give the desired product.

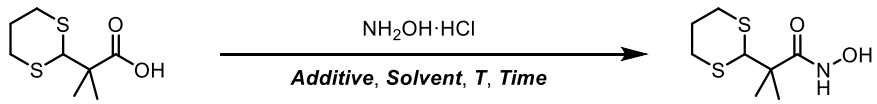


Scheme 87 Synthesis of 2-(1,3-dithian-2-yl)-2-methylpropanoic acid (**516**).

Based on our previous method to prepare dioxazolones, the carboxylic acid **516** was subsequently treated with CDI and hydroxylamine in order to generate the hydroxamic acid product. However, an attempt to utilise CDI as amide coupling reagent was unsuccessful (**Table 11, Entry 1**). The addition of 3 equivalents of K_2CO_3 was not helpful to activate the hydroxylamine hydrochloride and promote the reaction (**Table 11, Entry 2**), while replacing the solvent with mixture of THF/H_2O showed no reaction as well (**Table 11, Entry 3**).

Delightfully, analysis of the crude ^{1}H NMR spectrum demonstrated that using HATU (hexafluorophosphate azabenzotriazole tetramethyl tronium) as the peptide coupling reagent in the presence of hindered base DIPEA (*N*,*N*-Diisopropylethylamine), the expected compound **517** was furnished in 38% yield (**Table 11, Entry 4**). Additionally, the powerful oxalyl chloride was applied to the acid **516** and led to the target hydroxamic acid **517** in 90% yield *via* the nucleophilic substitution process of corresponding acid chloride (**Table 11, Entry 5**).

Table 11 Synthesis of hydroxamic acid.

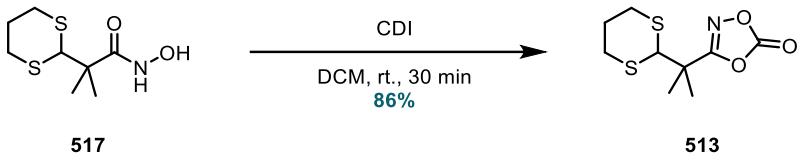


516 **517**

Entry	Additives (mol%)	Solvent	Time	T (°C)	Yield (%)[f]
1[a]	CDI	THF	1 h then o/n	rt	0
2[b]	CDI, K_2CO_3	THF	1 h then o/n	rt	0
3[c]	CDI	THF, H_2O	1 h then o/n	rt	0
4[d]	HATU, DIPEA	DMF	15 min then 2 h	rt	38
5[e]	$(COCl)_2$, DMF, K_2CO_3	EtOAc/H_2O	4 h then 12 h	rt then 0 °C to rt	90

Reaction condition: [a] **516** (0.05 mmol), $NH_2OH{\cdot}HCl$ (6 equiv), CDI (1.2 equiv), THF (0.5 M, 0.1 mL), rt, overnight; [b] **516** (0.05 mmol), $NH_2OH{\cdot}HCl$ (6 equiv), CDI (1.2 equiv), K_2CO_3 (3 equiv), THF (0.5 M, 0.1 mL), rt, overnight; [c] **516** (0.05 mmol), $NH_2OH{\cdot}HCl$ (6 equiv), CDI (1.2 equiv), THF/H_2O= 1:1 (0.5 M, 0.1 mL), rt, overnight; [d] **516** (0.05 mmol), $NH_2OH{\cdot}HCl$ (1.2 equiv), HATU (1.2 equiv), DIPEA (3.6 equiv), DMF (0.15 M, 0.1 mL), rt, overnight; [e] **516** (1.5 mmol), $NH_2OH{\cdot}HCl$ (1.2 equiv), $(COCl)_2$ (2 equiv), DMF (1 drop), K_2CO_3 (2 equiv) EtOAc/H_2O = 2:1 (0.9 M, 1.6 mL), rt, 12 h; [f] All ^{1}H NMR yield.

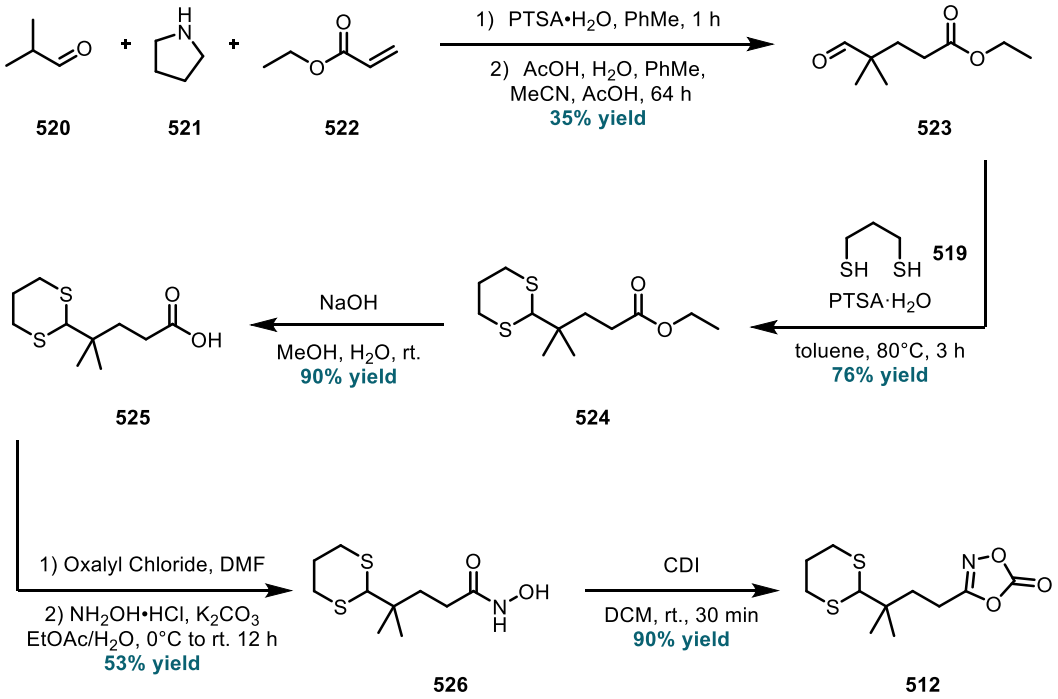
Finally, in the presence of CDI the desired model substrate **513** was successfully synthesised from hydroxamic acid **517** in 86% yield (**Scheme 88**).



Scheme 88 Cyclisation of hydroxamic acid (**517**).

3.4.2 Synthesis of 3-(3-(1,3-dithian-2-yl)-3-methylbutyl)-1,4,2-dioxazol-5-one

A one-pot reaction *via* a reduction of the initially generated enamine in combination with alkene **522**,[176] was first performed affording the starting material **523** in 35% yield, and then underwent the similar synthetic route mentioned above, it successfully obtained the desired model substrate **512** (**Scheme 89**).

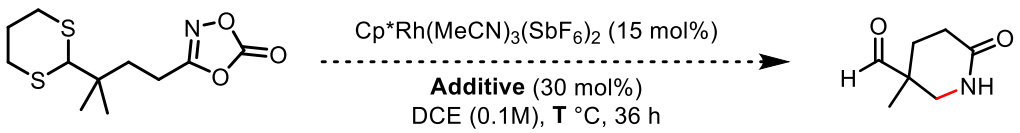


Scheme 89 Synthesis of model substrate **512**.

3.5 Preliminary Studies of Dithiane-directed Cp*Rh(III)-Catalysed Intramolecular C(sp^3)−H Cyclisation Reaction

With the model substrates in hand, we began our investigations by evaluating Cp*Rh(III) catalysis applied to the dioxazolone derived dithiane **512**. Following up on previous studies on intermolecular amidation of C(sp^3)−H bond carried out in Dixon group, the test reactions were performed with the use of 15 mol% $[Cp^*Rh(MeCN)_3][(SbF_6)_2]$ catalyst in combination with variety of sodium salt additives (30 mol%) in 0.1 M dichloroethane as solvent at different temperatures for 36 h (**Table 12**). The sodium salt additives were generated in situ by 30 mol% of carboxylic acid ligand with equimolar amounts of sodium *tert*-butoxide. Under the previous condition which was in the presence of Fmoc-Pro-ONa (**323**) at 80 °C, unfortunately, no desired δ-lactam product was detected after 36 h (**Table 12, Entry 1**). Increasing temperature to 120 °C was inefficient to push the reaction (**Table 12, Entry 2**). Replacing the Fmoc-Pro-OH (**322**) with benzoic acid, there was no intramolecular amidation observed, while acetic acid was unhelpful also (**Table 12, Entry 5 & 6**). The reaction was still unsuccessful to process without additives (**Table 12, Entry 3 & 4**). Additionally, applying the initial reaction condition on model substrate **512**, there was still no formation of the desire amidated product generated.

Table 12 Initial screening of the reaction condition[a]



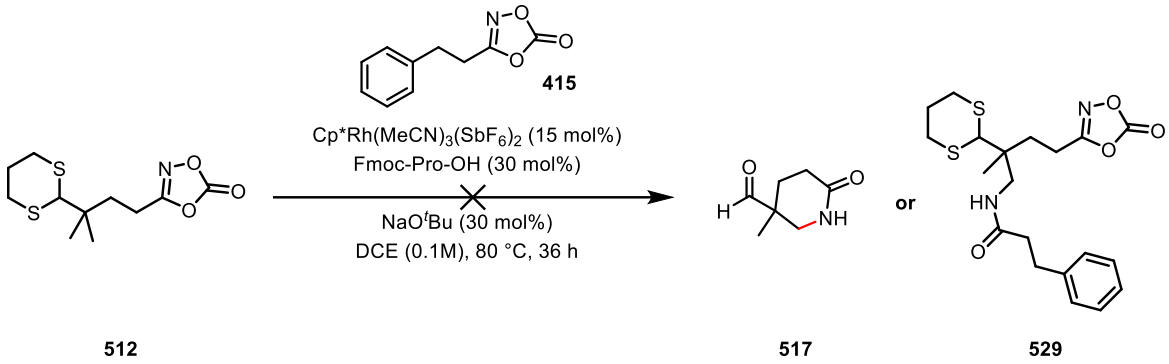
512 **517**

Entry	Additive	T (°C)	Yield (%)
1	Fmoc-Pro-ONa (**323**)	80	0
2	Fmoc-Pro-ONa (**323**)	120	0
3	-	120	0
4	PhCOOH (**333**)	80	0
5	PhCOONa (**527**)	80	0
6	NaOAc (**528**)	80	0

[a] Reaction conditions: **512** (0.05 mmol), $[Cp^*Rh(MeCN)_3][(SbF_6)_2]$ catalyst (15 mol%), **Additive** (30 mol%), DCE (0.1 M, 0.5 mL), 36 h;

It was a profound disappointment that the standard conditions employed for the intermolecular reaction utterly precluded any intramolecular reaction from occurring on the designed dithiane compound, despite merely altering the additive and reaction temperature. To substantiate the reactivity of the targeted C−H bond in the designed dithiane, a probative experiment was undertaken, which indicated that the targeted C−H bond could not undergo cleavage under the specified conditions (**Scheme 90**). An equimolar quantity of 3-phenethyl-1,4,2-dioxazol-5-one (**415**) was introduced into the system. If the directing group were to function optimally in accordance with the precepts of previously reported work, the $C(sp^3)$−H amidation should have occurred utilising compound **415** as the amide source and generated the amidated product **529**. However, no reaction was observed, intimating that the catalyst was likely deactivated owing to its stable binding when the dithiane-DG and

dioxazolone coexisted within a substrate. Given the characteristic structure of this type of model substrates, we nevertheless anticipated that it could engender a breakthrough in the intramolecular C−H lactamisation reaction. Regrettably, due to time constraints, we were unable to undertake further exploration for this project.



Scheme 90 Test experiment to detect the reactivity of the aimed C−H bond under the initial reaction condition.

3.6 Conclusion and Future Work

In conclusion, a novel class of dioxazolone-derived dithiane compounds has been synthesised successfully. Subsequently, preliminary investigations aimed at achieving the intramolecular C−H activation of such materials were undertaken, predicated upon our antecedent studies on dithiane-directed intermolecular C(sp^3)−H amidation. Unfortunately, it demonstrated to be an exceedingly formidable challenge, and we were unable to validate the transformation we had envisaged. In future endeavors, we anticipate that the hitherto undiscovered dithiane-directed intramolecular C−H cyclisation could be successfully achieved to synthesize the valuable lactam products, while the directing group could be employed efficiently to control the regioselectivity and thereby control the size of the resultant lactam rings.

Chapter 4 Final Remarks and Future Studies

This thesis investigates and develops a novel intermolecular Cp*Rh(III)-catalysed enantioselective C(sp^3)–H amidation of cyclobutanes, providing a new methodology to access enantioenriched *cis*-configured amido-cyclobutane scaffolds with good to excellent yield and enantioselectivity. For the first time, the widely employed strongly coordinating directing groups, such as pyrimidine and pyridine, were assembled with a saturated cyclobutane ring directly to facilitate the selective β-C(sp^3)–H amidation. A library of chiral ligands was designed and synthesised. Among them, a finely-tuned binaphthyl-based chiral mono-carboxylic acid modified with *N*,*N*-4,4-dimethylcyclohexyl amide was introduced to access high enantiocontrol. A wide range of substrate scopes for alkylpyrimidines and dioxazolones were evaluated, demonstrating great tolerance to diverse functional groups. Notably, bis-amidated cyclobutanes containing three contiguous chiral centres were successfully accessed within this catalytic system. Computational studies further elucidated the inter- and intramolecular interactions among the ligand and substrates.

As the inaugural work discovering the utilisation of strongly coordinating groups in C–H activation of cyclobutanes catalysed by Cp*Rh(III) complexes, the directing groups were installed directly onto the cyclobutane ring to simplify the transition-state geometries of the C–H activation step. However, this strategy also led to the challenge of directing group removal after C–H functionalisation. Hence, it is imperative to further modify the directing group in future work to improve its removability or further modifiability. Additionally, direct C–H functionalisation of some alkylpyrimidines, such as bicyclic or acyclic substrates, remained challenging within this catalytic system. Nevertheless, we believe that this

objective is viable through further modification of chiral ligands. More diverse electrophiles should be investigated to develop variants of this transformation.

Furthermore, a unique dioxazolone-derived dithiane was designed and synthesised to evaluate the Cp*Rh(III)-catalysed intramolecular C(sp^3)–H amidation for the establishment of lactams of varying ring sizes. However, due to time constraints, we were unable to validate this unexplored transformation.

Chapter 5 Experimental Section

5.1 General Information

Reactions were carried out under air in oven-dried glassware at room temperature (rt = 20 - 25 °C) unless stated otherwise. Standard inert atmosphere techniques were used in handling all air and moisture sensitive reagents. Solvents were removed under reduced pressure using BÜCHI rotavapor apparatus.

a) Solvents and reagents

All solvents were commercially supplied or dried by filtration through activated alumina (powder ~150 mesh, pore size 58 Å, basic, Sigma-Aldrich) columns. Organic solvents refer to the fraction collected between 30-40 °C. All water used was purified *via* a Merck Millipore reverse osmosis purification system prior to use. All reagents were obtained from commercial suppliers and used without further purification. All reactions were performed using oven-dried glassware and standard Schlenk technique, if necessary, unless otherwise stated.

b) Chromatography

Thin-layer chromatography (TLC) was performed using Merck aluminium backed sheets coated with Merck Kieselgel 60 F254 (230-400 mesh) fluorescent treated silica, which were visualised under UV light (λmax= 254 or 365 nm) or by staining with aqueous basic $KMnO_4$ or aqueous acidic vanillin. **Flash column chromatography** was performed using silica gel 60 (VWR, 40-63 μm).

c) Spectroscopy

All **^{1}H, ^{13}C, and F^{19} NMR spectra** were recorded using a Bruker DPX200 (200 MHz), Bruker AVIII HD 400 (400/101 MHz), Bruker AVIIIHD 500 (500/101 MHz), Bruker NEO 600 (600/101 MHz) spectrometers. Chemical shifts (δ) are given in ppm, coupling constants (*J*) are reported in hertz (Hz), and rounded to the nearest 0.5 Hz. Two-dimensional spectroscopy (COSY, HSQC and HMBC) was used to assist in the assignment and the data is not reported.

IR spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer deposited as a thin film on a diamond ATR module.

Low resolution mass spectra were recorded on a Waters LCT premier XE Micromass spectrometer (ESI) operating in positive and negative ionisation mode.

High resolution mass spectra (HRMS) were recorded on BioAccord 2 - Loop Injection MS (- ion) Flow injection analysis was performed on an ACQUITY I-Class PLUS UPLC System (Waters, Milford, MA, USA) coupled to an ACQUITY RDa mass spectrometer (Waters, Milford, MA, USA) equipped with an ESI probe, in negative ion mode. The flow rate was set to 0.300 mL/min using a 50% methanol(aq) + 0.1% formic acid eluent. Scan parameters were set as follows: analyser mode, full scan; scan range, 50 2000 m/z; scan rate, 2 Hz; cone voltage, 40 V; capillary voltage, 0.8 kV; desolvation temperature, 550 °C; and intelligent data capture, on.

$[\alpha]_D^T$ values are reported in 10^{-1} deg·cm^2·g^{-1}; concentrations (c) are quoted in g/100 mL; D refers to the D-line of sodium (589 nm); temperatures (T) are given in degrees Celsius (°C). (+) and (–) compound number prefixes indicate the sign of the optical rotation. Optical rotations were tested using a Perkin Elmer 241 optical activity polarimeter at 25 °C.

Enantiomeric ratios were determined by chiral high-performance liquid chromatography (**HPLC**) analysis or by chiral supercritical fluid chromatography (**SFC**) analysis. Chiral HPLC analysis was performed on an Agilent 1200 series instrument using an appropriate chiral stationary phase column, specified in the individual experiment, and by comparing the samples with the appropriate racemic mixtures. Chiral SFC analysis was performed on a Waters Acquity UPC2 instrument using an appropriate chiral stationary phase column, specified in the individual experiment, and by comparing the samples with the appropriate racemic mixtures.

d) Melting points

Melting points (m.p.) were recorded using a Leica Galen III hot-stage microscope apparatus and are reported uncorrected in degrees Celsius (°C).

e) X-Ray Crystallography

Low temperature single crystal X-ray diffraction data were collected using a Rigaku Oxford Diffraction SuperNova diffractometer. Raw frame data were reduced using CrysAlisPro and the structures were solved using 'Superflip' before refinement with CRYSTALS as per the SI (CIF).

f) Names

Compound names are those generated by ChemDraw version 22.0.0.22 following the IUPAC nomenclature.

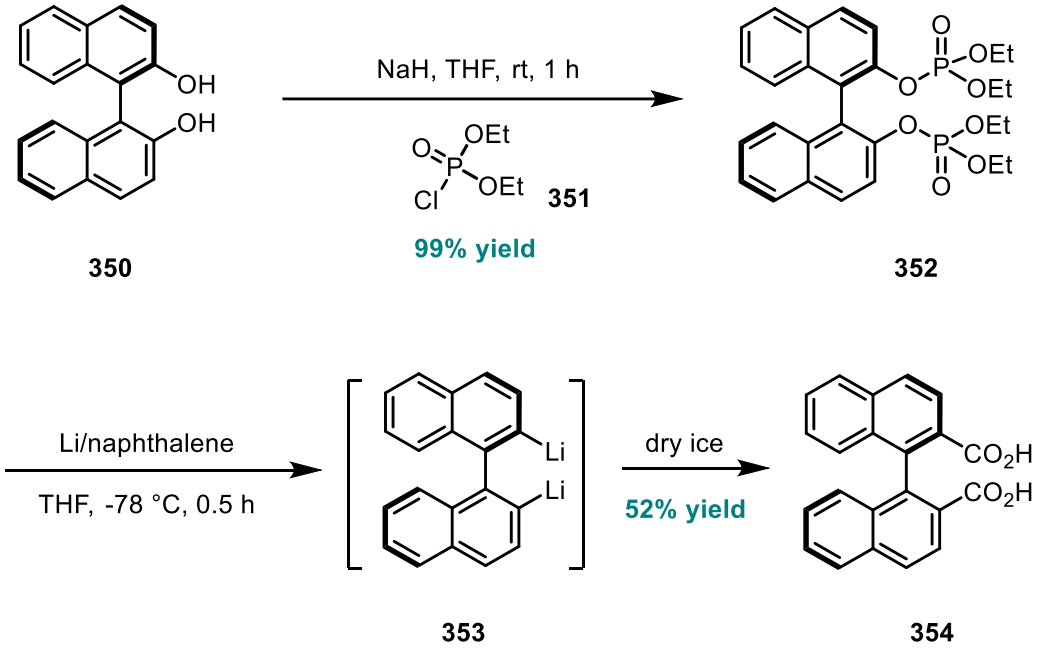
5.2 Experimental Details for Chapter 2

5.2.1 Preparation of ligands

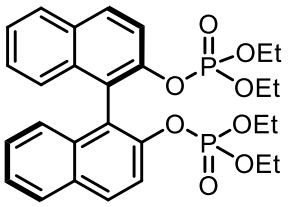
5.2.1.1 Synthesis of ligands 354 and 378

The **354**,[161] and **378**[177] were prepared according to the previously reported literature.

Synthesis of (*R*)-1,1'-binaphthyl-2,2'-dicarboxylic acid (354)



(*R*)-1,10-binaphthyl-2,20-bis(diethylphosphate) (352)



To a solution of (*R*)-BINOL (**350**) (10 g, 35 mmol) in THF (100 mL) was slowly added NaH (60% in oil, 3 g, 75 mmol) at 0 °C, and stirred for 30 min, then diethyl chlorophosphite (**351**) (11 mL, 76 mmol) was added, and stirred for 30 min at room temperature. The reaction was quenched with aqueous saturated NH_4Cl and the mixture was extracted with ethyl acetate. The organic layer was dried over Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate=1/1) to provide the diethylphosphate **352** as a colorless solid (18.9 g, quant. yield).

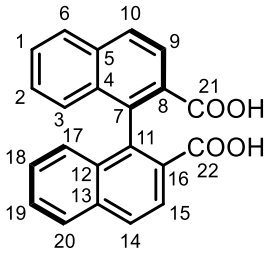
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97 (d, *J* = 9.0 Hz, 2H, Ar<u>H</u>), 7.90 (dt, *J* = 8.3, 8.0 Hz, 2H, Ar<u>H</u>), 7.79 (dd, *J* = 9.1 Hz, 2H, Ar<u>H</u>), 7.43 (m, 2H, Ar<u>H</u>), 7.36–7.24 (m, 4H, Ar<u>H</u>), 3.81–3.62 (m, 4H, OC<u>H</u>$_2$CH$_3$), 3.49 (m, 4H, OC<u>H</u>$_2$CH$_3$), 1.06 (t, *J* = 7.1 Hz, 6H, OCH$_2$C<u>H</u>$_3$), 0.84 (t, *J* = 7.1 Hz, 6H, OCH$_2$C<u>H</u>$_3$).

^{13}C NMR (101 MHz, $CDCl_3$): δ 146.9 (<u>C</u>–O), 133.7 (Ar<u>C</u>), 130.9 (Ar<u>C</u>), 128.0 (Ar<u>C</u>), 127.1 (Ar<u>C</u>), 126.3 (Ar<u>C</u>), 125.5 (Ar<u>C</u>), 121.8 (Ar<u>C</u>), 121.7 (Ar<u>C</u>), 119.4 (Ar<u>C</u>–Ar<u>C</u>), 64.5 (O<u>C</u>H$_2$CH$_3$), 64.2 (O<u>C</u>H$_2$CH$_3$), 15.9 (<u>C</u>H$_3$), 15.7 (<u>C</u>H$_3$).

HRMS (ESI) m/z calcd. for $C_{28}H_{33}O_8P_2$ ($[M+H]^+$) 559.1645, found 559.1640.

Analytical data for the isolated compound were identical with reported values.[162]

(*R*)-1,1'-binaphthyl-2,2'-dicarboxylic acid (354)



Lithium (104 mg, 6 equiv, 15 mmol) and naphthalene (1.229 g, 6 equiv, 15 mmol) were weighed into a flask, which had been flame-dried under vacuum. The flask was evacuated and refilled with argon, and THF (25 mL) was added to it. The mixture was sonicated for 2 h at room temperature to completely dissolve, then cooled to -78 ºC. A solution of (*R*)-1,10-binaphthyl-2,20-bis(diethylphosphate) **352** (1.397 g, 2.5 mmol) in THF (25 mL) was slowly added to the mixture. After stirring for 30 min, the dry ices were added into the reaction mixture quickly, and stirred for 2 h, then the mixture was allowed to warm up to room temperature, and finally quenched the reaction with aqueous 1 N HCl. The mixture was extracted with diethyl ether, and then 1 N NaOH was added to the organic phase. The resulting aqueous layer was washed with diethyl ether. The aqueous phase was acidified with 1 N HCl, and extracted with ethyl acetate. The organic phase was washed with brine, dried over $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (pentene/ethyl acetate = 6/4 with 1% AcOH) to give the dicarboxylic acid **354** (483.4 mg, 56%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.09 (d, J = 8.8 Hz, 2H, $H^{3, 17}$), 7.96 – 7.91 (m, 2H, $H^{4, 10}$), 7.91 – 7.87 (m, 2H, $H^{6, 20}$), 7.47 (ddd, J = 8.1, 6.7, 1.2 Hz, 2H, $H^{9, 15}$), 7.12 (ddd, J = 8.3, 6.7, 1.3 Hz, 2H, $H^{2, 18}$), 6.88 (dd, J = 8.5, 1.1 Hz, 2H, $H^{1, 2}$).

^{13}C NMR (101 MHz, $CDCl_3$): δ 172.3 ($C^{21, 22}$), 141.7 ($C^{5, 13}$), 135.4 ($C^{7, 11}$), 133.0 ($C^{4, 12}$), 129.2 ($C^{9, 15}$), 128.4 ($C^{6, 20}$), 128.1 ($C^{8, 16}$), 128.0 ($C^{10, 14}$), 127.5 ($C^{3, 17}$), 126.7 ($C^{2, 18}$), 126.6 ($C^{1, 19}$).

HRMS (ESI) m/z calcd. for $C_{52}H_{57}O_6$ ($[M+H]^+$) 343.0970, found 343.0968.

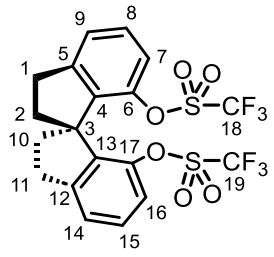
Analytical data for the isolated compound were identical with reported values.[178]

Synthesis of (*R*)-1,1′-spirobiindanyl-7,7′-dicarboxylic acid (378)



530 **531** **532** **378**

(*R*)-7,7'-bis(trifluoromethanesulfonyloxy)-1,1‘-spirobiindane (531)



In a 10 mL round-bottom flask, (*R*)-SPINOL (**530**) (155 mg, 0.62 mmol, 1 equiv) and pyridine (0.22 mL, 2.73 mmol, 4.4 equiv) were dissolved in DCM (3 mL, 0.2 M). The resulting solution was cooled down to 0 °C and trifluoromethanesulfonic anhydride (0.23 mL, 1.36 mmol, 2.2 equiv) was added dropwise. The resulting mixture was stirred overnight at room temperature. After that, the mixture was removed the solvent, diluted with EtOAc, and then washed with 5% HCl, sat. NaHCO3 and brine respectively. The organic layer was

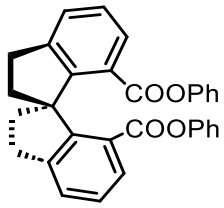
dried over Na_2SO_4 and evaporated. The resulting crude oil was purified by flash chromatography on silica gel (pentane/EtOAc = 20/1) to get the product **531** as a white solid (315 mg, quant. yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33 – 7.21 (m, 4H, Ar<u>H</u>), 7.13 (d, *J* = 1.9 Hz, 1H, Ar<u>H</u>), 7.11 (d, *J* = 2.0, 1.0 Hz, 1H, Ar<u>H</u>), 3.17 – 3.05 (m, 2H, C<u>H</u>$_2$), 3.09 – 3.00 (m, 2H, C<u>H</u>$_2$), 2.42 – 2.33 (m, 2H, C<u>H</u>$_2$), 2.33 – 2.24 (m, 2H, C<u>H</u>$_2$).

^{13}C NMR (101 MHz, $CDCl_3$): δ 147.8 (C^6), 146.0 (C^{17}), 138.2 ($C^{5, 12}$), 129.5 ($C^{4, 13}$), 124.4 ($C^{8, 15}$), 119.3 ($C^{9, 14}$), 118.4 ($C^{18, 19}$), 116.6 ($C^{7, 16}$), 59.5 (C^3), 38.8 ($C^{2, 10}$), 31.2 ($C^{1, 11}$).

Analytical data for the isolated compound were identical with reported values.[177]

Diphenyl (*R*)-2,2',3,3'-tetrahydro-1,1'-spirobi[indene]-7,7'-dicarboxylate (532)



An autoclave tube was loaded with $Pd(OAc)_2$ (26.12 mg, 0.116 mmol, 10 mol%), (*R*)-7,7'-bis(trifluoromethanesulfonyloxy)-1,1‘-spirobiindane **531** (600 mg, 1.16 mmol) and 1,3-bis(diphenyphosphino)propane (71.88 mg, 15.68 mmol, 15 mol%). The vessel was sealed with a septum and purged 3 times with N_2. DIPEA (2.4 mL, 14 mmol, 12 equiv) and phenyl formate (1.04 mL, 9.28 mmol, 8 eq.) were added via syringe under flux of nitrogen, the tube was shortly open to air to be inserted in the autoclave which was next purged three times with argon. The autoclave was sealed, and the reaction mixture was stirred for 48 hours at

120 °C. The reaction mixture was cooled down to room temperature, diluted with DCM and washed with water and brine, dried over Na_2SO_4 and evaporated. Product **24** was purified by flash chromatography on silica gel (Pentane/DCM = 2/1) as a white solid (448 mg, 84 %).

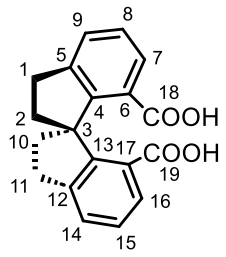
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 (d, *J* = 7.9, 1.1 Hz, 2H, Ar<u>H</u>), 7.36 (d, *J* = 7.5, 1.1 Hz, 2H, Ar<u>H</u>), 7.28 – 7.19 (m, 8H, Ar<u>H</u>), 7.16 – 7.07 (m, 2H, Ar<u>H</u>), 6.79 – 6.71 (m, 4H, Ar<u>H</u>), 3.19 – 2.97 (m, 4H, C<u>H</u>$_2$), 2.83 – 2.70 (m, 2H, C<u>H</u>$_2$), 2.35 (ddd, *J* = 11.9, 7.6, 1.2 Hz, 2H, C<u>H</u>$_2$).

^{13}C NMR (101 MHz, $CDCl_3$): δ 166.6, 150.5, 150.1, 146.0, 129.1, 128.9, 128.7, 126.5, 125.9, 125.5, 121.4, 63.0, 37.3, 29.9.

HRMS (ESI) m/z calcd. for $C_{31}H_{24}NO_4Na$ ($[M+Na]^+$) 483.1567, found 483.1565.

Analytical data for the isolated compound were identical with reported values.[177]

(*R*)-1,1′-spirobiindanyl-7,7′-dicarboxylic acid (378)



To a solution of compound **532** (400 mg, 0.87 mmol) in MeOH (3.8 mL, 0.23 M) was added 30% KOH 4 mL. The mixture was refluxed overnight. Then the mixture was cooled to room temperature and diluted with water. HCl (6 M) was added to adjust to pH = 2-3 and extracted with EtOAc (3 x 3 mL). The organic layer was then washed with water and brine and dried

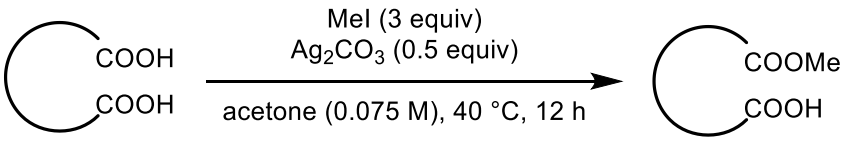
over $MgSO_4$ and concentrated under reduced pressure. The crude was purified by silica gel column chromatography (Pentane/EtOAc = 1/1, 1% AcOH) to give the desired ligand **378** as white soild (242.97 mg, 91%).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.63 (d, *J* = 7.7 Hz, 2H, $H^{7, 16}$), 7.40 (d, *J* = 7.5 Hz, 2H, $H^{9, 14}$), 7.13 (t, *J* = 7.5 Hz, 2H, $H^{8, 15}$), 3.13 – 3.06 (m, 2H, $H^{1a, 11a}$), 3.09 – 2.98 (m, 2H, $H^{1b, 11b}$), 2.53 – 2.45 (m, 2H, $H^{2a, 12a}$), 2.25 (m, 2H, $H^{2b, 12b}$).

^{13}C NMR (151 MHz, $CDCl_3$): δ 171.5 ($C^{18, 19}$), 151.4 ($C^{4, 13}$), 145.4 ($C^{5, 12}$), 129.4 ($C^{2, 10}$), 128.8 ($C^{6, 17}$), 126.4 ($C^{9, 14}$), 125.1 ($C^{8, 15}$), 63.2 (C^3), 38.2 ($C^{2, 10}$), 30.9 ($C^{1, 11}$).

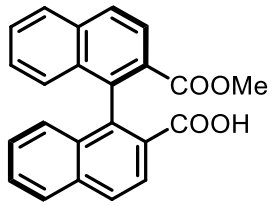
Analytical data for the isolated compound were identical with reported values.[177]

5.2.1.2 General Procedure A: Synthesis of ligand 366 and 379



To a solution of dicarboxylic acid (1.2 mmol), and Ag_2CO_3 (161 mg, 0.6 mmol, 0.5 equiv) in acetone (15 mL, 0.075 M) was added MeI (220 µL, 3.6 mmol, 3 equiv) at room temperature. After stirring at 40 °C for 12 h, the reaction was quenched with 2 M aq. HCl (20 mL), and extracted with EtOAc (2 × 80 mL). The combined organic layers were washed with H_2O (80 mL), dried over the Na_2SO_4, filtered, and concentrated in vacuo. The monoesters **366** and **379** were obtained by further purification *via* silica gel column chromatography.

(*R*)-7'-(methoxycarbonyl)-2,2',3,3'-tetrahydro-1,1'-spirobi[indene]-7-carboxylic acid (366)



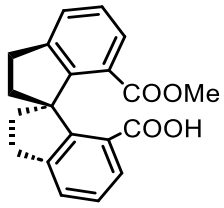
The monoester **366** was prepared from chiral carboxylic acid **354** (400 mg, 1.2 mmol) according to **General Procedure A** and purified by flash chromatography on silica gel (Pentane/EtOAc = 2/1, 1% AcOH) to be obtained as a white solid (370.2 mg, 89%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12 (d, *J* = 8.7, 7.2 Hz, 2H, Ar<u>H</u>), 8.01 (d, *J* = 8.7 Hz, 2H, Ar<u>H</u>), 7.94 (d, *J* = 8.2 Hz, 2H, Ar<u>H</u>), 7.52 (t, *J* = 7.7 Hz, 2H, Ar<u>H</u>), 7.22 (d, *J* = 7.0, 1.8 Hz, 2H, Ar<u>H</u>), 7.02 (dd, *J* = 16.1, 8.6 Hz, 2H, Ar<u>H</u>), 3.54 (s, *J* = 0.7 Hz, 3H, C<u>H</u>$_3$).

^{13}C NMR (101 MHz, $CDCl_3$): δ 128.4, 128.1, 128.0, 127.1, 125.7. Due to the complexity of the aromatic region and overlapping signals, several signals may be missing.

Analytical data for the isolated compound were identical with reported values.[179]

(*R*)-7'-(methoxycarbonyl)-2,2',3,3'-tetrahydro-1,1'-spirobi[indene]-7-carboxylic acid (379)



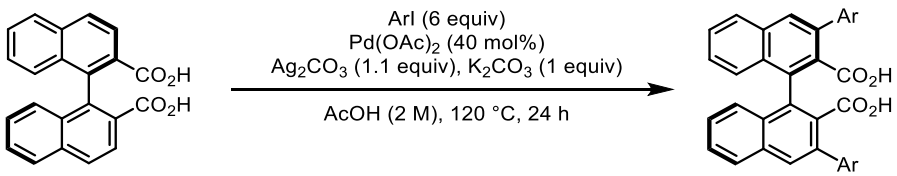
The monoester **379** was prepared from chiral carboxylic acid **354** (369.6 mg, 1.2 mmol) according to **General Procedure A** and purified by flash chromatography on silica gel (Pentane/EtOAc = 9/1, 1% AcOH) to be obtained as a white solid (308.2 mg, 80%).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.70 (d, *J* = 7.7 Hz, 1H, Ar<u>H</u>), 7.53 (d, *J* = 7.7 Hz, 1H, Ar<u>H</u>), 7.47 (d, *J* = 7.5, 1.2 Hz, 1H, Ar<u>H</u>), 7.39 (d, *J* = 7.6, 1.3 Hz, 1H, Ar<u>H</u>), 7.23 (t, *J* = 7.6 Hz, 1H, Ar<u>H</u>), 7.17 (t, *J* = 7.6 Hz, 1H, Ar<u>H</u>), 3.16 (s, 3H, C<u>H</u>$_3$), 3.15 – 2.99 (m, 6H, C<u>H</u>$_2$), 2.61 – 2.48 (m, 3H, C<u>H</u>$_2$), 2.31 (m, *J* = 12.1, 7.7, 1.4 Hz, 1H, C<u>H</u>$_2$), 2.26 (m, *J* = 12.0, 7.8, 1.1 Hz, 1H, C<u>H</u>$_2$).

^{13}C NMR (151 MHz, $CDCl_3$): δ 169.5, 168.2, 151.1, 149.6, 145.7, 145.2, 129.4, 129.1, 128.3, 127.9, 126.7, 126.5, 126.4, 125.2, 63.2, 51.2, 38.5, 38.0, 30.9, 30.8.

Analytical data for the isolated compound were identical with reported values.[179]

5.2.1.3 General Procedure B: Synthesis of 356, 357, 358 and 359



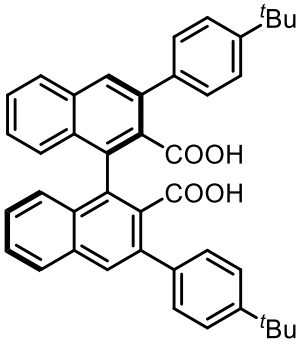
354 **355**

Compound **354** (86.5 mg, 0.25 mmol), $Pd(OAc)_2$ (5.6 mg, 40 mol%), Ag_2CO_3 (76 mg, 1.1 equiv), and K_2CO_3 (35 mg, 1 equiv) were weighed into a Schlenk tube, which had been flame-dried under vacuum. The tube was evacuated and back-filled with argon. Then, AcOH (0.13 mL) and iodobenzene (6 equiv) were added. The mixture was stirred for 24 h at 120 °C, then allowed to cool to room temperature, and extracted with EtOAc. The organic layer was

washed with brine, dried over Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure and the residue was purified by column chromatography on silica gel (pentane/EtOAc = 4/1 with 1% AcOH) to provide **356**, **357**, **358** and **359**.

Analytical data for compound **356**, **357**, **358** were identical with reported values.

(*R*)-3,3'-bis(4-*tert*-butylphenyl)-1,1'-binaphthyl-2,2'-dicarboxylic acid (356)



The compound **356** was prepared according to **General Procedure B** with commercial *tert*-butyl-4-iodobenzene (170 mL, 6 equiv) and purified by flash chromatography on silica gel (pentene/ethyl acetate = 4/1 with 1% AcOH) as a white solid (110.7 mg, 73%).

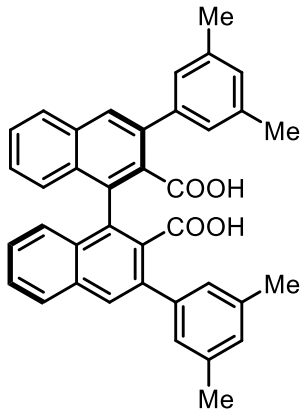
^{1}H NMR (400 MHz, CD_3OD): δ 7.95 (s, 2H, Ar<u>H</u>), 7.92 (d, *J* = 8.1 Hz, 2H, Ar<u>H</u>), 7.59 (d, *J* = 8.6 Hz, 4H, Ar<u>H</u>), 7.45 (d, *J* = 8.6 Hz, 4H, Ar<u>H</u>), 7.42 (m, 2H, Ar<u>H</u>), 7.21 (m, 2H, Ar<u>H</u>), 7.01 (d, *J* = 8.3 Hz, 2H, Ar<u>H</u>), 1.36 (s, 18H, *t*-Bu<u>H</u>).

^{13}C NMR (101 MHz, CD_3OD): δ 176.7, 153.4, 139.6, 137.6, 134.5, 133.3, 132.8, 131.0, 129.5, 129.1, 127.7, 127.6, 126.4, 35.3, 31.6.

HRMS (ESI) m/z calcd. for $C_{42}H_{38}NO_4Na$ ($[M+Na]^+$) 629.2662, found 629.2667.

Analytical data for the isolated compound were identical with reported values.[161]

(*R*)-1,10-Binaphthyl-3,3'-bis(3,5-dimethylphenyl)-2,20-di-carboxylic acid (357)



The compound **357** was prepared according to **General Procedure B** with commercial 3,5-dimethylphenyl iodide (164 mL, 6 equiv) and purified by flash chromatography on silica gel (hexane/ethyl acetate = 4/1 with 1% AcOH) as a colorless solid (123.9 mg, 90%).

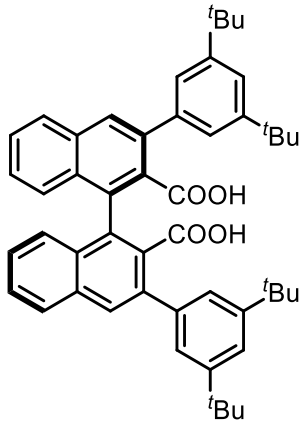
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01 (d, 2H, Ar<u>H</u>), 7.98–7.89 (m, 2H, Ar<u>H</u>), 7.52 (t, *J* = 6.8 Hz, 2H, Ar<u>H</u>), 7.30 (t, *J* = 6.8, 2H, Ar<u>H</u>), 7.23–7.16 (s, 4H, Ar<u>H</u>), 7.14–7.08 (m, 2H, Ar<u>H</u>), 7.05 (s, 2H, Ar<u>H</u>), 2.39 (s, 12H, C<u>H</u>$_3$).

^{13}C NMR (101 MHz, $CDCl_3$): δ 138.3, 136.8, 130.4, 129.8, 128.3, 128.1, 127.7, 126.9, 126.7, 21.5.

HRMS (ESI) m/z calcd. for $C_{38}H_{29}O_4$ ($[M+H]^+$) 549.2060, found 549.2066.

Analytical data for the isolated compound were identical with reported values.[162]

(*R*)-1,10-Binaphthyl-3,3'-bis(3,5-di-*tert*-butylphenyl)-2,20-di-carboxylic acid (358)



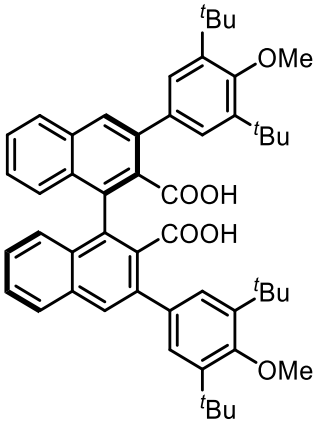
The compound **358**was prepared according to **General Procedure B** with 1,3-di(*tert*-butyl)-5-iodobenzene (157 mL, 6 equiv) and purified by flash chromatography on silica gel (hexane/ethyl acetate = 4/1 with 1% AcOH) as a white solid (113.2 mg, 63%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06 (d, 2H, ArH), 7.99–7.92 (m, 2H, ArH), 7.53 (t, *J* = 7.5 Hz, 2H, ArH), 7.44 (d, 4H, ArH), 7.33 (t, *J* =7.5 Hz, 2H, ArH), 7.17 (dt, 2H, ArH), 7.05 (d, 2H, ArH), 1.39 (s, 36H, *t*-BuH).

^{13}C NMR (101 MHz, $CDCl_3$): δ 151.1, 139.1, 133.9, 130.3, 128.3, 127.9, 127.6, 126.9, 123.3, 121.9, 77.5, 77.2, 76.8, 35.1, 31.6, 31.6.

Analytical data for the isolated compound were identical with reported values.[180]

(*R*)-3,3'-bis(3,5-di-tert-butyl-4-methoxyphenyl)-[1,1'-binaphthalene]-2,2'-dicarboxylic acid (359)



Compound **359** was prepared according to **General Procedure B** with 1,3-di-*tert*-butyl-5-iodo-2-methoxy benzene (311.6 mg, 6 equiv, 0.9 mmol) and purified by flash chromatography on silica gel (pentane/EtOAc = 4/1 with 1% AcOH) as a white solid (82.9 mg, 71%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.03 (d, 2H, ArH), 7.95 (d, *J* = 4.5 Hz, 2H, ArH), 7.53 (d, 2H, ArH), 7.48 (s, 4H, ArH), 7.31 (d, 2H, ArH), 7.15 (dq, *J* = 4.5 Hz, 2H, ArH), 3.74 (s, 6H, OCH_3), 1.48 (s, 36H, *t*-BuH).

^{13}C NMR (101 MHz, $CDCl_3$): δ 159.5, 143.9, 137.0, 134.1, 133.9, 132.9, 131.2, 130.1, 128.3, 127.9, 127.5, 127.3, 126.9, 64.5, 36.1, 32.3.

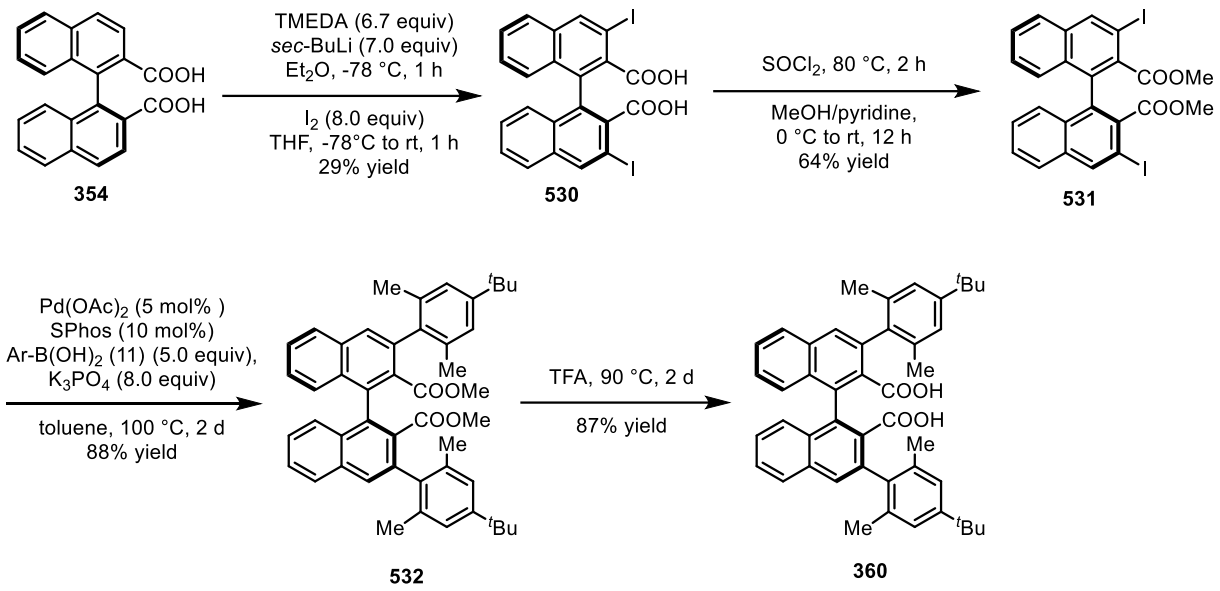
IR (film)/cm^{-1}: 2963, 2868, 1730, 1666, 1467, 1362, 1262, 1011, 909, 884.

HRMS (ESI) m/z calcd. for $C_{52}H_{57}O_6$ ([M-H]$^-$) 777.4161, found 777.4157.

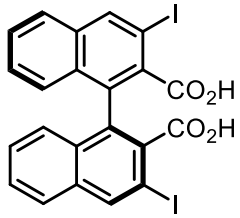
$[\alpha]_D^{25}$ = -6.1 (c = 0.9, $CHCl_3$).

m.p.: 197-200 °C

5.2.1.4 Synthesis of compound 360



(*S*)-3,3'-diiodo-[1,1'-binaphthalene]-2,2'-dicarboxylic acid (530)



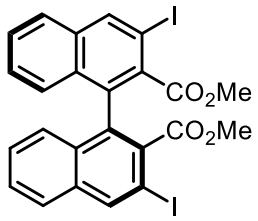
(*S*)-3,3'-diiodo-[1,1'-binaphthalene]-2,2'-dicarboxylic acid (**530**) was prepared according to a modified literature procedure. To a solution of acid **354** (281 mg, 0.8 mmol, 1.0 equiv) and TMEDA (639 mg, 0.8 mL, 5.50 mmol, 6.7 equiv) in dry diethylether (8.2 mL) was added a 1.4 M *sec*-BuLi solution in cyclohexane (4.10 mL, 5.8 mmol, 7.0 equiv) at -78 °C. The mixture was stirred for 1 h at -78 °C, and then iodine (1.67 g, 6.6 mmol, 8.0 equiv) in dry diethylether (8.2 mL) was added. The solution was stirred for an additional 1 h and the cooling was removed, then quenched with aqueous $Na_2S_2O_3$ and extracted with EtOAc after acidifying with 1N HCl. The organic layer was dried over Na_2SO_4 and filtered. The filtrate was evaporated under reduced pressure and the residue was purified by column

chromatography on silica gel (EtOAc/pentane = 1/1 to 8/2 with 1% AcOH) to provide (**530**) (141 mg, 36%). Analytical data for the isolated compound were identical with reported values.[162]

^{1}H NMR (400 MHz, MeOD): δ 8.61 (s, 2H, ArH), 7.86 (d, J = 8.2 Hz, 2H, ArH), 7.49 (ddd, J = 8.2, 6.8, 1.2 Hz, 2H, ArH), 7.32 (ddd, J = 8.3, 6.8, 1.3 Hz, 2H, ArH), 7.03 (d, J = 8.6 Hz, 2H, ArH).

^{13}C NMR (101 MHz, MeOD): δ 174.7, 142.6, 141.0, 135.6, 132.8, 132.7, 128.7, 128.4, 128.1, 127.7, 88.8.

Dimethyl (*S*)-3,3'-diiodo-[1,1'-binaphthalene]-2,2'-dicarboxylate (531)



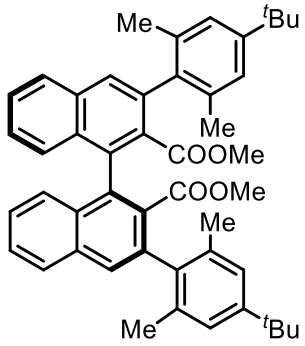
To a flask containing (*S*)-3,3'-diiodo-[1,1'-binaphthalene]-2,2'-dicarboxylic acid (**530**) (141 mg, 0.24 mmol, 1.0 equiv) was added $SOCl_2$ (4.75 mL, 0.05 M). After stirring for 2 h at 80 °C, residual $SOCl_2$ was removed by evaporation to give the acid chloride as a white solid. The solid thus obtained was then diluted with dry MeOH (2.37 mL, 0.1 M), cooled to 0 °C and pyridine (2.37 mL, 0.1 M) was added dropwise. After stirring for 12 h at room temperature, the reaction solution was treated with saturated aqueous NH_4Cl and extracted with EtOAc. The combined organic layers were dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel (EtOAc/pentane = 2/8 to 3/7)

to furnish compound (**531**) (94.4 mg, 64%). Analytical data for the isolated compound were identical with reported values.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.52 (s, 2H, ArH), 7.79 (d, J = 8.2 Hz, 2H, ArH), 7.52 (ddd, J = 8.1, 6.9, 1.2 Hz, 2H, ArH), 7.33 (ddd, J = 8.3, 6.8, 1.3 Hz, 2H, ArH), 7.10 (dd, J = 8.6, 1.0 Hz, 2H, ArH), 3.48 – 3.44 (m, 6H, CH_3).

^{13}C NMR (101 MHz, $CDCl_3$): δ 167.9, 139.9, 136.6, 134.5, 134.5, 131.9, 128.1, 127.8, 127.5, 127.0, 87.9, 52.1.

Dimethyl (1*S*,3's)-3,3'-bis(4-(tert-butyl)-2,6-dimethylphenyl)-[1,1'-binaphthalene]-2,2'-dicarboxylate (532)



To a flask was added $Pd(OAc)_2$ (1.2 mg, 7.23 μmol, 5 mol%), SPhos (5.9 mg, 14.5 μmol, 10 mol%), 4-*tert*-butyl-2,6-dimethylphenylboronic acid (149 mg, 0.72 mmol, 5.0 equiv), anhyd. K_3PO_4 (246 mg, 1.16 mmol, 8.0 equiv) and **531** (90.0 mg, 0.14 mmol, 1.0 equiv). The flask was then evacuated and backfilled with argon. Dry toluene (0.72 mL) was added and the mixture was stirred at 100 °C for 10 h. The mixture was then allowed cool to r.t and diluted with EtOAc. The solution was passed through short pad of silica gel and concentrated

in vacuo. The residue was then purified by column chromatography (EtOAc/pentane = 3/97) to give **532** (88.2 mg, 88%).

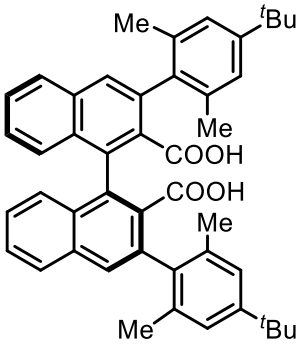
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88 (d, J = 8.2 Hz, 2H, Ar<u>H</u>), 7.76 (s, 2H, Ar<u>H</u>), 7.52 (ddd, J = 8.2, 6.5, 1.6 Hz, 2H, Ar<u>H</u>), 7.41 – 7.26 (m, 4H, Ar<u>H</u>), 7.11 – 7.04 (m, 4H, Ar<u>H</u>), 2.98 (s, 6H, COOC<u>H</u>$_3$), 2.10 (s, 6H, ArC<u>H</u>$_3$), 2.09 (s, 6H, ArC<u>H</u>$_3$), 1.32 (s, 18H, *t*Bu<u>H</u>).

^{13}C NMR (101 MHz, $CDCl_3$): δ 168.2, 150.2, 136.8, 136.6, 136.3, 135.9, 134.7, 133.7, 132.2, 129.1, 127.9, 127.6, 127.2, 126.7, 124.0, 124.0, 51.1, 34.5, 31.6, 21.1.

m.p.: 238-239 °C

Analytical data for the isolated compound were identical with reported values.

(1*S*,3's)-3,3'-bis(4-(tert-butyl)-2,6-dimethylphenyl)-[1,1'-binaphthalene]-2,2'-dicarboxylic acid (360)



To methylester **532** (64.7 mg, 93.6 µmol, 1.0 equiv) was added TFA (1.87 mL, 0.05 M). The resulting solution was refluxed for 48 h (80 °C), then cooled to room temperature. The mixture was treated with water and extracted with Et_2O. The combined organic layers were dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography

on silica gel (EtOAc/pentane = 1/1) to furnish **360** (54.0 mg, 87%) as a colourless solid. Analytical data for the isolated compound were identical with reported values.[161]

^{1}H NMR (400 MHz, MeOD): δ 7.97 (d, J = 8.4 Hz, 2H, ArH), 7.78 (s, 2H), 7.55 (ddd, J = 8.2, 6.8, 1.2 Hz, 2H, ArH), 7.36 (ddd, J = 8.2, 6.8, 1.3 Hz, 2H, ArH), 7.26 – 7.18 (m, 2H, ArH), 7.18 – 7.09 (m, 4H, ArH), 2.22 (s, 6H, ArCH$_3$), 2.04 (s, 6H, ArCH$_3$), 1.33 (s, 18H, *t*BuH).

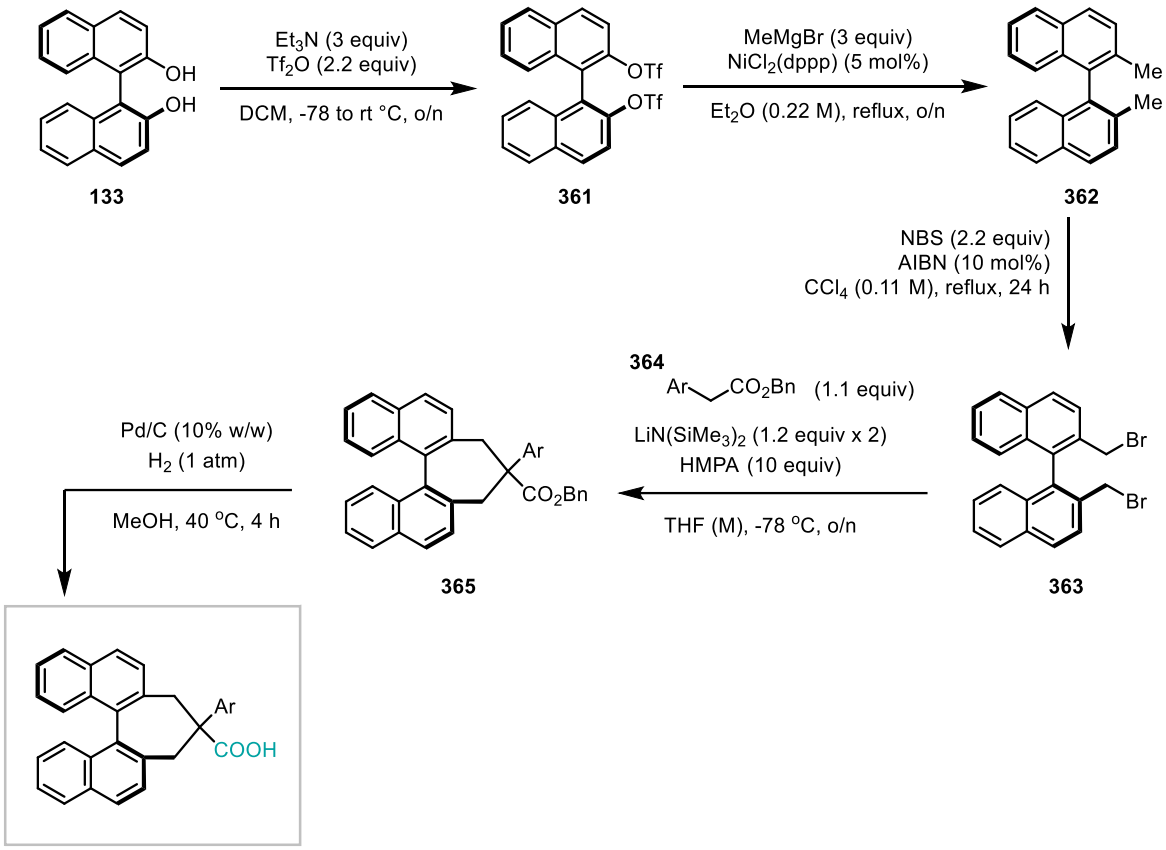
^{13}C NMR (101 MHz, MeOD): δ 172.9, 151.5, 137.9, 137.1, 137.0, 135.3, 134.3, 132.8, 130.8, 129.1, 128.5, 128.0, 127.8, 125.1, 35.2, 31.8, 21.6, 21.2.

m.p.: 238-239 °C

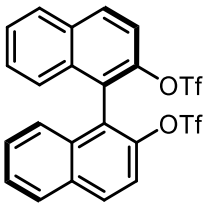
$[\alpha]_D^{25}$ =-58.2 (c = 0.5, MeOH).

5.2.1.5 General Procedure C: Synthesis of 377 and 380

The 377 and 380 were prepared according to the previously reported literature.[66]



(*R*)-[1,1'-binaphthalene]-2,2'-diyl bis(trifluoromethanesulfonate) (361)



In a 250 mL round-bottom flask, (*R*)-BINOL (**133**) (15 g, 52.4 mmol, 1 equiv) and triethylamine (21.9 mL, 157.2 mmol, 3 equiv) were dissolved in DCM (175 mL). The resulting solution was cooled down to -78 °C and trifluoromethanesulfonic anhydride (19.4 mL, 115.3 mmol, 2.2 equiv) was added dropwise via addition funnel. The resulting mixture was stirred overnight and allowed to warm up to room temperature. After that, the mixture was quenched with HCl (1M), washed with water and diluted by DCM. Organic layer was

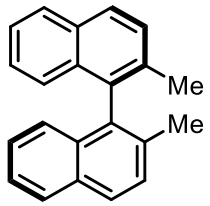
separated and aqueous layer was additionally extracted twice with DCM. Combined organic layers were dried over $MgSO_4$ and evaporated. The resulting crude dark orange oil was purified by filtration over plug of silica followed by flash chromatography on silica gel (Pentane/EtOAc = 20/1) gave the title compound (**361**) as a white solid (31.2 g, quant. yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.14 (d, *J* = 9.1Hz, 2H, ArH), 8.01 (d, *J* = 8.2 Hz, 2H, ArH), 7.66 – 7.60 (m, 2H, ArH), 7.60 – 7.55 (m, 2H, ArH), 7.41 (t, *J* = 8.3, 6.8, 1.3 Hz, 2H, ArH), 7.30 – 7.22 (d, 2H, ArH).

^{13}C NMR (101 MHz, $CDCl_3$): δ 145.5, 133.3, 132.5, 132.1, 128.5, 128.1, 127.5, 126.9, 123.6, 119.9, 119.5, 116.7.

Analytical data for the isolated compound were identical with reported values.[181]

(*R*)-2,2'-Dimethyl-1,1'-binaphthyl (362)



The compound (**361**) (2.5 g, 4.6 mmol) was dissolved in diethyl ether (20 mL), and the successive addition of $NiCl_2$(dppp) (205.3 mg, 5 mol %) and MeMgBr (4.3 mL, 13.8 mmol, 3 equiv) was dropwise added at 0 °C under argon atmosphere followed by refluxing overnight. This mixture was poured into ice-cooled 1 N HCl, and the whole mixture was filtered to remove the catalyst. The filtrate was extracted with ether. The organic extracts were washed with brine and dried over Na_2SO_4. Evaporation of solvents and purification of

the residue by column chromatography on silica gel (Pentane/EtOAc = 20/1) gave the title compound (**362**) as a colorless solid (1.28 g, quant. yield).

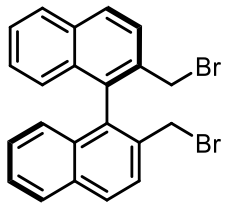
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94 – 7.85 (m, 4H, Ar<u>H</u>), 7.52 (d, *J* = 8.4 Hz, 2H, Ar<u>H</u>), 7.40 (ddd, *J* = 8.1, 6.7, 1.2 Hz, 2H, Ar<u>H</u>), 7.21 (ddd, *J* = 8.2, 6.7, 1.3 Hz, 2H, Ar<u>H</u>), 7.06 (d, *J* = 8.7, 0.9 Hz, 2H), 2.05 (s, 6H, C<u>H</u>$_3$).

^{13}C NMR (101 MHz, $CDCl_3$): δ 135.3, 134.4, 132.9, 132.4, 128.9, 128.9, 128.1, 127.6, 126.2, 125.8, 125.0, 20.2.

IR (film)/cm^{-1}: 3062, 3010.

Analytical data for the isolated compound were identical with reported values.[181]

(*R*)-2,2′-Bis(bromomethyl)-1,1′-binaphthyl (363)



A mixture of **362** (1.2 g, 4.25 mmol), *N*-bromosuccinimide (NBS) (1.66 g, 9.35 mmol, 2.2 equiv), and 2,2′-azobis(isobutyronitrile) (AIBN) (69.8 mg, 0.425 mmol, 10 mol %) in degassed CCl_4 (0.1 M, 35 mL) was heated and refluxed for 24 h. After being cooled to room temperature, this mixture was filtered through a Celite Pad (washed with DCM). The organic extracts were washed by $NaHCO_3$, brine and dried over the $MgSO_4$. Evaporation of solvents and purification of the residue by column chromatography on silica gel (Hexane/EtOAc = 100/1) gave the title compound (**363**) as a white solid (1.18 g, 63%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.03 (d, *J* = 8.5, 0.8 Hz, 2H, ArH), 7.93 (d, *J* = 8.2, 1.0 Hz, 2H, ArH), 7.75 (d, *J* = 8.6 Hz, 2H, ArH), 7.49 (ddd, *J* = 8.2, 6.8, 1.2 Hz, 2H, ArH), 7.31 – 7.24 (ddd, 2H, ArH), 7.08 (d, *J* = 8.5, 1.0 Hz, 2H, ArH), 4.26 (s, 4H, CH_2).

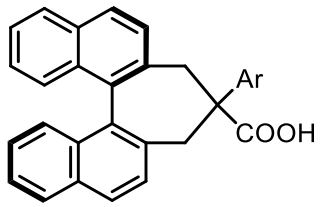
^{13}C NMR (101 MHz, $CDCl_3$): δ 134.2, 134.1, 133.3, 132.5, 129.4, 128.0, 127.8, 126.9, 126.8, 126.8, 32.6.

IR (film)/cm^{-1}: 3053, 2260, 1508, 1435, 1214, 819, 750.

[a]$_D$ ^{25} = +154.5 (c = 1.1, $CHCl_3$).

Analytical data for the isolated compound were identical with reported values.[181]

Synthesis of compound 377 and 380

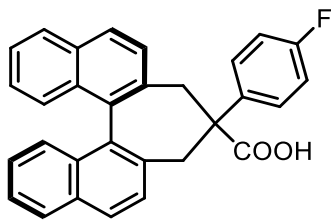


To a solution of benzyl acetate (0.75 mmol, 1.1 equiv) and HMPA (1.2 mL, 6.8 mmol, 10 equiv) in THF (22 mL) was added $LiN(SiMe_3)_2$ (1 M in THF, 0.8 mL, 0.82 mmol, 1.2 equiv) dropwise at –78 °C. After 1.5 hours, the solution was warmed up to 0 °C and stirred for 1.5 hours and then stirred at –78 °C for 1 h. To the rection mixture was added compound **363** (300 mg, 0.68 mmol) in THF (1.5 mL) dropwise at –78 °C. After 1.5 hours with stirring, the solution was warmed up to 0 °C and stirred for 1.5 hours. The reaction mixture was cooled to –78 °C and stirred for 1 h. To the rection mixture was added $LiN(SiMe_3)_2$ (1 M in THF, 0.8 mL, 0.82 mmol) dropwise at –78 °C. The reaction mixture was stirred overnight at –

78 °C. The rection was quenched by adding water at 0 °C, and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and evaporated under vacuum. The residue was purified by silica gel column chromatography (hexane/EtOAc = 20/1 to 10/1) to give **365**.

Subsequently, a mixture of **365** (100 mg, 0.2 mmol) and Pd/C (10% w/w, 10 mg) in MeOH (1.9 mL) was stirred under H_2 (1 atm) at 40 °C for 4 hours. The reaction mixture was cooled to room temperature, filtered through a Celite pad, and evaporated under vacuum. The residue was purified by silica gel flash column chromatography (hexane/AcOEt = 2/1) to give **ligand 377** (or **380**).

(11b*R*)-4-(4-fluorophenyl)-4,5-dihydro-3H-cyclohepta[2,1-a:3,4-a']dinaphthalene-4-carboxylic acid (377)



The compound **377** was prepared according to **General Procedure C** and purified by flash chromatography on silica gel (hexane/EtOAc = 2/1) as a pale yellow solid (78.7 mg, 96%), Rf = 0.19.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96 (d, *J* = 8.2 Hz, 1H, Ar<u>H</u>), 7.89 – 7.85 (m, 2H, Ar<u>H</u>), 7.72 (d, *J* = 8.3 Hz, 1H, Ar<u>H</u>), 7.61 (d, *J* = 8.3 Hz, 1H, Ar<u>H</u>), 7.52 – 7.35 (m, 6H, Ar<u>H</u>), 7.30 – 7.20 (m, 2H, Ar<u>H</u>), 7.11 – 6.97 (m, 3H, Ar<u>H</u>), 3.65 (d, *J* = 12.8 Hz, 1H, C<u>H</u>$_2$), 3.30 (d, *J* = 13.8 Hz, 1H, C<u>H</u>$_2$), 3.17 (d, *J* = 13.7 Hz, 1H, C<u>H</u>$_2$), 2.91 (d, *J* = 12.8 Hz, 1H, C<u>H</u>$_2$).

^{13}C NMR (101 MHz, $CDCl_3$): δ 180.2, 163.4, 160.9, 136.6, 135.6, 134.9, 134.7, 134.6, 133.2, 133.0, 131.9, 131.8, 128.7, 128.6, 128.5, 128.4, 128.5, 128.2, 127.9, 127.4, 127.3, 125.9, 125.9, 125.4, 125.4, 115.6, 115.4, 61.7, 41.2, 39.2. Due to the complexity of the aromatic region and overlapping signals, several signals may be missing.

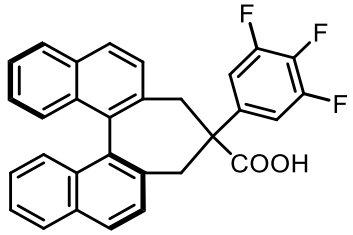
IR (film)/cm^{-1}: 3502, 1699, 1509, 1237, 1169, 817, 751.

HRMS (ESI) m/z calcd. for $C_{30}H_{20}O_2F$ ($[M-H]^-$) 431.1453, found 431.1449.

$[\alpha]_D^{25}$ = +35.6 (c = 0.15, $CHCl_3$).

Analytical data for the isolated compound were identical with reported values.[66]

(*S*)-4-(3,4,5-trifluorophenyl)-4,5-dihydro-3H-cyclohepta[2,1-a:3,4-a']dinaphthalene-4-carboxylic acid (380)



Compound **380** was prepared according to **General Procedure C** and purified by flash chromatography on silica gel (pentane/EtOAc = 2/1) as a white solid (73.1 mg, 83%), Rf = 0.19.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.96 (d, *J* = 8.3 Hz, 1H, Ar<u>H</u>), 7.90 (dd, *J* = 13.8, 8.2 Hz, 2H, Ar<u>H</u>), 7.77 (d, *J* = 8.3 Hz, 1H, Ar<u>H</u>), 7.59 (d, *J* = 8.3 Hz, 1H, Ar<u>H</u>), 7.46 (dddd, *J* = 19.5, 8.1, 6.7, 1.2 Hz, 2H, Ar<u>H</u>), 7.40 – 7.34 (m, 2H, Ar<u>H</u>), 7.28 – 7.23 (m, 3H, Ar<u>H</u>), 7.13 – 7.08

(m, 3H, ArH), 3.60 (d, *J* = 12.8 Hz, 1H, CH$_2$), 3.26 – 3.16 (m, 2H, CH$_2$), 2.83 (d, *J* = 12.8 Hz, 1H, CH$_2$).

^{13}C NMR (151 MHz, $CDCl_3$): δ 178.5, 152.0, 152.0, 151.9, 151.9, 150.4, 150.4, 150.3, 150.3, 140.0, 139.9, 139.8, 138.4, 138.3, 138.2, 137.3, 137.2, 134.7, 134.7, 134.6, 134.0, 133.3, 133.1, 131.8, 131.8, 128.6, 128.5, 128.4, 128.3, 127.8, 127.8, 127.4, 127.3, 126.1, 126.1, 125.7, 125.6, 111.7, 111.7, 111.6, 111.5, 61.4 (CCOOH), 41.0 (CH$_2$), 39.0 (CH$_2$).

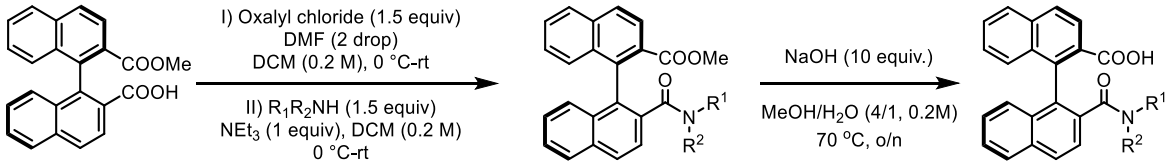
IR (film)/cm^{-1}: 2980, 1702, 1531, 1382, 1345, 1252, 1158, 820, 751.

HRMS (ESI) m/z calcd. for $C_{30}H_{19}F_3O_2$ ([M-H]$^-$) 467.1264, found 467.1259.

[α]$_D$ ^{25} = -35.5 (c = 1.2, $CHCl_3$).

m.p.: 142-144 °C

5.2.1.6 General Procedure D: Synthesis of 383, 384, 385, 386, 387, 388, 389, 390, 391, 392, 392, 394, 395 and 396

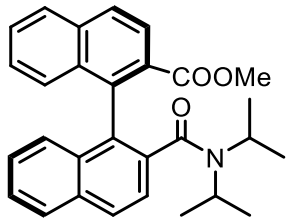


366 **368** **C**

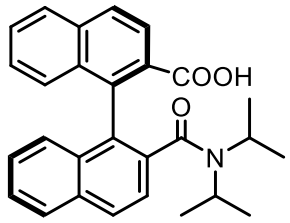
Axially chiral mono acid **383**, **384**, **385**, **386**, **387**, **388**, **389**, **390**, **391**, **392**, **392**, **394**, **395** and **396** was prepared according to the reported procedures.[182] To a flask containing mixture of axially chiral monomethyl ester (**366**) (0.34 mmol), dry DCM (1.7 mL) and catalytic amount of DMF (2 drop) was added oxalyl chloride (0.89 mL, 1.5 equiv) dropwise at 0 °C.

The mixture was stirred at room temperature for 4 h. The resulting mixture was concentrated under reduced pressure to afford acid chloride which was used directly without further purification for the next step. To a mixture of secondary amine (NHR^1R^2) (1.5 equiv), Et_3N (1.0 equiv), dry DCM (1.0 mL) was added acid chloride (1.0 equiv) solution in dry DCM (0.7 mL) dropwise at 0 °C. The reaction mixture was then stirred at room temperature overnight. The mixture was treated with water and extracted with DCM (x3). The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/pentane = 1/2) to furnish ester-amide. To a solution of ester-amide (1.0 equiv) in MeOH/H_2O = 4/1 (0.2 M) was added NaOH (10.0 equiv). The mixture was heated to 70 °C (oil bath) overnight. Then HCl (1 M) was added to adjust to pH = 2-3 and extracted with EtOAc (x3). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude mass was purified by silica gel column chromatography (Pentane/EtOAc = 3/1, 1% AcOH) to give the desired ligand as a white foamy solid.

(*R*)-2'-(diisopropylcarbamoyl)-[1,1'-binaphthalene]-2-carboxylic acid (383)



(*R*)-methyl 2'-(diisopropylcarbamoyl)-[1,1'-binaphthalene]-2-carboxylate was prepared according to **General Procedure D** with chiral monomethyl ester (**366**) (120 mg) and purified by flash chromatography on silica gel (Pentane/EtOAc = 5/1 to 1/1) as a white solid (109.5 mg, 74%).



The compound **383** was prepared according to **General Procedure D** with (*R*)-methyl 2'-(diisopropylcarbamoyl)-[1,1'-binaphthalene]-2-carboxylate (100 mg, 0.23 mmol) and purified by flash chromatography on silica gel (pentane/EtOAc = 3/1, 1% AcOH) as a white foamy solid (83.3 mg, 86%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 14.85 (s, 1H, COOH), 8.01 (ddd, *J* = 8.5, 3.1, 0.9 Hz, 2H, ArH), 7.96 – 7.89 (m, 2H, ArH), 7.81 (d, *J* = 8.5 Hz, 1H, ArH), 7.50 (dddd, *J* = 9.2, 8.1, 6.8, 1.2 Hz, 2H, ArH), 7.42 (d, *J* = 8.5 Hz, 1H, ArH), 7.32 (ddd, *J* = 8.2, 6.8, 1.3 Hz, 1H, ArH), 7.28 – 7.22 (ddd, *J* = 8.3, 6.8, 1.3 Hz, 1H, ArH), 7.17 (dq, *J* = 8.6, 0.9 Hz, 1H, ArH), 7.06 (dq, *J* = 8.5, 1.0 Hz, 1H, ArH), 4.03 (p, *J* = 6.6 Hz, 1H, CH), 3.23 (p, *J* = 6.8 Hz, 1H, CH), 1.40 (d, *J* = 6.8 Hz, 3H, CH3), 1.25 (d, *J* = 6.7 Hz, 3H, CH3), 0.70 (d, *J* = 6.8 Hz, 3H, CH3), 0.57 (d, *J* = 6.6 Hz, 3H, CH3).

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.1, 171.2, 135.1, 134.0, 133.6, 133.6, 133.2, 133.1, 132.0, 131.1, 129.3, 129.1, 128.5, 128.2, 128.1, 127.6, 127.3, 126.9, 126.8, 126.5, 125.4, 121.7, 51.5, 46.6, 21.2, 20.6, 20.0, 19.4.

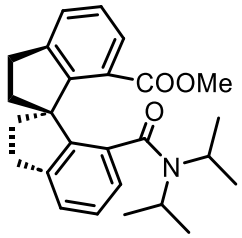
IR (film)/cm^{-1}: 3357, 2981, 1719, 1573, 1483, 1384, 1157, 952, 754.

m.p.: >200 °C

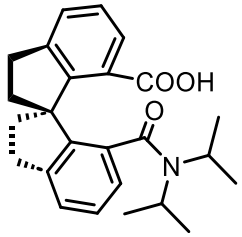
HRMS (ESI) m/z calcd. for $C_{28}H_{27}NO_3Na$ ($[M+Na]^+$) 448.1883, found 448.1886.

$[\alpha]_D^{25}$ = +162.4 (c = 1.2, $CHCl_3$).

(*R*)-7'-(diisopropylcarbamoyl)-2,2',3,3'-tetrahydro-1,1'-spirobi[indene]-7- carboxylic acid (384)



(*R*)-methyl-7'-(diisopropylcarbamoyl)-2,2',3,3'-tetrahydro-1,1'-spirobi[indene]-7-carboxylate was prepared according to **General Procedure D** with chiral monomethyl ester (**379**) (110 mg) and purified by flash chromatography on silica gel (pentane/EtOAc = 9/1) as a colorless oil (91.0 mg, 66%).



Compound **384** was prepared according to **General Procedure D** with (*R*)-methyl 7'-(diisopropylcarbamoyl)-2,2',3,3'-tetrahydro-1,1'-spirobi[indene]-7-carboxylate (91 mg, 0.23 mmol) and purified by flash chromatography on silica gel (pentane/EtOAc = 2/1, 1% AcOH) as a white solid (78.2 mg, 89%).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.31 (dd, *J* = 7.3, 1.3 Hz, 1H, ArH), 7.28 – 7.13 (m, 5H, ArH), 6.91 (d, *J* = 7.4 Hz, 1H, ArH), 3.78 (hept, *J* = 6.6 Hz, 1H, CH_2), 3.34 (hept, *J* = 6.8 Hz, 1H, CH_2), 3.07 – 2.90 (m, 4H, CH_2), 2.36 (s, 1H, CH_2), 2.42 – 2.29 (m, 2H, CH_2), 2.21 (ddd, *J* = 12.9, 7.7, 1.6 Hz, 1H, CH), 1.93 (dtd, *J* = 12.3, 9.8, 1.3 Hz, 1H, CH), 1.35 (d, *J* =

6.8 Hz, 3H, C<u>H</u>$_3$), 1.26 (s, 1H, C<u>H</u>), 1.13 (dd, *J* = 14.6, 6.6 Hz, 6H, C<u>H</u>$_3$), 0.78 (d, *J* = 6.8 Hz, 3H, C<u>H</u>$_3$).

^{13}C NMR (151 MHz, $CDCl_3$): δ 172.1, 171.6, 145.9, 145.3, 143.4, 142.6, 134.6, 131.8, 127.6, 127.5, 126.3, 125.7, 125.3, 124.3, 61.7, 51.4, 46.5, 39.7, 39.1, 30.6, 30.4, 21.1, 20.2, 20.1, 19.3.

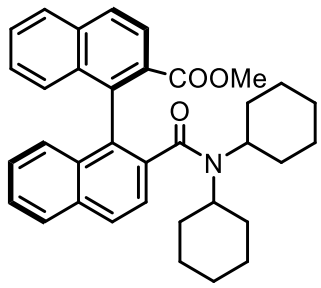
IR (film)/cm^{-1}: 3395, 2937, 1723, 1567, 1449, 1369, 1201, 1139, 1039, 756.

HRMS (ESI) m/z calcd. For $C_{25}H_{30}NO_3$ ($[M+H]^+$) 392.2220, found 392.2226.

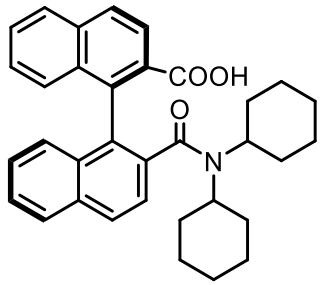
m.p.: >200 °C

$[\alpha]_D^{25}$ = +118.2 (c = 1.2, $CHCl_3$).

(*R*)-2'-(dicyclohexylcarbamoyl)-[1,1'-binaphthalene]-2-carboxylic acid (385)



(*R*)-methyl 2'-(dicyclohexylcarbamoyl)-[1,1'-binaphthalene]-2-carboxylate was prepared according to **General Procedure D** with chiral monomethyl ester (**366**) (120 mg) and purified by flash chromatography on silica gel (Pentane/EtOAc = 2/1) as a yellow oil (136.3 mg, 85%).



The compound **385** was prepared according to **General Procedure D** with (*R*)-methyl 2'-(dicyclohexylcarbamoyl)-[1,1'-binaphthalene]-2-carboxylate (125.9 mg, 0.23 mmol) and purified by flash chromatography on silica gel (pentane/EtOAc = 2/1, 1% AcOH) as a white solid (115.6 mg, 99%).

^{1}H NMR (600 MHz, $CDCl_3$): δ 8.02 (d, *J* = 8.5 Hz, 2H, ArH), 7.94 (dd, *J* = 8.2, 4.4 Hz, 2H, ArH), 7.83 (d, *J* = 8.5 Hz, 1H, ArH), 7.52 (ddd, *J* = 8.0, 6.7, 1.2 Hz, 1H, ArH), 7.47 (ddd, *J* = 8.1, 6.7, 1.2 Hz, 1H, ArH), 7.41 (d, *J* = 8.5 Hz, 1H, ArH), 7.32 (ddd, *J* = 8.2, 6.7, 1.2 Hz, 1H, ArH), 7.26 – 7.22 (m, 1H, ArH), 7.15 (d, *J* = 8.5 Hz, 1H, ArH), 7.02 (d, *J* = 8.5 Hz, 1H, ArH), 3.51 (ddd, *J* = 11.5, 8.0, 3.3 Hz, 1H, CyH), 2.77 (tt, *J* = 11.9, 3.5 Hz, 1H, CyH), 2.43 (qd, *J* = 12.5, 3.8 Hz, 1H, CyH), 1.95 – 1.89 (m, 1H, CyH), 1.86 – 1.76 (m, 2H, CyH), 1.75 (dq, *J* = 9.0, 2.9 Hz, 1H, CyH), 1.55 (dd, *J* = 13.7, 5.0 Hz, 2H, CyH), 1.50 (dq, *J* = 12.4, 6.1 Hz, 4H, CyH), 1.28 – 1.24 (m, 1H, CyH), 1.14 (pt, *J* = 12.9, 3.5 Hz, 2H, CyH), 1.09 – 0.87 (m, 4H, CyH), 0.68 – 0.62 (m, 1H, CyH), 0.53 (d, *J* = 12.6 Hz, 1H, CyH).

^{13}C NMR (151 MHz, $CDCl_3$): δ 172.5, 171.2, 135.1, 134.0, 133.7, 133.5, 133.3, 132.2, 131.1, 129.3, 129.1, 128.6, 128.2, 128.1, 127.6, 126.9, 126.7, 126.4, 125.5, 121.6, 60.5, 56.9, 31.6, 30.6, 29.2, 28.7, 26.5, 26.2, 25.6, 25.0.

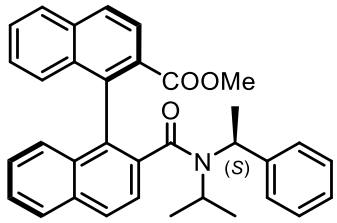
IR (film)/cm^{-1}: 3058, 2930, 2854, 1720, 1571, 1446, 1381, 1125, 825, 753.

HRMS (ESI) m/z calcd. for $C_{34}H_{36}NO_3$ ($[M+H]^+$) 506.2690, found 506.2692.

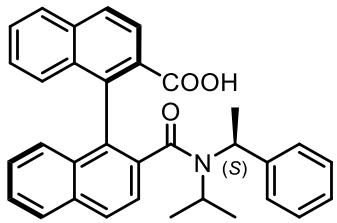
m.p.: 158-160 °C

[α]D ^{25} = +102.0 (c = 1.1, $CHCl_3$).

2'-(isopropyl((*S*)-1-phenylethyl) carbamoyl)-[1,1'-binaphthalene]-2-carboxylic acid (386)



The methyl 2'-(isopropyl((*S*)-1-phenylethyl) carbamoyl)-[1,1'-binaphthalene]-2-carboxylate was prepared according to **General Procedure D** with chiral monomethyl ester (**366**) (120 mg) and purified by flash chromatography on silica gel (pentane/EtOAc = 5/1 to 1/1) as a white solid (92.9 mg, 66%).



The compound **386** was prepared according to **General Procedure D** with methyl 2'-(isopropyl((*S*)-1-phenylethyl) carbamoyl)-[1,1'-binaphthalene]-2-carboxylate (96.1 mg, 0.18 mmol) and purified by flash chromatography on silica gel (pentane/EtOAc = 2/1, 1% AcOH) as a white solid (78.7 mg, 90%, mixture of rotamers **A** and **B**)

^{1}H NMR (600 MHz, $CDCl_3$): δ 8.07 – 8.01 (m, 3H, Ar<u>H</u> (**A**)), 7.98 (dt, *J* = 8.3, 1.7 Hz, 2H, Ar<u>H</u> (**B**)), 7.96 – 7.91 (m, 2H, Ar<u>H</u> (**A**)), 7.90 (dt, *J* = 8.3, 0.9 Hz, 1H, Ar<u>H</u> (**B**)), 7.86 (d, *J* = 8.5 Hz, 1H, Ar<u>H</u> (**B**)), 7.81 (d, *J* = 8.5 Hz, 1H, Ar<u>H</u> (**A**)), 7.55 – 7.49 (m, 5H, Ar<u>H</u> (**A**)), 7.47 (d, *J* = 8.5 Hz, 1H, Ar<u>H</u> (**B**)), 7.45 – 7.43 (m, 1H, Ar<u>H</u> (**A**)), 7.40 – 7.37 (m, 2H, Ar<u>H</u> (**A**)), 7.35 – 7.29 (m, 3H, Ar<u>H</u> (**B**)), 7.29 – 7.27 (m, 2H, Ar<u>H</u> (**A**)), 7.22 – 7.17 (m, 3H, Ar<u>H</u> (**B**)), 7.14 (dd, *J* = 8.5, 1.1 Hz, 1H, Ar<u>H</u> (**B**)), 7.10 (dd, *J* = 8.4, 1.1 Hz, 1H, Ar<u>H</u> (**A**)), 5.13 (q, *J* = 6.8 Hz, 1H, Ar<u>H</u> (**B**)), 4.35 (q, *J* = 6.9 Hz, 1H, Ar<u>H</u> (**A**)), 4.22 (p, *J* = 6.6 Hz, 1H, Ar<u>H</u> (**A**)), 3.14 (p, *J* = 6.7 Hz, 1H, Ar<u>H</u> (**B**)), 1.39 (d, *J* = 6.6 Hz, 3H, C<u>H</u>$_3$ (**A**)), 1.33 (d, *J* = 6.7 Hz, 2H, C<u>H</u>$_3$ (**B**)), 1.13 (d, *J* = 6.9 Hz, 3H, C<u>H</u>$_3$ (**A**)), 0.94 (d, *J* = 6.9 Hz, 2H, C<u>H</u>$_3$ (**B**)), 0.68 (d, *J* = 6.7 Hz, 2H, C<u>H</u>$_3$ (**B**)), 0.65 (d, *J* = 6.6 Hz, 3H, C<u>H</u>$_3$ (**A**)).

^{13}C NMR (151 MHz, $CDCl_3$): δ 173.3, 172.4, 171.1, 170.9, 140.8, 139.9, 135.1, 135.0, 134.1, 134.1, 133.9, 133.7, 133.2, 133.2, 132.8, 132.1, 132.1, 131.3, 131.1, 129.3, 129.2, 129.2, 128.9, 128.6, 128.3, 128.2, 128.0, 127.8, 127.8, 127.4, 127.1, 127.0, 126.9, 126.8, 126.6, 126.5, 125.6, 125.5, 122.0, 121.6, 58.4, 52.2, 51.9, 49.2, 22.2, 21.5, 20.1, 19.8, 19.2, 17.7.

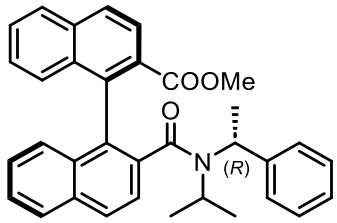
IR (film)/cm^{-1}: 3060, 2935, 1719, 1573, 1480, 1448, 1404, 1364, 1340, 1126, 1028, 869, 753, 665.

HRMS (ESI) m/z calcd. for $C_{33}H_{30}NO_3$ ($[M+H]^+$) 488.2220, found 488.2216.

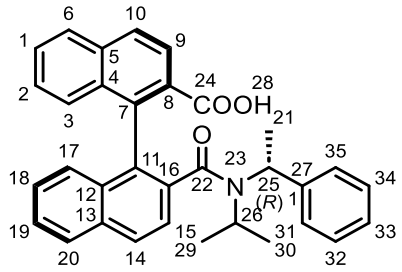
m.p.: >200 °C

$[\alpha]_D^{25}$ = +87.4 (c = 1.0, $CHCl_3$).

2'-(isopropyl((*R*)-1-phenylethyl) carbamoyl)-[1,1'-binaphthalene]-2-carboxylic acid (387)



The methyl 2'-(isopropyl((*R*)-1-phenylethyl) carbamoyl)-[1,1'-binaphthalene]-2-carboxylate was prepared according to **General Procedure D** with chiral monomethyl ester (**366**) (120 mg) and purified by flash chromatography on silica gel (pentane/EtOAc = 5/1 to 1/1) as a white solid (98.5 mg, 70%).



The compound **387** was prepared according to **General Procedure D** with methyl 2'-(isopropyl((*R*)-1-phenylethyl) carbamoyl)-[1,1'-binaphthalene]-2-carboxylate (96.1 mg, 0.18 mmol) and purified by flash chromatography on silica gel (pentane/EtOAc = 2/1, 1% AcOH) as a white solid (73.5 mg, 84%, mixture of rotamers **A** and **B**)

^{1}H NMR (600 MHz, $CDCl_3$): δ 8.13 (d, *J* = 8.5 Hz, 1H, H^3), 8.07 (dd, *J* = 12.3, 8.3 Hz, 2H, $H^{10, 17}$), 7.96 (d, *J* = 8.2 Hz, 1H, H^6), 7.79 (d, *J* = 8.5 Hz, 1H, H^{14}), 7.53 (dq, *J* = 8.2, 6.4 Hz, 3H, $H^{9, 15, 20}$), 7.35 (ddd, *J* = 8.2, 6.8, 1.3 Hz, 1H, H^2), 7.30 (ddd, *J* = 8.2, 6.7, 1.2 Hz, 1H, H^1), 7.19 (dd, *J* = 12.3, 8.5 Hz, 2H, $H^{18, 19}$), 6.98 (t, *J* = 7.4 Hz, 1H, H^{32}), 6.79 (t, *J* = 7.7 Hz, 2H, $H^{31, 33}$), 6.13 (d, *J* = 7.7 Hz, 2H, $H^{30, 34}$), 4.38 (q, *J* = 7.0 Hz, 1H, H^{24}), 4.28 (p, *J* = 6.6

Hz, 1H, H^{25}), 1.83 (d, J = 7.0 Hz, 3H, $H^{27a, 27b, 27c}$), 1.40 (d, J = 6.6 Hz, 3H, $H^{28a, 28b, 28c}$), 0.59 (d, J = 6.6 Hz, 3H, $H^{29a, 29b, 29c}$).

^{13}C NMR (151 MHz, $CDCl_3$): δ 172.5 (C^{21}), 170.9 (C^{35}), 140.2 (C^{26}), 135.3 (C^{Ar}), 134.3 (C^{Ar}), 133.8 (d, J = 5.4 Hz) (C^{Ar}), 133.3 (C^{Ar}), 132.8 (C^{Ar}), 132.4 (C^{Ar}), 129.4 (C^{Ar}), 129.3 (C^{Ar}), 128.6 (C^{Ar}), 128.2 (d, J = 4.0 Hz) (C^{Ar}), 127.9 (C^{Ar}), 127.8 (C^{Ar}), 127.6 (C^{Ar}), 127.3 (C^{Ar}), 126.9 (C^{Ar}), 126.6 (C^{Ar}), 126.1 (C^{Ar}), 125.8 (C^{Ar}), 125.2 (C^{Ar}), 121.6 (C^{Ar}), 52.9 (C^{24}), 52.0 (C^{25}), 21.7 (C^{27}), 20.7 (C^{28}), 20.0 (C^{29}).

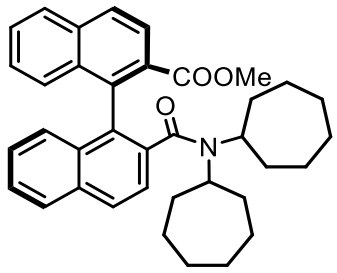
IR (film)/cm^{-1}: 3014, 1719, 1575, 1483, 1446, 1395, 1217, 1184, 1137, 1029, 821, 753.

HRMS (ESI) m/z calcd. for $C_{33}H_{30}NO_3$ ($[M+H]^+$) 488.2220, found 488.2226.

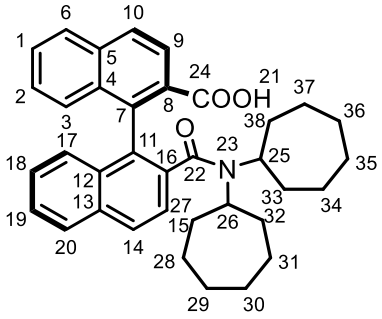
m.p.: >200 °C

$[\alpha]_D^{25}$ = +98.7 (c = 1.1, $CHCl_3$).

(*R*)-2'-(dicycloheptylcarbamoyl)-[1,1'-binaphthalene]-2-carboxylic acid (388)



The methyl (*R*)-2'-(dicycloheptylcarbamoyl)-[1,1'-binaphthalene]-2-carboxylate was prepared according to **General Procedure D** with chiral monomethyl ester (**366**) (120 mg) and purified by flash chromatography on silica gel (pentane/EtOAc = 5/1 to 1/1) as a white solid (119.1 mg, 64%).



The compound **366** was prepared according to **General Procedure D** with methyl (*R*)-2'-(dicycloheptylcarbamoyl)-[1,1'-binaphthalene]-2-carboxylate (98.4 mg, 0.18 mmol) and purified by flash chromatography on silica gel (pentane/EtOAc = 2/1, 1% AcOH) as a white solid (88.3 mg, 92%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 15.16 (s, 1H, H^{21}), 8.01 (d, *J* = 8.5 Hz, 2H, H^{Ar}), 7.98 – 7.88 (m, 2H, H^{Ar}), 7.82 (d, *J* = 8.5 Hz, 1H, H^{Ar}), 7.49 (dddd, *J* = 11.6, 8.1, 6.8, 1.2 Hz, 2H, H^{Ar}), 7.40 (d, *J* = 8.5 Hz, 1H, H^{Ar}), 7.28 (dddd, *J* = 16.6, 8.3, 6.7, 1.3 Hz, 2H, H^{Ar}), 7.13 (dd, *J* = 8.5, 1.0 Hz, 1H, H^{Ar}), 7.05 – 6.98 (m, 1H, H^{Ar}), 3.72 (tt, *J* = 10.4, 3.7 Hz, 1H, H^{24}), 2.94 (tt, *J* = 10.1, 3.8 Hz, 1H, H^{25}), 2.48 – 2.33 (m, 1H, H^{Cy}), 2.10 – 1.99 (m, 1H, H^{Cy}), 1.80 – 1.59 (m, 5H, H^{Cy}), 1.57 – 1.32 (m, 12H, H^{Cy}), 1.36 – 1.01 (m, 3H, H^{Cy}), 0.84 (tt, *J* = 8.7, 5.3 Hz, 1H, H^{Cy}), 0.59 (ddt, *J* = 14.5, 7.9, 3.8 Hz, 1H, H^{Cy}).

^{13}C NMR (101 MHz, $CDCl_3$): δ 171.3, 171.1, 135.1, 133.9, 133.8, 133.7, 133.3, 132.9, 132.1, 131.1, 129.1, 129.1, 128.6, 128.7, 127.9, 127.6, 126.9, 126.7, 126.5, 125.4, 121.8, 62.6, 58.8, 34.4, 32.6, 32.5, 31.9, 27.9, 27.3, 26.9, 26.7, 26.3, 25.4, 24.5.

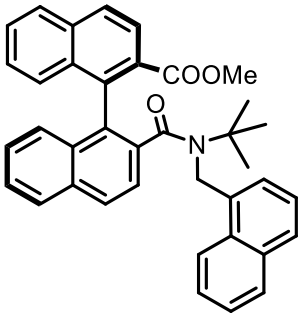
IR (film)/cm^{-1}: 3628, 2927, 1719, 1557, 1448, 1381, 1216, 1138, 1027, 830, 754.

HRMS (ESI) m/z calcd. for $C_{36}H_{39}NO_3Na$ ($[M+Na]^+$) 556.2822, found 556.2828.

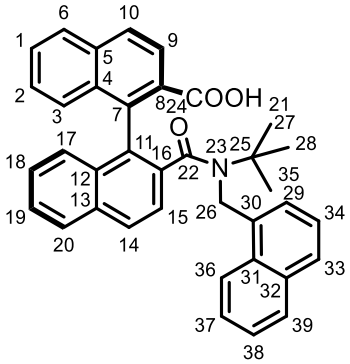
m.p.: >200 °C

$[\alpha]_D^{25}$ = +117.4 (c = 1.2, $CHCl_3$).

(*R*)-2'-(*tert*-butyl(naphthalen-1-ylmethyl)carbamoyl)-[1,1'-binaphthalene]-2-carboxylic acid (389)



The methyl (*R*)-2'-(*tert*-butyl(naphthalen-1-ylmethyl)carbamoyl)-[1,1'-binaphthalene]-2-carboxylate was prepared according to **General Procedure D** with chiral monomethyl ester (**366**) (120 mg) and purified by flash chromatography on silica gel (pentane/EtOAc = 5/1 to 1/1) as a white solid (108.7 mg, 58%).



The compound **389** was prepared according to **General Procedure D** with methyl methyl (*R*)-2'-(*tert*-butyl(naphthalen-1-ylmethyl)carbamoyl)-[1,1'-binaphthalene]-2-carboxylate (90 mg, 0.18 mmol) and purified by flash chromatography on silica gel (Pentane/EtOAc = 2/1, 1% AcOH) as a white solid (89.0 mg, 92%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.08 (d, *J* = 8.5 Hz, 1H, H^{Ar}), 8.04 (dd, *J* = 8.3, 1.2 Hz, 1H, H^{Ar}), 7.96 – 7.82 (m, 3H, H^{Ar}), 7.77 (d, *J* = 8.2 Hz, 1H, H^{Ar}), 7.71 – 7.48 (m, 8H, H^{Ar}), 7.45 (ddd, *J* = 8.2, 6.6, 1.4 Hz, 1H, H^{Ar}), 7.38 (d, *J* = 8.5 Hz, 1H, H^{Ar}), 7.35 – 7.23 (m, 3H, H^{Ar}),

5.00 (d, *J* = 18.2 Hz, 1H, CH2), 4.65 (d, *J* = 18.0 Hz, 1H, CH2), 1.26 (s, 1H, CH), 0.94 (s, 9H, CH3).

^{13}C NMR (101 MHz, $CDCl_3$): δ 175.3, 170.9, 135.1, 134.3, 133.8, 133.6, 132.9, 132.1, 129.4, 129.3, 129.2, 128.8, 128.2, 128.0, 127.5, 127.3, 126.7, 126.7, 126.5, 126.3, 125.5, 125.5, 123.5, 121.5, 59.8, 49.9, 27.5.

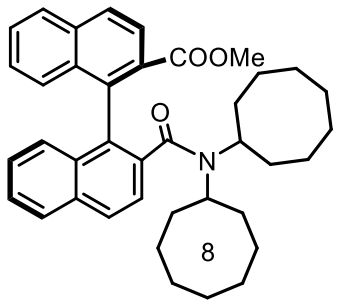
IR (film)/cm^{-1}: 3022, 2982, 2622, 1725, 1579, 1473, 1397, 1137, 823, 755.

HRMS (ESI) m/z calcd. for $C_{37}H_{32}NO_3$ ($[M+H]^+$) 538.2377, found 538.2373.

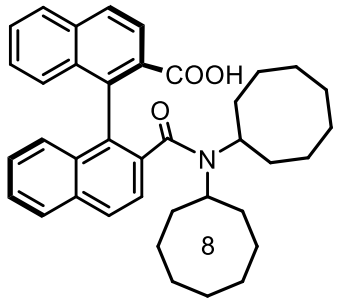
m.p.: >200 °C

$[\alpha]_D^{25}$ = +123.1 (c = 1.2, $CHCl_3$).

(*R*)-2'-(dicyclooctylcarbamoyl)-[1,1'-binaphthalene]-2-carboxylic acid (391)



The methyl (*R*)-2'-(dicyclooctylcarbamoyl)-[1,1'-binaphthalene]-2-carboxylate was prepared according to **General Procedure D** with chiral monomethyl ester (**366**) (120 mg) and purified by flash chromatography on silica gel (Pentane/EtOAc = 5/1 to 1/1) as a white solid (136.9 mg, 70%).



The compound **391** was prepared according to **General Procedure D** with methyl (*R*)-2'-(dicyclooctylcarbamoyl)-[1,1'-binaphthalene]-2-carboxylate (103.6 mg, 0.18 mmol) and purified by flash chromatography on silica gel (Pentane/EtOAc = 2/1, 1% AcOH) as a white solid (96.8 mg, 96%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 15.25 (s, 1H, COOH), 8.02 (dd, *J* = 8.5, 4.6 Hz, 2H, H^{Ar}), 7.98 – 7.90 (m, 2H, H^{Ar}), 7.81 (d, *J* = 8.5 Hz, 1H, H^{Ar}), 7.50 (dddd, *J* = 11.4, 8.1, 6.8, 1.2 Hz, 2H, H^{Ar}), 7.42 (d, *J* = 8.4 Hz, 1H, H^{Ar}), 7.33 – 7.26 (m, 2H, H^{Ar}), 7.11 (dd, *J* = 8.5, 1.1 Hz, 1H, H^{Ar}), 7.04 (dd, *J* = 8.5, 1.1 Hz, 1H, H^{Ar}), 3.91 (tt, *J* = 10.0, 3.1 Hz, 1H, H^{Cy}), 3.06 (tt, *J* = 9.4, 3.1 Hz, 1H, H^{Cy}), 2.45 – 2.31 (m, 1H, H^{Cy}), 1.99 (ddt, *J* = 14.5, 7.5, 3.8 Hz, 1H, H^{Cy}), 1.76 – 1.21 (m, 24H, H^{Cy}), 1.13 – 0.97 (m, 1H), 0.93 – 0.81 (m, 1H, H^{Cy}).

^{13}C NMR (101 MHz, $CDCl_3$): δ 171.4, 170.7, 135.2, 134.1, 133.9, 133.7, 133.3, 132.6, 132.1, 131.2, 129.0, 128.6, 128.2, 128.0, 127.6, 126.9, 126.8, 126.6, 125.4, 122.1, 60.9, 57.6, 33.2, 32.3, 26.9, 26.6, 26.2, 25.9, 25.5, 24.9, 24.4.

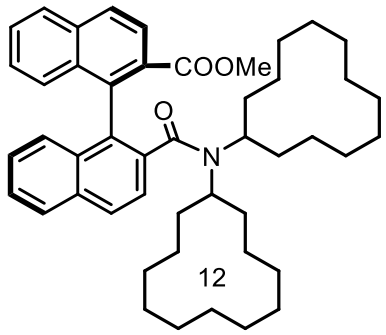
IR (film)/cm^{-1}: 3435,2927, 2857, 1719, 1659, 1566, 1449, 1385, 1130, 826, 757.

HRMS (ESI) m/z calcd. for $C_{38}H_{44}NO_3$ ($[M+H]^+$) 562.3316, found 562.3310.

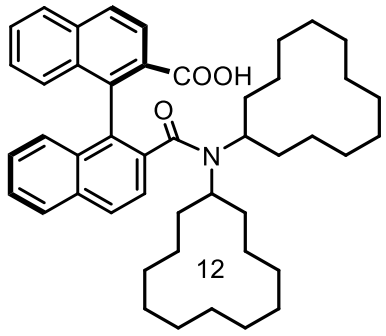
m.p.: >200 °C

$[\alpha]_D^{25}$ = +110.3 (c = 0.9, $CHCl_3$).

(*R*)-2'-(dicyclododecylcarbamoyl)-[1,1'-binaphthalene]-2-carboxylic acid (392)



The methyl (*R*)-2'-(dicyclododecylcarbamoyl)-[1,1'-binaphthalene]-2-carboxylate was prepared according to **General Procedure D** with chiral monomethyl ester (**366**) (120 mg) and purified by flash chromatography on silica gel (Pentane/EtOAc = 5/1 to 1/1) as a white solid (102.8 mg, 44%).



The compound **392** was prepared according to **General Procedure D** with methyl (*R*)-2'-(dicyclooctylcarbamoyl)-[1,1'-binaphthalene]-2-carboxylate (96.2 mg, 0.14 mmol) and purified by flash chromatography on silica gel (Pentane/EtOAc = 2/1, 1% AcOH) as a white solid (90.5 mg, 96%).

^{1}H NMR (600 MHz, $CDCl_3$): δ 8.15 (d, *J* = 8.7 Hz, 1H, H^{Ar}), 7.99 – 7.90 (m, 4H, H^{Ar}), 7.49 (dt, *J* = 13.7, 7.3 Hz, 2H, H^{Ar}), 7.43 (d, *J* = 8.4 Hz, 1H, H^{Ar}), 7.31 – 7.21 (m, 3H, H^{Ar}), 7.18 (d, *J* = 8.4 Hz, 1H, H^{Ar}), 3.63 (dq, *J* = 11.4, 3.9 Hz, 1H, H^{Cy}), 2.43 – 2.36 (m, 1H, H^{Cy}), 1.55

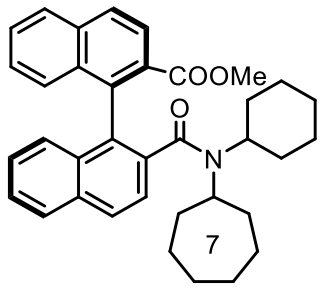
– 1.45 (m, 3H, H^{Cy}), 1.41 – 1.11 (m, 33H, H^{Cy}), 0.98 (tt, *J* = 11.2, 5.4 Hz, 4H, H^{Cy}), 0.92 – 0.84 (m, 1H, H^{Cy}), 0.76 (q, *J* = 11.6 Hz, 3H, H^{Cy}).

^{13}C NMR (151 MHz, $CDCl_3$): δ 170.1, 167.6, 136.5, 134.9, 134.4, 133.9, 133.7, 132.8, 132.4, 131.4, 128.7, 128.2, 127.3, 126.6, 126.5, 126.5, 126.0, 124.3, 56.6, 52.1, 30.8, 25.9, 25.7, 25.4, 25.1, 23.9, 23.6, 23.4, 23.3, 22.6.

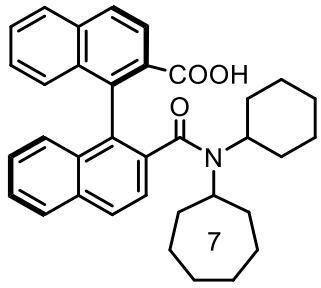
m.p.: >200 °C

$[\alpha]_D^{25}$ = +122.7 (c = 0.7, $CHCl_3$).

2'-(cycloheptyl(cyclohexyl)carbamoyl)-[1,1'-binaphthalene]-2-carboxylic acid (394)



Methyl 2'-(cycloheptyl(cyclohexyl)carbamoyl)-[1,1'-binaphthalene]-2-carboxylate was prepared according to **General Procedure D** with chiral monomethyl ester (**366**) (120 mg) and purified by flash chromatography on silica gel (Pentane/EtOAc = 2/1) as a yellow oil (145.1 mg, 80%).



The compound **394** was prepared according to **General Procedure D** with methyl 2'-(cycloheptyl(cyclohexyl)carbamoyl)-[1,1'-binaphthalene]-2-carboxylate (122.7 mg, 0.23 mmol) and purified by flash chromatography on silica gel (Pentane/EtOAc = 2/1, 1% AcOH) as a white solid (118.1 mg, 99%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.05 – 7.98 (m, 2H, H^{Ar}), 7.94 (ddd, *J* = 8.4, 4.5, 1.2 Hz, 2H, H^{Ar}), 7.82 (d, *J* = 8.4 Hz, 1H, H^{Ar}), 7.50 (dddd, *J* = 16.6, 8.1, 6.8, 1.2 Hz, 2H, H^{Ar}), 7.40 (dd, *J* = 16.2, 8.4 Hz, 1H, H^{Ar}), 7.32 (ddd, *J* = 8.3, 6.8, 1.3 Hz, 1H, H^{Ar}), 7.27 – 7.24 (m, 1H, H^{Ar}), 7.15 (dd, *J* = 8.5, 1.0 Hz, 1H, H^{Ar}), 7.06 – 6.98 (m, 1H, H^{Ar}), 3.49 (tt, *J* = 11.6, 3.5 Hz, 1H, C<u>H</u>), 2.94 (tt, *J* = 10.4, 4.1 Hz, 1H, C<u>H</u>), 2.42 (ddt, *J* = 17.4, 10.3, 3.6 Hz, 1H, H^{Cy}), 1.97 – 1.26 (m, 15H, H^{Cy}), 1.22 – 0.94 (m, 5H, H^{Cy}), 0.57 (ddt, *J* = 11.0, 7.3, 3.5 Hz, 1H, H^{Cy}).

^{13}C NMR (101 MHz, $CDCl_3$): δ 171.9, 171.3, 135.1, 133.9, 133.7, 133.6, 133.2, 133.1, 132.2, 131.0, 129.3, 129.1, 128.6, 128.2, 128.1, 127.6, 126.9, 126.7, 126.4, 125.5, 121.6, 60.2, 58.2, 32.4, 31.8, 30.8, 27.9, 26.6, 26.3, 25.6, 25.0.

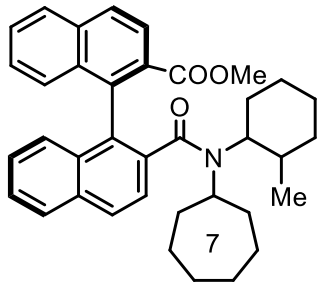
IR (film)/cm^{-1}: 3015, 2930, 2857, 1717, 1569, 1454, 1381, 1137, 829, 753.

HRMS (ESI) m/z calcd. for $C_{35}H_{38}NO_3$ ($[M+H]^+$) 520.2846, found 520.2845.

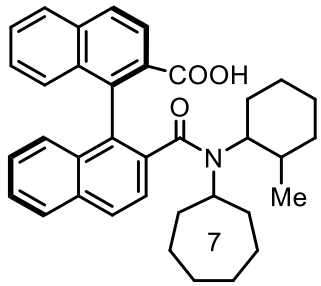
m.p.: 160-162 °C

$[\alpha]_D^{25}$ = +112.0 (c = 0.9, $CHCl_3$).

2'-(cycloheptyl(2-methylcyclohexyl)carbamoyl)-[1,1'-binaphthalene]-2-carboxylic acid (395)



Methyl 2'-(cycloheptyl(2-methylcyclohexyl)carbamoyl)-[1,1'-binaphthalene]-2-carboxylate was prepared according to **General Procedure D** with chiral monomethyl ester (**366**) (120 mg) and purified by flash chromatography on silica gel (Pentane/EtOAc = 2/1) as a yellow oil (148.8 mg, 80%).



The compound **395** was prepared according to **General Procedure D** with methyl 2'-(cycloheptyl(cyclohexyl)carbamoyl)-[1,1'-binaphthalene]-2-carboxylate (125.9 mg, 0.23 mmol) and purified by flash chromatography on silica gel (Pentane/EtOAc = 2/1, 1% AcOH) as a white solid (110.4 mg, 90%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.05 – 7.98 (m, 2H, H^{Ar}), 7.97 – 7.89 (m, 2H, H^{Ar}), 7.85 – 7.80 (m, 1H, H^{Ar}), 7.54 – 7.45 (m, 2H, H^{Ar}), 7.36 – 7.26 (m, 2H, H^{Ar}), 7.20 – 7.08 (m, 2H, H^{Ar}), 7.08 – 7.01 (m, 1H, H^{Ar}), 3.93 – 3.64 (m, 1H, H^{Cy}), 2.42 (ddd, *J* = 13.9, 7.7, 2.6 Hz, 1H, H^{Cy}), 2.33 – 2.16 (m, 1H, H^{Cy}), 2.16 – 2.01 (m, 1H, H^{Cy}), 1.72 (dtdd, *J* = 27.0, 10.7, 7.4,

2.9 Hz, 4H, H^{Cy}), 1.63 – 1.27 (m, 11H, H^{Cy}), 1.27 – 1.08 (m, 4H, H^{Cy}), 1.05 – 0.80 (m, 3H, H^{CH3}), 0.77 – 0.57 (m, 1H, H^{Cy}).

^{13}C NMR (101 MHz, $CDCl_3$): δ 171.8, 171.2, 135.2, 134.3, 133.6, 133.3, 132.3, 129.2, 129.1, 128.5, 128.4, 128.2, 128.1, 127.6, 127.0, 126.9, 126.7, 126.7, 126.6, 125.6, 125.4, 63.6, 63.0, 37.7, 35.8, 35.3, 33.9, 33.1, 30.7, 26.9, 26.6, 25.9, 24.8, 24.3, 18.1.

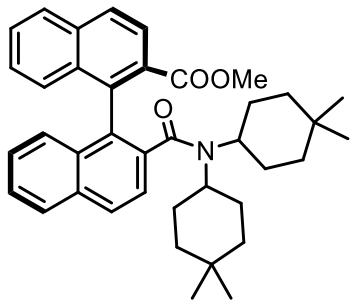
IR (film)/cm^{-1}: 3012, 2931, 2857, 1716, 1556, 1482, 1379, 1138, 829, 753.

HRMS (ESI) m/z calcd. for $C_{36}H_{40}NO_3$ ($[M+H]^+$) 534.3003, found 534.3010.

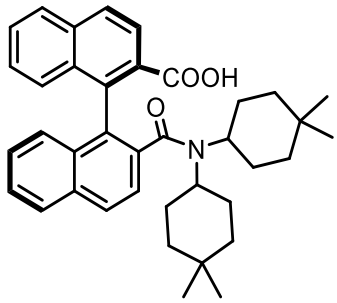
m.p.: 154-158 °C

$[\alpha]_D^{25}$ = +127.3 (c = 0.8, $CHCl_3$).

(*R*)-2'-(bis(4,4-dimethylcyclohexyl)carbamoyl)-[1,1'-binaphthalene]-2-carboxylic acid (396)



Methyl (R)-2'-(bis(4,4-dimethylcyclohexyl)carbamoyl)-[1,1'-binaphthalene]-2-carboxylate was prepared according to **General Procedure D** with chiral monomethyl ester (**366**) (120 mg) and purified by flash chromatography on silica gel (Pentane/EtOAc = 2/1) as a yellow oil (170.2 mg, 86%).



The compound **396** was prepared according to **General Procedure D** with methyl (*R*)-2'-(bis(4,4-dimethylcyclohexyl)carbamoyl)-[1,1'-binaphthalene]-2-carboxylate (132.3 mg, 0.23 mmol) and purified by flash chromatography on silica gel (Pentane/EtOAc = 3/1, 1% AcOH) as a white solid (126.5 mg, 98%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 – 7.99 (m, 2H, H^{Ar}), 7.94 (dd, *J* = 8.2, 1.3 Hz, 2H, H^{Ar}), 7.84 (d, *J* = 8.5 Hz, 1H, H^{Ar}), 7.49 (dddd, *J* = 24.0, 8.1, 6.8, 1.2 Hz, 2H, H^{Ar}), 7.32 (ddd, *J* = 8.3, 6.8, 1.3 Hz, 1H, H^{Ar}), 7.25 (ddd, *J* = 8.3, 6.8, 1.3 Hz, 2H, H^{Ar}), 7.14 (dd, *J* = 8.5, 1.1 Hz, 1H, H^{Ar}), 7.02 (dd, *J* = 8.4, 1.2 Hz, 1H, H^{Ar}), 3.45 (ddp, *J* = 9.5, 6.7, 3.6 Hz, 1H, C<u>H</u>), 2.78 – 2.57 (m, 2H, C<u>H</u>), 2.09 – 1.96 (m, 1H, C<u>H</u>), 1.71 (dt, *J* = 9.7, 5.0 Hz, 2H, C<u>H</u>), 1.42 (ddq, *J* = 18.9, 13.0, 3.1 Hz, 2H, H^{Cy}), 1.34 – 0.89 (m, 10H, H^{Cy}), 0.84 (t, *J* = 6.6 Hz, 12H, C<u>H</u>3), 0.47 – 0.34 (m, 2H, H^{Cy}).

^{13}C NMR (101 MHz, $CDCl_3$): δ 172.5, 134.0, 133.7, 132.2, 129.4, 129.1, 128.6, 128.2, 128.1, 127.6, 126.9, 126.9, 126.7, 126.4, 125.6, 121.6, 60.8, 57.1, 39.2, 38.9, 38.2, 32.5, 29.8, 29.5, 27.0, 25.9, 24.8, 24.2.

IR (film)/cm^{-1}: 3016, 2951, 2846, 1720, 1571, 1559, 1483, 1451, 1378, 1137, 831, 754.

HRMS (ESI) m/z calcd. for $C_{38}H_{44}NO_3$ ($[M+H]^+$) 562.3316, found 562.3309.

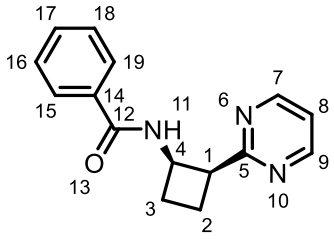
m.p.: 165-170 °C

$[\alpha]_D^{25}$ = +102.0 (c = 0.8, $CHCl_3$).

5.2.2 General Procedure E: Cp*Rh(III)-catalysed enantioselective C(sp^3)–H functionalisation of cycloalkylpyrimidines

To a small vial was added 2-cyclobutylpyrimidine **332** (0.15 mmol, 20.13 mg), dioxazolone **336** (0.26 mmol, 42.41 mg), ligand **396** (16.75 mg, 0.2 equiv), Ag_2CO_3 (2.06 mg, 0.05 equiv), $Cp^*Rh(MeCN)_3(SbF_6)_2$ (12.41 mg, 0.1 equiv) and 1.4-dioxane (0.3 mL, 0.5 M) under air. Then stirred at 80 °C for 20 h. After cooling to room temperature, the mixture was concentrated and purified by silica gel column chromatography (neat pentane to pentane/EtOAc = 1/9 to neat EtOAc) to afford the desired product **341**.

***N*-(2-(pyrimidin-2-yl)cyclobutyl)benzamide (341)**



With 2-cyclobutylpyrimidine **332** (0.15 mmol, 20.13 mg), dioxazolone **336** (0.26 mmol, 42.41 mg), the compound **341** was obtained according to the **General Procedure E** as a pale yellow solid (34.20 mg, 90 % yield, 99:1 er).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.76 (d, *J* = 4.9 Hz, 2H, $H^{7, 9}$), 8.41 (s, 1H, H^{11}), 7.74 – 7.66 (dt, 2H, $H^{16, 18}$), 7.51 – 7.41 (tt, 1H, H^{17}), 7.45 – 7.34 (tt, 2H, $H^{15, 19}$), 7.20 (t, *J* = 4.9 Hz, 1H, H^{8}), 5.20 – 5.07 (m, 1H, H^{4}), 4.16 (m, *J* = 8.6, 3.6, 2.0 Hz, 1H, H^{1}), 2.65 – 2.50 (m, 1H, H^{3a}), 2.46 – 2.31 (m, 2H, $H^{2a, 3b}$), 2.25 – 2.09 (m, 1H, H^{2b}).

^{13}C NMR (101 MHz, $CDCl_3$): δ 171.7 (C^{5}), 166.2 (C^{12}), 157.2 ($C^{7, 9}$), 134.9 (C^{14}), 131.3 (C^{17}), 128.6 ($C^{16, 18}$), 126.9 ($C^{15, 19}$), 119.0 (C^{8}), 47.5 (C^{4}), 46.2 (C^{1}), 29.8 (C^{3}), 23.3 (C^{2}).

er: 99:1 [determined by HPLC Chiralpak® AD-H, hexane/isopropanol = 85/15, 1 ml/min, λ = 240 nm, $t_{(major)}$ = 20.07 min, $t_{(minor)}$ = 18.23 min].

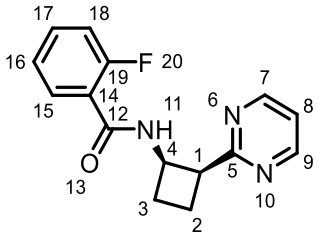
IR (film)/cm^{-1}: 3279, 2932, 1646, 1578, 1531, 1285, 1073, 819, 703.

HRMS (ESI) m/z calcd. for $C_{52}H_{58}O_6{}^{23}Na$ ($[M+Na]^+$) 276.1107, found 276.1105.

$[\alpha]_D{}^{25}$ = +37.14 (c = 0.9, MeOH).

m.p.: 139-141 °C

2-fluoro-*N*-((*1R*,2*S*)-2-(pyrimidin-2-yl)cyclobutyl)benzamide (454)



With 2-cyclobutylpyrimidine **332** (0.15 mmol, 20.13 mg), dioxazolone **400** (0.26 mmol, 47.09 mg), the compound **454** was obtained according to the **General Procedure E** as a pale brown solid (32.15 mg, 79 % yield, 90:10 er).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.75 (d, *J* = 4.9 Hz, 2H, $H^{7, 9}$), 8.52 (s, 1H, H^{11}), 8.04 (td, *J* = 7.9, 1.9 Hz, 1H, H^{15}), 7.45 – 7.35 (m, 1H, H^{17}), 7.24 – 7.15 (m, 2H, $H^{8, 16}$), 7.03 (dd, *J* = 8.2, 1.1 Hz, 1H, H^{18}), 5.27 – 5.14 (m, 1H, H^{4}), 4.20 – 4.10 (m, 1H, H^{1}), 2.59 (m, 1H, H^{2a}), 2.53 – 2.29 (m, 2H, $H^{2b, 3a}$), 2.26 – 2.14 (m, 1H, H^{3b}).

^{13}C NMR (101 MHz, $CDCl_3$): δ 171.3 (C^{12}), 162.1 (C^{5}), 159.5 (C^{19}), 157.2 ($C^{7, 9}$), 133.0 (C^{17}), 132.3 (C^{15}), 124.7 (C^{16}), 121.5 (C^{14}), 118.9 (C^{8}), 115.9 (C^{18}), 47.8 (C^{1}), 46.3 (C^{4}), 29.9 (C^{3}), 22.6 (C^{2}).

^{19}F NMR (376 MHz, $CDCl_3$): δ -113.99.

er: 90:10 [determined by HPLC Chiralpak® AD-H, hexane/isopropanol = 80/20, 1 ml/min, λ = 254 nm, $t_{(major)}$ = 16.59 min, $t_{(minor)}$ = 18.74 min].

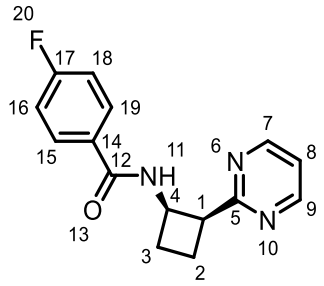
IR (film)/cm^{-1}: 3303, 2990, 2950, 1660, 1561, 1520, 1481, 1427, 1295, 1211, 1032, 758.

HRMS (ESI) m/z calcd. for $C_{15}H_{15}FN_3O$ ($[M+H]^+$) 272.1194, found 272.1189.

$[\alpha]_D^{25}$ = +73.64 (c = 0.67, $CHCl_3$).

m.p.: 78-80°C

4-fluoro-*N*-((1*R*,2*S*)-2-(pyrimidin-2-yl)cyclobutyl)benzamide (455)



With 2-cyclobutylpyrimidine **332** (0.15 mmol, 20.13 mg), dioxazolone **401** (0.26 mmol, 47.09 mg), the compound **455** was obtained according to the **General Procedure E** as a yellow solid (38.26 mg, 94 % yield, 97:3 er).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.76 (d, *J* = 4.9 Hz, 2H, $H^{7, 9}$), 8.45 (s, 1H, H^{11}), 7.76 – 7.66 (m, 2H, $H^{15, 19}$), 7.21 (t, *J* = 4.9 Hz, 1H, H^{8}), 7.11 – 7.01 (m, 2H, $H^{16, 18}$), 5.17 – 5.04 (m, 1H, H^{4}), 4.21 – 4.09 (m, 1H, H^{1}), 2.65 – 2.49 (m, 1H, H^{3a}), 2.46 – 2.30 (m, 2H, $H^{2a, 3b}$), 2.25 – 2.09 (m, 1H, H^{2b}).

^{13}C NMR (101 MHz, $CDCl_3$): δ 171.75 (C^{12}), 165.9 (C^{5}), 165.2 (C^{17}), 157.2 ($C^{7, 9}$), 131.1 (C^{14}), 129.3 (C^{15}), 129.2 (C^{19}), 119.1 (C^{8}), 115.7 (C^{16}), 115.5 (C^{18}), 47.3 (C^{1}), 46.3 (C^{4}), 29.8 (C^{3}), 23.4 (C^{2}).

^{19}F NMR (376 MHz, $CDCl_3$): δ -108.80.

er: 97:3 [determined by HPLC Chiralpak® AD-H, hexane/isopropanol = 85/15, 1 ml/min, λ = 254 nm, $t_{(major)}$ = 18.40 min, $t_{(minor)}$ = 15.21 min].

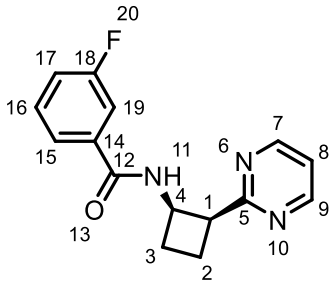
IR (film)/cm^{-1}: 3257, 2999, 2949, 1645, 1561, 1535, 1428, 1310, 1282, 1159, 853, 767.

HRMS (ESI) m/z calcd. for $C_{15}H_{14}N_3O^{23}Na$ ($[M+Na]^+$) 294.1013, found 294.1012.

$[\alpha]_D^{25}$ = +107.59 (c = 0.88, $CHCl_3$).

m.p.: 157-158 °C

3-fluoro-*N*-((1*R*,2*S*)-2-(pyrimidin-2-yl)cyclobutyl)benzamide (456)



With 2-cyclobutylpyrimidine **332** (0.15 mmol, 20.13 mg), dioxazolone **402** (0.26 mmol, 47.09 mg), the compound **456** was obtained according to the **General Procedure E** as a white solid (36.63 mg, 90 % yield, 95:5 er).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.76 (d, *J* = 4.9 Hz, 2H, $H^{7, 9}$), 8.56 (s, 1H, H^{11}), 7.47 (ddd, *J* = 7.7, 1.6, 1.1 Hz, 1H, H^{15}), 7.44 – 7.39 (m, 1H, H^{19}), 7.39 – 7.31 (m, 1H, H^{17}), 7.22 (t, *J* = 4.9 Hz, 1H, H^{8}), 7.15 (tdd, *J* = 8.3, 2.6, 1.0 Hz, 1H, H^{16}), 5.17 – 5.03 (m, 1H, H^{4}), 4.20 – 4.10 (m, 1H, H^{1}), 2.65 – 2.50 (m, 1H, H^{3a}), 2.46 – 2.30 (m, 2H, $H^{2a, 3b}$), 2.25 – 2.10 (m, 1H, H^{2b}).

^{13}C NMR (101 MHz, $CDCl_3$): δ 171.7 (C^{12}), 164.9 (C^{5}), 164.1 (C^{18}), 157.2 ($C^{7, 9}$), 137.3 (C^{14}), 130.3 (C^{17}), 122.5 (C^{15}), 119.1 (C^{8}), 118.4 (C^{16}), 114.4 (C^{19}), 47.2 (C^{1}), 46.3 (C^{4}), 29.7 (C^{3}), 23.5 (C^{2}).

^{19}F NMR (376 MHz, $CDCl_3$): δ -112.14.

er: 95:5 [determined by SFC Chiralpak® IC, 1500 psi, 30 °C; flow: 1.0 mL/min; 0% to 70% MeOH over 10 min, then from 70% to 50% MeOH in 0.5 min, then hold 50% MeOH for 2.5 min, λ = 205 nm, $t_{(major)}$ = 5.78 min, $t_{(minor)}$ = 4.80 min].

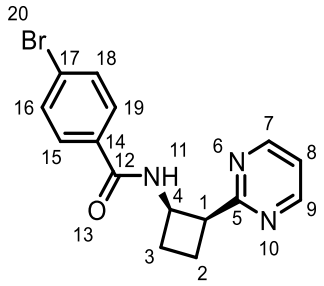
IR (film)/cm^{-1}: 3288, 2995, 1717, 1587, 1560, 1530, 1483, 1428, 1346, 1290, 1210, 810, 756, 684.

HRMS (ESI) m/z calcd. for $C_{15}H_{15}FN_3O$ ($[M+H]^+$) 272.1194, found 272.1200.

$[\alpha]_D^{25}$ = +117.31 (c = 0.93, $CHCl_3$).

m.p.: 109-110 °C

4-bromo-*N*-((1*R*,2*S*)-2-(pyrimidin-2-yl)cyclobutyl)benzamide (457)



With 2-cyclobutylpyrimidine **332** (0.15 mmol, 20.13 mg), dioxazolone **403** (0.26 mmol, 62.93 mg), the compound **457** was obtained according to the **General Procedure E** as a yellow solid (45.35 mg, 91 % yield, 95:5 er).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.75 (d, *J* = 4.9 Hz, 2H, $H^{7, 9}$), 8.50 (s, 1H, H^{11}), 7.62 – 7.46 (m, 4H, $H^{15, 16, 18, 19}$), 7.21 (t, *J* = 4.9 Hz, 1H, H^{8}), 5.16 – 5.03 (m, 1H, H^{1}), 4.21 – 4.08 (m, 1H, H^{4}), 2.65 – 2.51 (m, 1H, H^{3a}), 2.46 – 2.30 (m, 2H, $H^{2a, 3b}$), 2.24 – 2.09 (m, 1H, H^{2b}).

^{13}C NMR (101 MHz, $CDCl_3$): δ 171.7 (C^{12}), 165.3 (C^{5}), 157.2 ($C^{7, 9}$), 133.8 (C^{14}), 131.8 ($C^{16, 18}$), 128.6 ($C^{15, 19}$), 125.9 (C^{17}), 119.1 (C^{8}), 47.2 (C^{1}), 46.3 (C^{4}), 29.7 (C^{3}), 23.4 (C^{2}).

er: 95:5 [determined by HPLC Chiralpak® AD-H, hexane/isopropanol = 85/15, 1 ml/min, λ = 254 nm, $t_{(major)}$ = 41.12 min, $t_{(minor)}$ = 21.21 min].

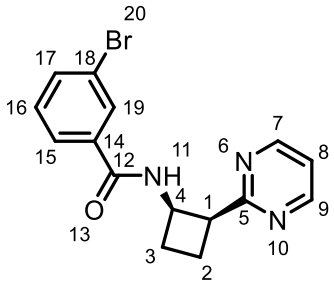
IR (film)/cm^{-1}: 3270, 2995, 1648, 1560, 1533, 1482, 1428, 1278, 1011, 846, 759, 636.

HRMS (ESI) m/z calcd. for $C_{15}H_{14}BrN_3O^{23}Na$ ($[M+Na]^+$) 354.0212, found 354.0206.

$[\alpha]_D^{25}$ = +60.28 (c = 1.01, $CHCl_3$).

m.p.: 172-173 °C

3-bromo-*N*-((1*R*,2*S*)-2-(pyrimidin-2-yl)cyclobutyl)benzamide (458)



With 2-cyclobutylpyrimidine **332** (0.15 mmol, 20.13 mg), dioxazolone **404** (0.26 mmol, 62.93 mg), the compound **458** was obtained according to the **General Procedure E** as a yellow solid (46.34 mg, 93 % yield, 97:3 er).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.74 (d, *J* = 4.9 Hz, 2H, $H^{7, 9}$), 8.57 (s, 1H, H^{11}), 7.80 (t, *J* = 1.8 Hz, 1H, H^{19}), 7.61 (dt, *J* = 7.8, 1.4 Hz, 1H, H^{15}), 7.55 (ddd, *J* = 8.0, 2.1, 1.1 Hz, 1H, H^{17}), 7.28 – 7.17 (m, 2H, $H^{16, 8}$), 5.10 – 5.01 (m, 1H, H^{4}), 4.15 – 4.08 (m, 1H, H^{1}), 2.55 (m, 1H, H^{3a}), 2.42 – 2.27 (m, 2H, $H^{2a, 3b}$), 2.21 – 2.12 (m, 1H, H^{2b}).

^{13}C NMR (101 MHz, $CDCl_3$): δ 171.6 (C^{12}), 164.7 (C^{5}), 157.2 ($C^{7, 9}$), 136.9 (C^{14}), 134.2 (C^{17}), 130.3 (d, *J* = 2.3 Hz) (C^{19}), 130.2 (C^{16}), 125.6 (C^{15}), 122.7 (C^{18}), 119.2 (C^{8}), 47.1 (C^{1}), 46.4 (C^{4}), 29.7 (C^{3}), 23.6 (C^{2}).

er: 97:3 [determined by HPLC Chiralpak® AD-H, hexane/isopropanol = 90/10, 1 ml/min, λ = 230 nm, $t_{(major)}$ = 26.68 min, $t_{(minor)}$ = 24.18 min].

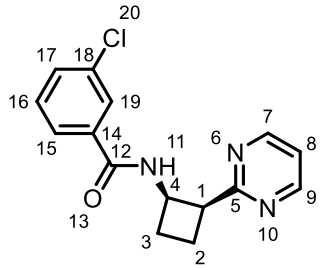
IR (film)/cm^{-1}: 3263, 2994, 2981, 2949, 1649, 1561, 1532, 1427, 1286, 1264, 813, 770, 688.

HRMS (ESI) m/z calcd. for $C_{15}H_{14}BrN_3O^{23}Na$ ($[M+Na]^+$) 354.0212, found 354.0215.

$[\alpha]_D^{25}$ = +88.87 (c = 0.97, $CHCl_3$).

m.p.: 121-124°C

3-chloro-*N*-((1*R*,2*S*)-2-(pyrimidin-2-yl)cyclobutyl)benzamide (459)



With 2-cyclobutylpyrimidine **332** (0.15 mmol, 20.13 mg), dioxazolone **405** (0.26 mmol, 51.26 mg), the compound **459** was obtained according to the **General Procedure E** as a yellow solid (39.71 mg, 92 % yield, 96:4 er).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.77 (d, *J* = 4.9 Hz, 2H, $H^{7, 9}$), 8.59 (s, 1H, H^{11}), 7.68 (t, *J* = 1.9 Hz, 1H, H^{19}), 7.58 (dt, *J* = 7.8, 1.4 Hz, 1H, H^{15}), 7.43 (ddd, *J* = 8.0, 2.1, 1.1 Hz, 1H, H^{17}), 7.33 (t, *J* = 7.8 Hz, 1H, H^{16}), 7.23 (t, *J* = 4.9 Hz, 1H, H^{8}), 5.14 – 5.02 (m, 1H, H^{4}), 4.19 – 4.10 (m, 1H, H^{1}), 2.63 – 2.52 (m, 1H, H^{2a}), 2.45 – 2.30 (m, 2H, $H^{3a, 2b}$), 2.24 – 2.15 (m, 1H, H^{3b}).

^{13}C NMR (101 MHz, $CDCl_3$): δ 171.6 (C^{12}), 164.8 (C^{5}), 157.2 ($C^{7, 9}$), 136.8 (C^{14}), 134.7 (C^{17}), 131.3 (C^{19}), 129.9 (C^{16}), 127.4 (C^{15}), 125.1 (C^{18}), 119.1 (C^{8}), 47.1 (C^{1}), 46.4 (C^{4}), 29.7 (C^{3}), 23.5 (C^{2}).

er: 96:4 [determined by HPLC Chiralpak® AD-H, hexane/isopropanol = 95/5, 1 ml/min, λ = 220 nm, $t_{(major)}$ = 51.81 min, $t_{(minor)}$ = 47.81 min].

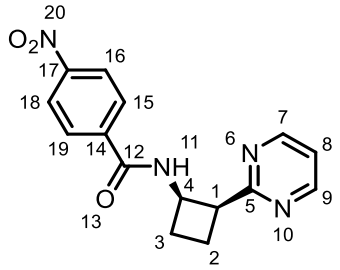
IR (film)/cm^{-1}: 3308, 2991, 2947, 1647, 1571, 1560, 1525, 1426, 1291, 806, 749, 682.

HRMS (ESI) m/z calcd. for $C_{15}H_{14}ClN_3O^{23}Na$ ($[M+Na]^+$) 310.0718, found 310.0714.

$[\alpha]_D^{25}$ = +91.94 (c = 1.1, $CHCl_3$).

m.p.: 118-120°C

4-nitro-*N*-((1*R*,2*S*)-2-(pyrimidin-2-yl)cyclobutyl)benzamide (460)



With 2-cyclobutylpyrimidine **332** (0.15 mmol, 20.13 mg), dioxazolone **406** (0.26 mmol, 54.11 mg), the compound **460** was obtained according to the **General Procedure E** as a white solid (22.82 mg, 51 % yield, 90:10 er).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.86 (s, 1H, H^{11}), 8.77 (d, *J* = 4.9 Hz, 2H, $H^{7, 9}$), 8.26 (d, 2H, $H^{16, 18}$), 7.88 (d, 2H, $H^{15, 19}$), 7.24 (t, *J* = 4.9 Hz, 1H, H^{8}), 5.17 – 5.06 (m, 1H, H^{4}), 4.23 – 4.11 (m, 1H, H^{1}), 2.66 – 2.54 (m, 1H, H^{3a}), 2.50 – 2.31 (m, 2H, $H^{2a, 3b}$), 2.23 – 2.15 (m, 1H, H^{2b}).

^{13}C NMR (101 MHz, $CDCl_3$): δ 171.7 (C^{12}), 164.1 (C^{5}), 157.2 ($C^{7, 9}$), 149.6 (C^{17}), 140.6 (C^{14}), 128.1 ($C^{15, 19}$), 123.9 ($C^{16, 18}$), 119.2 (C^{8}), 46.9 (C^{1}), 46.5 (C^{4}), 29.7 (C^{3}), 23.7 (C^{2}).

er: 90:10 [determined by HPLC Chiralpak® AD-H, hexane/isopropanol = 80/20, 1 ml/min, λ = 230 nm, $t_{(major)}$ = 23.44 min, $t_{(minor)}$ = 14.32 min].

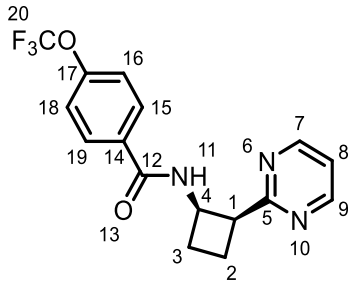
IR (film)/cm^{-1}: 3217, 2999, 2947, 1652, 1561, 1519, 1430, 1347, 868, 712.

HRMS (ESI) m/z calcd. for $C_{15}H_{15}N_4O_3$ ($[M+H]^+$) 299.1139, found 299.1132.

$[\alpha]_D^{25}$ = +63.34 (c = 0.6, $CHCl_3$).

m.p.: 164-168 °C

***N*-((1*R*,2*S*)-2-(pyrimidin-2-yl)cyclobutyl)-4-(trifluoromethoxy)benzamide (461)**



With 2-cyclobutylpyrimidine **332** (0.15 mmol, 20.13 mg), dioxazolone **407** (0.26 mmol, 64.25 mg), the compound **461** was obtained according to the **General Procedure E** as a yellow solid (41.48 mg, 82 % yield, 94:6 er).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.77 (d, *J* = 4.9 Hz, 2H, $H^{7, 9}$), 8.56 (s, 1H, H^{11}), 7.78 – 7.71 (m, 2H, $H^{15, 19}$), 7.25 – 7.20 (m, 3H, $H^{8, 16, 19}$), 5.16 – 5.06 (m, 1H, H^{4}), 4.19 – 4.10 (m, 1H, H^{1}), 2.64 – 2.52 (m, 1H, H^{3a}), 2.45 – 2.31 (m, 2H, $H^{2a, 3b}$), 2.22 – 2.11 (m, 1H, H^{2a}).

^{13}C NMR (101 MHz, $CDCl_3$): δ 171.7 (C^{12}), 164.9 (C^{5}), 157.2 ($C^{7, 9}$), 151.4 (C^{17}), 133.5 (C^{14}), 128.8 ($C^{15, 19}$), 120.7 ($C^{16, 18}$), 119.1 (C^{8}), 47.2 (d, *J* = 2.6 Hz) (C^{1}), 46.3 (C^{4}), 29.8 (d, *J* = 2.0 Hz) (C^{3}), 23.5 (C^{2}).

^{19}F NMR (376 MHz, $CDCl_3$): δ -57.72.

er: 94:6 [determined by HPLC Chiralpak® AD-H, hexane/isopropanol = 85/15, 1 ml/min, λ = 240 nm, $t_{(major)}$ = 28.31 min, $t_{(minor)}$ = 16.50 min].

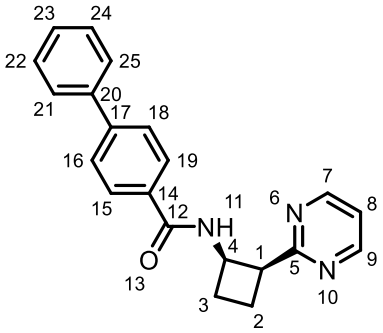
IR (film)/cm^{-1}: 3309, 2992, 2952, 1646, 1561, 1427, 1265, 1220, 1168, 862, 767.

HRMS (ESI) m/z calcd. for $C_{16}H_{14}F_3N_3O_2{}^{23}Na$ ($[M+Na]^+$) 360.0930, found 360.0936.

[α]$_D$ ^{25} = +115.32 (c = 0.6, $CHCl_3$).

m.p.: 88-92 °C

***N*-((1*R*,2*S*)-2-(pyrimidin-2-yl)cyclobutyl)-[1,1'-biphenyl]-4-carboxamide (462)**



With 2-cyclobutylpyrimidine **332** (0.15 mmol, 20.13 mg), dioxazolone **408** (0.26 mmol, 62.20 mg), the compound **462** was obtained according to the **General Procedure E** as a white solid (23.72 mg, 48 % yield, 85:15 er).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.78 (d, *J* = 4.9 Hz, 2H, $H^{7, 9}$), 8.48 (s, 1H, H^{11}), 7.78 (d, 2H, $H^{15, 19}$), 7.65 – 7.56 (m, 4H, $H^{16, 18, 22, 24}$), 7.45 (t, 2H, $H^{21, 25}$), 7.38 (t, 1H, H^{23}), 7.22 (t, *J* = 4.9 Hz, 1H, H^{8}), 5.22 – 5.11 (m, 1H, H^{4}), 4.22 – 4.14 (m, 1H, H^{1}), 2.66 – 2.55 (m, 1H, H^{3a}), 2.47 – 2.35 (m, 2H, $H^{2a, 3b}$), 2.25 – 2.14 (m, 1H, H^{2b}).

^{13}C NMR (101 MHz, $CDCl_3$): δ 171.8 (C^{12}), 165.9 (C^{5}), 157.2 ($C^{7, 9}$), 144.1 (C^{17}), 140.3 (C^{20}), 133.6 (C^{14}), 129.0 ($C^{21, 25}$), 128.1 (C^{23}), 127.5 ($C^{15, 19}$), 127.3 ($C^{16, 18}$), 127.3 ($C^{22, 24}$), 119.1 (C^{8}), 47.5 (C^{1}), 46.3 (C^{4}), 29.8 (C^{3}), 23.3 (C^{2}).

er: 85:15 [determined by HPLC Chiralpak® AD-H, hexane/isopropanol = 70/30, 1 ml/min, λ = 230 nm, $t_{(major)}$ = 22.88 min, $t_{(minor)}$ = 14.98 min].

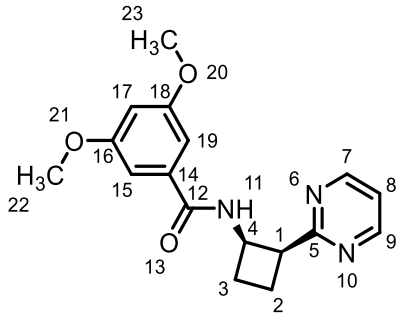
IR (film)/cm^{-1}: 3342, 2983, 2948, 1633, 1557, 1534, 1515, 1423, 1294, 1188, 747.

HRMS (ESI) m/z calcd. for $C_{21}H_{20}N_3O$ ($[M+H]^+$) 330.1601, found 330.2599.

$[\alpha]_D^{25}$ = +7.09 (c = 1.3, $CHCl_3$).

m.p.: 179-180 °C

3,5-dimethoxy-*N*-((1*R*,2*S*)-2-(pyrimidin-2-yl)cyclobutyl)benzamide (463)



With 2-cyclobutylpyrimidine **332** (0.15 mmol, 20.13 mg), dioxazolone **409** (0.26 mmol, 58.03 mg), the compound **463** was obtained according to the **General Procedure E** as a yellow solid (32.07 mg, 70 % yield, 93:7 er).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.75 (d, *J* = 4.9 Hz, 2H, $H^{7, 9}$), 8.37 (s, 1H, H^{11}), 7.20 (t, *J* = 4.9 Hz, 1H, H^{8}), 6.82 (d, *J* = 2.3 Hz, 2H, $H^{15, 19}$), 6.53 (t, *J* = 2.3 Hz, 1H, H^{17}), 5.16 – 5.03 (m, 1H, H^{4}), 4.18 – 4.10 (m, 1H, H^{1}), 3.79 (s, 6H, $H^{21a, 21b, 21c, 23a, 23b, 23c}$), 2.65 – 2.49 (m, 1H, H^{3a}), 2.45 – 2.30 (m, 2H, $H^{2a, 3b}$), 2.25 – 2.10 (m, 1H, H^{2b}).

^{13}C NMR (101 MHz, $CDCl_3$): δ 171.7 (C^{12}), 166.0 (C^{5}), 160.9 ($C^{16,18}$), 157.2 ($C^{7, 9}$), 137.2 (C^{14}), 119.0 (C^{8}), 104.9 ($C^{15, 19}$), 103.5 (C^{17}), 55.6 ($C^{21, 23}$), 47.4 (C^{1}), 46.3 (C^{4}), 29.7 (C^{3}), 23.3 (C^{2}).

er: 93:7 [determined by HPLC Chiralpak® OD-H, hexane/isopropanol = 88/12, 1 ml/min, λ = 220 nm, $t_{(major)}$ = 29.01 min, $t_{(minor)}$ = 39.25 min].

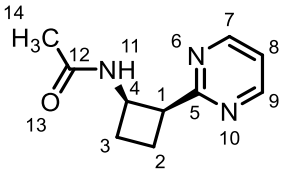
IR (film)/cm^{-1}: 3329, 2948, 2839, 1653, 1594, 1560, 1524, 1426, 1206, 1157, 1064, 763.

HRMS (ESI) m/z calcd. for $C_{17}H_{19}N_3O_3{}^{23}Na$ ($[M+Na]^+$) 336.1319, found 336.1314.

[α]$_D$ ^{25} = +72.97 (c = 1.4, $CHCl_3$).

m.p.: 118-122 °C

***N*-((1*R*,2*S*)-2-(pyrimidin-2-yl)cyclobutyl)acetamide (464)**



With 2-cyclobutylpyrimidine **332** (0.15 mmol, 20.13 mg), dioxazolone **410** (0.26 mmol, 26.28 mg), the compound **464** was obtained according to the **General Procedure E** as a pale yellow solid (18.60 mg, 65 % yield, 93:7 er).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.73 (d, *J* = 5.0 Hz, 2H, $H^{7,9}$), 7.19 (t, *J* = 4.9 Hz, 1H, H^{8}), 5.01 – 4.88 (m, 1H, H^{4}), 4.10 – 4.00 (m, 1H, H^{1}), 2.52 – 2.41 (m, 1H, H^{3a}), 2.36 – 2.23 (m, 2H, $H^{2a, 3b}$), 2.13 – 2.03 (m, 1H, H^{2b}), 1.85 (s, 3H, H^{14}).

^{13}C NMR (101 MHz, $CDCl_3$): δ 171.6 (C^{12}), 169.1 (C^{5}), 157.2 ($C^{7,9}$), 118.9 (C^{8}), 47.9 (C^{4}), 45.8 (C^{1}), 29.7 (C^{3}), 23.6 (C^{2}), 22.7 (C^{14}).

er: 93:7 [determined by HPLC Chiralpak® AD-H, hexane/isopropanol = 95/5, 1 ml/min, λ = 254 nm, $t_{(major)}$ = 46.02 min, $t_{(minor)}$ = 42.43 min].

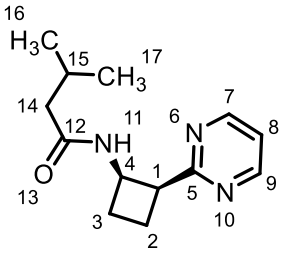
IR (film)/cm^{-1}: 3244, 2946, 1674, 1561, 1433, 1372, 1287, 1048, 813, 727.

HRMS (ESI) m/z calcd. for $C_{10}H_{14}N_3O$ ($[M+H]^+$) 192.1131, found 192.1128.

$[\alpha]_D^{25}$ = +207.76 (c = 0.8, MeOH).

m.p.: 126-128 °C

3-methyl-*N*-((1*R*,2*S*)-2-(pyrimidin-2-yl)cyclobutyl)butanamide (465)



With 2-cyclobutylpyrimidine **332** (0.15 mmol, 20.13 mg), dioxazolone **411** (0.26 mmol, 37.22 mg), the compound **465** was obtained according to the **General Procedure E** as a white solid (30.45 mg, 87 % yield, 95:5 er).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.72 (d, *J* = 4.9 Hz, 2H, $H^{7, 9}$), 7.17 (t, *J* = 4.9 Hz, 1H, H^{8}), 7.07 (s, 1H, H^{11}), 5.03 – 4.89 (m, 1H, H^{4}), 4.11 – 4.01 (m, 1H, H^{1}), 2.54 – 2.41 (m, 1H, H^{3a}), 2.38 – 2.20 (m, 2H, $H^{2a, 3b}$), 2.18 – 2.03 (m, 1H, H^{2b}), 2.01 – 1.79 (m, 2H, $H^{14a, 14b}$), 0.98 – 0.95 (m, 1H, H^{15}), 0.83 (d, 3H, H^{16}), 0.74 (d, 3H, H^{17}).

^{13}C NMR (101 MHz, $CDCl_3$): δ 171.6 (C^{12}), 171.4 (C^{5}), 157.1 ($C^{7, 9}$), 118.9 (C^{8}), 48.0 (C^{4}), 46.4 (C^{1}), 45.6 (C^{14}), 29.6 (C^{3}), 26.1 (C^{2}), 22.6 (C^{15}), 22.5 (C^{16}), 22.4 (C^{17}).

er: 95:5 [determined by SFC Chiralpak® IC, 1500 psi, 30 °C; flow: 1.0 mL/min; 0% to 70% MeOH over 10 min, then from 70% to 50% MeOH in 0.5 min, then hold 50% MeOH for 2.5 min, λ = 205 nm, $t_{(major)}$ = 5.09 min, $t_{(minor)}$ = 5.25 min].

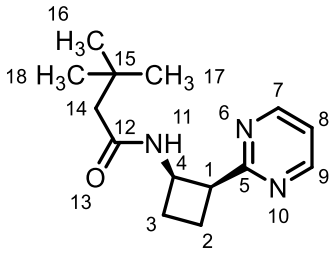
IR (film)/cm^{-1}: 3241, 2956, 1662, 1561, 1429, 1304, 1054, 822, 726.

HRMS (ESI) m/z calcd. for $C_{13}H_{19}N_3O^{23}Na$ ($[M+Na]^+$) 256.1420, found 256.1419.

$[\alpha]_D^{25}$ = +199.06 (c = 1.27, MeOH).

m.p.: 118-120 °C

3,3-dimethyl-*N*-((1*R*,2*S*)-2-(pyrimidin-2-yl)cyclobutyl)butanamide (466)



With 2-cyclobutylpyrimidine **332** (0.15 mmol, 20.13 mg), dioxazolone **412** (0.26 mmol, 40.86 mg), the compound **466** was obtained according to the **General Procedure E** as a white solid (32.28 mg, 87 % yield, 94:6 er).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.71 (d, *J* = 4.9 Hz, 2H, $H^{7, 9}$), 7.17 (t, *J* = 4.9 Hz, 1H, H^{8}), 7.00 (d, *J* = 9.1 Hz, 1H, H^{11}), 5.01 – 4.90 (m, 1H, H^{4}), 4.09 – 4.01 (m, 1H, H^{1}), 2.55 – 2.40 (m, 1H, H^{3a}), 2.40 – 2.20 (m, 2H, $H^{3b, 2a}$), 2.14 – 2.04 (m, 1H, H^{2b}), 1.91 (q, *J* = 12.8 Hz, 2H, $H^{14a, 14b}$), 0.86 (s, 9H, $H^{16a, 16b, 16c, 17a, 17b, 17c, 18a, 18b, 18c}$).

^{13}C NMR (101 MHz, $CDCl_3$): δ 171.6 (C^{12}), 170.6 (C^{5}), 157.2 ($C^{7, 9}$), 118.9 (C^{8}), 51.0 (C^{14}), 48.1 (C^{1}), 45.6 (C^{4}), 30.8 (C^{3}), 29.8 ($C^{16, 17, 18}$), 29.7 (C^{15}), 22.6 (C^{2}).

er: 94:6 [determined by HPLC Chiralpak® AD-H, hexane/isopropanol = 90/10, 1 ml/min, λ = 240 nm, $t_{(major)}$ = 13.25 min, $t_{(minor)}$ = 14.96 min].

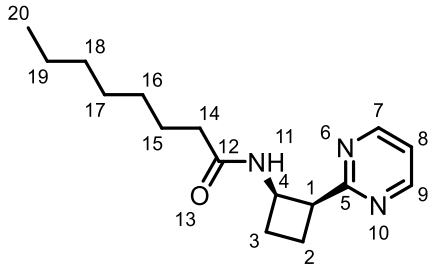
IR (film)/cm^{-1}: 3254, 2956, 1656, 1644, 1576, 1562, 1465, 1236, 752.

HRMS (ESI) m/z calcd. for $C_{14}H_{21}N_3O^{23}Na$ ($[M+Na]^+$) 270.1577, found 270.1573.

$[\alpha]_D^{25}$ = +151.01 (c = 1.3, $CHCl_3$).

m.p.: 122-125°C

***N*-((1*R*,2*S*)-2-(pyrimidin-2-yl)cyclobutyl)octanamide (467)**



With 2-cyclobutylpyrimidine **332** (0.15 mmol, 20.13 mg), dioxazolone **413** (0.26 mmol, 48.16 mg), the compound **467** was obtained according to the **General Procedure E** as a white solid (37.15 mg, 90 % yield, 94:6 er).

1H NMR (400 MHz, CDCl3) δ 8.74 (d, J = 4.9 Hz, 2H), 7.20 (t, J = 4.9 Hz, 2H), 5.01 – 4.89 (m, 1H), 4.12 – 4.02 (m, 1H), 2.55 – 2.41 (m, 1H), 2.35 – 2.25 (m, 2H), 2.19 – 2.09 (m, 1H), 2.09 – 1.98 (m, 2H), 1.46 (p, J = 7.6 Hz, 2H), 1.35 – 1.07 (m, 8H, $H^{16a\&16b\&17a\&17b\&18a\&18b\&19a\&19b}$), 0.85 (t, J = 7.0 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 172.2 (C^{12}), 171.4 (C^5), 157.1 ($C^{7,9}$), 118.9 (C^8), 47.9 (C^1), 45.8 (C^4), 37.0 (C^{14}), 31.8 (C^{18}), 29.5 (C^3), 29.2 (C^{16}), 29.1 (C^{17}), 25.8 (C^{15}), 22.6 (C^2), 22.7 (C^{19}), 14.2 (C^{20}).

er: 94:6 [determined by HPLC Chiralpak® AD-H, hexane/isopropanol = 85/15, 1 ml/min, λ = 254 nm, $t_{(major)}$ = 10.51 min, $t_{(minor)}$ = 9.32 min].

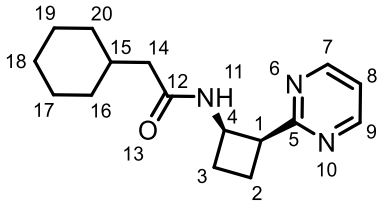
IR (film)/cm^{-1}: 3359, 3245, 2953, 2927, 2855, 1665, 1561, 1426, 1237, 814, 760.

HRMS (ESI) m/z calcd. for $C_{16}H_{25}N_3O^{23}Na$ ($[M+Na]^+$) 298.1890, found 298.1893.

$[\alpha]_D^{25}$ = +148.45 (c = 0.8, $CHCl_3$).

m.p.: 63-66 °C

2-cyclohexyl-*N*-((1*R*,2*S*)-2-(pyrimidin-2-yl)cyclobutyl)acetamide (468)



With 2-cyclobutylpyrimidine **332** (0.15 mmol, 20.13 mg), dioxazolone **414** (0.26 mmol, 47.63 mg), the compound **468** was obtained according to the **General Procedure E** as a white solid (36.07 mg, 88 % yield, 90:10 er).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.74 (d, J = 4.9 Hz, 2H, $H^{7, 9}$), 7.21 (t, J = 4.9 Hz, 1H, H^{8}), 7.04 (d, J = 8.9 Hz, 1H, H^{11}), 5.03 – 4.89 (m, 1H, H^{4}), 4.14 – 4.01 (m, 1H, H^{1}), 2.54 – 2.43 (m, 1H, H^{3a}), 2.39 – 2.23 (m, 2H, $H^{3b, 2a}$), 2.21 – 2.11 (m, 1H, H^{2b}), 1.94 (dd, J = 13.8, 7.0 Hz, 1H, H^{14a}), 1.85 (dd, J = 13.8, 7.0 Hz, 1H, H^{14b}), 1.65 – 1.52 (m, 5H, $H^{16, 17}$), 1.43 (d, J = 1.6 Hz, 1H, H^{15}), 1.23 – 1.02 (m, 3H, $H^{19, 20}$), 0.89 – 0.76 (m, 1H, H^{18a}), 0.75 – 0.63 (m, 1H, H^{18b}).

^{13}C NMR (101 MHz, $CDCl_3$): δ 171.4 (C^{12}), 157.1 ($C^{7, 9}$), 118.9 (C^{8}), 48.1 (C^{1}), 45.8 (C^{4}), 45.2 (C^{14}), 35.3 (C^{15}), 33.2 (C^{16}), 33.0 (C^{20}), 29.5 (C^{3}), 26.3 (C^{18}), 26.2 ($C^{17, 19}$), 22.5 (C^{2}).

er: 90:10 [determined by SFC Chiralpak® IC, 1500 psi, 30 °C; flow: 1.0 mL/min; 0% to 70% MeOH over 10 min, then from 70% to 50% MeOH in 0.5 min, then hold 50% MeOH for 2.5 min, λ = 205 nm, $t_{(major)}$ = 5.84 min, $t_{(minor)}$ = 5.99 min].

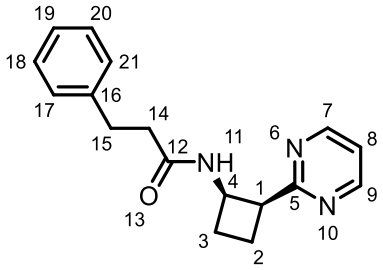
IR (film)/cm^{-1}: 3390, 2924, 2851, 1656, 1560, 1428, 1235, 760.

HRMS (ESI) m/z calcd. for $C_{16}H_{23}N_3O^{23}Na$ ($[M+Na]^+$) 296.1733, found 296.1736.

$[\alpha]_D^{25}$ = +158.23 (c = 1.2, $CHCl_3$).

m.p.: 98-104 °C

3-phenyl-*N*-((1*R*,2*S*)-2-(pyrimidin-2-yl)cyclobutyl)propanamide (469)



With 2-cyclobutylpyrimidine **332** (0.15 mmol, 20.13 mg), dioxazolone **415** (0.26 mmol, 49.71 mg), the compound **469** was obtained according to the **General Procedure E** as a yellow solid (37.56 mg, 89 % yield, 94:6 er).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.68 (d, J = 4.9 Hz, 2H, $H^{7, 9}$), 7.24 – 7.19 (m, 2H, $H^{17, 21}$), 7.18 – 7.09 (m, 3H, $H^{18, 19, 20}$), 5.00 – 4.87 (m, 1H, H^{4}), 4.09 – 3.99 (m, 1H, H^{1}), 2.92 – 2.77 (m, 2H, $H^{14a, 14b}$), 2.50 – 2.41 (m, 1H, H^{2a}), 2.40 – 2.31 (m, 2H, $H^{15a, 15b}$), 2.31 – 2.19 (m, 2H, $H^{3a, 3b}$), 2.15 – 2.02 (m, 1H, H^{2b}).

^{13}C NMR (101 MHz, $CDCl_3$): δ 171.3 (C^{12}), 171.1 (C^{5}), 157.0 ($C^{7, 9}$), 141.1 (C^{16}), 128.5 ($C^{18, 20}$), 128.4 (C^{19}), 126.2 ($C^{17, 21}$), 118.9 (C^{8}), 47.7 (C^{1}), 45.8 (C^{4}), 38.7 (C^{14}), 31.7 (C^{15}), 29.4 (C^{3}), 22.8 (C^{2}).

er: 94:6 [determined by HPLC Chiralpak® AD-H, hexane/isopropanol = 80/20, 1 ml/min, λ = 254 nm, $t_{(major)}$ = 12.14 min, $t_{(minor)}$ = 9.77 min].

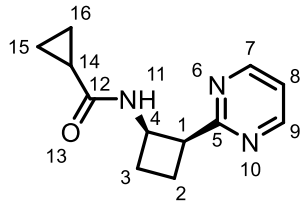
IR (film)/cm^{-1}: 3255, 2986, 2941, 1658, 1560, 1547, 1429, 1260, 815, 748, 700.

HRMS (ESI) m/z calcd. for $C_{17}H_{19}N_3O^{23}Na$ ($[M+Na]^+$) 304.1420, found 304.1419.

$[\alpha]_D^{25}$ = +164.88 (c = 1.3, $CHCl_3$).

m.p.: 118-119°C

***N*-((1*R*,2*S*)-2-(pyrimidin-2-yl)cyclobutyl)cyclopropanecarboxamide (470)**



With 2-cyclobutylpyrimidine **332** (0.15 mmol, 20.13 mg), dioxazolone **416** (0.26 mmol, 33.05 mg), the compound **470** was obtained according to the **General Procedure E** as a white solid (26.08 mg, 80 % yield, 92:8 er).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.74 (d, *J* = 4.9 Hz, 2H, $H^{7, 9}$), 7.40 (s, 1H, H^{11}), 7.20 (d, *J* = 4.9 Hz, 1H, H^{8}), 5.04 – 4.90 (m, 1H, H^{4}), 4.05 (m, 1H, H^{1}), 2.54 – 2.42 (m, 1H, H^{3a}), 2.42 – 2.20 (m, 2H, $H^{2a, 3b}$), 2.15 – 2.01 (m, 1H, H^{2b}), 1.21 (m, 1H, H^{14}), 0.93 – 0.75 (m, 2H, $H^{15a, 16a}$), 0.71 – 0.55 (m, 2H, $H^{15b, 16b}$).

^{13}C NMR (101 MHz, $CDCl_3$): δ 172.5 (C^{12}), 171.7 (C^{5}), 157.1 ($C^{7, 9}$), 118.9 (C^{8}), 48.0 (C^{1}), 45.8 (C^{4}), 29.8 (C^{3}), 22.6 (C^{2}), 15.0 (C^{14}), 7.1 (C^{15}), 7.1 (C^{16}).

er: 92:8 [determined by SFC Chiralpak® ID, 1500 psi, 30 °C; flow: 1.0 mL/min; 0% to 70% MeOH over 10 min, then from 70% to 50% MeOH in 0.5 min, then hold 50% MeOH for 2.5 min, λ = 210 nm, $t_{(major)}$ = 4.85 min, $t_{(minor)}$ = 4.72 min].

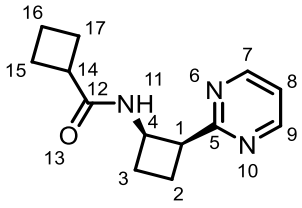
IR (film)/cm^{-1}: 3291, 2992, 2947, 1662, 1561, 1429, 1258, 1058, 943, 760.

HRMS (ESI) m/z calcd. for $C_{12}H_{15}N_3O^{23}Na$ ($[M+Na]^+$) 240.1107, found 240.1104.

$[\alpha]_D^{25}$ = +144.78 (c = 1.02, $CHCl_3$).

m.p.: 68-69 °C

***N*-((1*R*,2*S*)-2-(pyrimidin-2-yl)cyclobutyl)cyclobutanecarboxamide (471)**



With 2-cyclobutylpyrimidine **332** (0.15 mmol, 20.13 mg), dioxazolone **417** (0.26 mmol, 36.69 mg), the compound **471** was obtained according to the **General Procedure E** as a white solid (23.94 mg, 69 % yield, 92:8 er).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.72 (d, *J* = 5.0 Hz, 2H, $H^{7, 9}$), 7.18 (t, *J* = 4.9 Hz, 1H, H^{8}), 7.12 (d, *J* = 8.8 Hz, 1H, H^{11}), 4.99 – 4.90 (m, 1H, H^{4}), 4.09 – 4.02 (m, 1H, H^{1}), 2.92 – 2.79 (m, 1H, H^{14}), 2.52 – 2.43 (m, 1H, H^{3a}), 2.35 – 2.23 (m, 2H, $H^{3b, 2a}$), 2.22 – 2.14 (m, 1H, H^{2b}), 2.14 – 2.02 (m, 2H, $H^{15a, 17a}$), 2.02 – 1.96 (m, 2H, $H^{15b, 17b}$), 1.91 – 1.82 (m, 1H, H^{16a}), 1.82 – 1.70 (m, 1H, H^{16b}).

^{13}C NMR (101 MHz, $CDCl_3$): δ 173.9 (C^{12}), 171.6 (C^{5}), 157.1 ($C^{7, 9}$), 118.9 (C^{8}), 47.9 (C^{1}), 45.5 (C^{4}), 40.2 (C^{14}), 29.6 (C^{3}), 25.4 (d, *J* = 18.5 Hz) (C^{15}), 22.6 (C^{17}), 18.2 (C^{16}).

er: 92:8 [determined by SFC Chiralpak® IC, 1500 psi, 30 °C; flow: 1.0 mL/min; 0% to 70% MeOH over 10 min, then from 70% to 50% MeOH in 0.5 min, then hold 50% MeOH for 2.5 min, λ = 205 nm, $t_{(major)}$ = 5.99 min, $t_{(minor)}$ = 6.32 min].

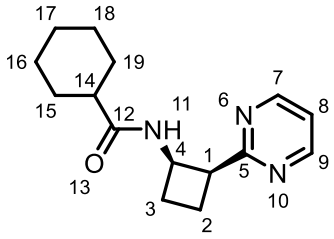
IR (film)/cm^{-1}: 3247, 2987, 2944, 1661, 1561, 1260, 756.

HRMS (ESI) m/z calcd. for $C_{13}H_{18}N_3O$ ($[M+H]^+$) 232.1444, found 232.1440.

$[\alpha]_D^{25}$ = +181.78 (c = 0.9, $CHCl_3$).

m.p.: 102-104 °C

***N*-((1*R*,2*S*)-2-(pyrimidin-2-yl)cyclobutyl)cyclohexanecarboxamide (472)**



With 2-cyclobutylpyrimidine **332** (0.15 mmol, 20.13 mg), dioxazolone **418** (0.26 mmol, 43.98 mg), the compound **472** was obtained according to the **General Procedure E** as a white solid (35.64 mg, 92 % yield, 95:5 er).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.73 (d, *J* = 4.9 Hz, 2H, $H^{7, 9}$), 7.18 (t, *J* = 4.9 Hz, 1H, H^{8}), 5.00 – 4.87 (m, 1H, H^{4}), 4.09 – 4.01 (m, 1H, H^{1}), 2.53 – 2.39 (m, 1H, H^{3a}), 2.33 – 2.22 (m, 2H, $H^{2a, 3b}$), 2.18 – 2.04 (m, 1H, H^{2b}), 1.93 (m, 1H, H^{14}), 1.83 – 1.49 (m, 4H, $H^{15a, 15b, 19a, 19b}$), 1.37 – 1.04 (m, 5H, $H^{16a, 16b, 17, 18a, 18b}$).

^{13}C NMR (101 MHz, $CDCl_3$): δ 175.0 (C^{12}), 171.6 (C^{5}), 157.1 ($C^{7, 9}$), 118.9 (C^{8}), 47.9 (C^{1}), 45.5 (C^{4}), 45.4 (C^{14}), 29.8 (C^{3}), 29.6 (C^{16}), 29.5 (C^{18}), 25.9 (C^{15}), 25.9 (C^{19}), 25.8 (C^{17}), 22.5 (C^{2}).

er: 95:5 [determined by SFC Chiralpak® IC, 1500 psi, 30 °C; flow: 1.0 mL/min; 0% to 70% MeOH over 10 min, then from 70% to 50% MeOH in 0.5 min, then hold 50% MeOH for 2.5 min, λ = 205 nm, $t_{(major)}$ = 5.90 min, $t_{(minor)}$ = 6.12 min].

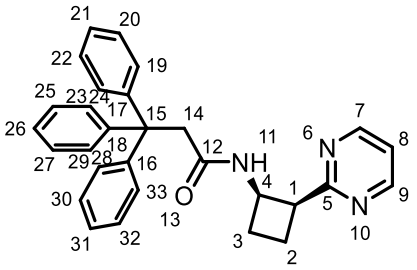
IR (film)/cm^{-1}: 3245, 2992, 2930, 2854, 1658, 1561, 1428, 1259, 1048, 755.

HRMS (ESI) m/z calcd. for $C_{15}H_{21}N_3O^{23}Na$ ($[M+Na]^+$) 282.1577, found 282.1577.

$[\alpha]_D^{25}$ = +137.0 (c = 1.6, $CHCl_3$).

m.p.: 160-162 °C

3,3,3-triphenyl-*N*-((1*R*,2*S*)-2-(pyrimidin-2-yl)cyclobutyl)propanamide (473)



With 2-cyclobutylpyrimidine **332** (0.15 mmol, 20.13 mg), dioxazolone **419** (0.26 mmol, 89.28 mg), the compound **473** was obtained according to the **General Procedure E** as a pale yellow solid (60.48 mg, 93 % yield, 89:11 er).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.70 (d, *J* = 4.9 Hz, 2H, $H^{7, 9}$), 7.44 – 7.26 (m, 15H, $H^{11, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 28, 30, 31, 32, 33}$), 7.23 (t, *J* = 4.9 Hz, 1H, H^{8}), 6.72 (s, 1H, H^{11}), 4.88 – 4.79 (m, 1H, H^{4}), 4.02 – 3.93 (m, 1H, H^{1}), 3.69 (d, *J* = 14.8 Hz, 1H, H^{14a}), 3.57 (d, *J* = 14.8 Hz, 1H, H^{14b}), 2.30 – 2.21 (m, 2H, $H^{2a, 3a}$), 2.02 – 1.88 (m, 2H, $H^{2b, 3b}$).

^{13}C NMR (101 MHz, $CDCl_3$): δ 171.2 (C^{12}), 169.3 (C^{5}), 156.9 ($C^{7, 9}$), 146.5 ($C^{16, 17, 18}$), 129.3 ($C^{19, 23, 24, 28, 29, 33}$), 127.9 ($C^{20, 22, 25, 27, 30, 32}$), 126.3 ($C^{21, 26, 31}$), 118.7 ($C^{8}$), 56.2 ($C^{15}$), 48.8 ($C^{14}$), 47.7 ($C^{1}$), 45.6 ($C^{4}$), 29.1 ($C^{3}$), 22.5 ($C^{2}$).

er: 89:11 [determined by HPLC Chiralpak® OD-H, hexane/isopropanol = 90/10, 1 ml/min, λ = 240 nm, $t_{(major)}$ = 16.84 min, $t_{(minor)}$ = 23.30 min].

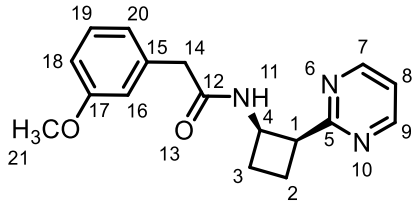
IR (film)/cm^{-1}: 3402, 3019, 2944, 1653, 1560, 1506, 1495, 1426, 1238, 806, 752, 667.

HRMS (ESI) m/z calcd. for $C_{29}H_{27}N_3O^{23}Na$ ($[M+Na]^+$) 456.2046, found 456.2051.

$[\alpha]_D^{25}$ = +164.1 (c = 0.6, $CHCl_3$).

m.p.: 82-84°C

2-(3-methoxyphenyl)-*N*-((1*R*,2*S*)-2-(pyrimidin-2-yl)cyclobutyl)acetamide (474)



With 2-cyclobutylpyrimidine **332** (0.15 mmol, 20.13 mg), dioxazolone **420** (0.26 mmol, 53.87 mg), the compound **474** was obtained according to the **General Procedure E** as a pale yellow solid (32.55 mg, 73 % yield, 93:7 er).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.43 (d, *J* = 4.9 Hz, 2H, $H^{7, 9}$), 7.19 (dd, *J* = 8.3, 7.5 Hz, 1H, H^{19}), 7.03 (t, *J* = 4.9 Hz, 1H, H^{8}), 6.81 (ddd, *J* = 8.3, 2.6, 1.0 Hz, 1H, H^{20}), 6.67 (d, *J* = 1.0 Hz, 1H, H^{18}), 6.59 (t, *J* = 1.7 Hz, 1H, H^{16}), 4.99 – 4.86 (m, 1H, H^{4}), 4.02 – 3.90 (m, 1H, H^{1}), 3.74 (s, 3H, H^{22}), 3.45 (dd, 2H, $H^{14a, 14b}$), 2.50 – 2.34 (m, 1H, H^{3a}), 2.30 – 2.14 (m, 2H, $H^{2a, 3b}$), 2.04 – 1.90 (m, 1H, H^{2b}).

^{13}C NMR (101 MHz, $CDCl_3$): δ 171.2 (C^{12}), 169.9 (C^{5}), 156.9 ($C^{7, 9}$), 129.9 (C^{19}), 122.2 (C^{18}), 118.6 (C^{8}), 114.9 (C^{16}), 113.1 (C^{20}), 55.3 (C^{22}), 47.7 (C^{1}), 45.4 (C^{4}), 44.1 (C^{14}), 29.7 (C^{3}), 22.5 (C^{2}).

er: 93:7 [determined by HPLC Chiralpak® AD-H, hexane/isopropanol = 80/20, 1 ml/min, λ = 240 nm, $t_{(major)}$ = 19.09 min, $t_{(minor)}$ = 14.27 min].

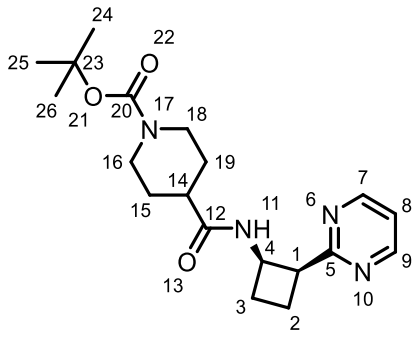
IR (film)/cm^{-1}: 3303, 2994, 2947, 1656, 1561, 1427, 1258, 1166, 1048, 767, 696.

HRMS (ESI) m/z calcd. for $C_{17}H_{19}N_3O_2{}^{23}Na$ ($[M+Na]^+$) 320.1370, found 320.1357.

$[\alpha]_D{}^{25}$ = +123.89 (c = 1.7, $CHCl_3$).

m.p.: 70-72 °C

***tert*-butyl 4-(((1*R*,2*S*)-2-(pyrimidin-2-yl)cyclobutyl)carbamoyl)piperidine-1-carboxylate (475)**



With 2-cyclobutylpyrimidine **332** (0.15 mmol, 20.13 mg), dioxazolone **421** (0.26 mmol, 70.28 mg), the compound **475** was obtained according to the **General Procedure E** as a white solid (47.04 mg, 87 % yield, 86:14 er).

1H NMR (600 MHz, $CDCl_3$): δ 8.71 (d, J = 4.9 Hz, 2H, $H^{7, 9}$), 7.43 – 7.32 (m, 1H, H^{11}), 7.18 (t, J = 4.9 Hz, 1H, H^{8}), 4.99 – 4.85 (m, 1H, H^{4}), 4.20 – 3.97 (m, 3H, $H^{1, 16a, 18a}$), 2.74 – 2.60 (m, 2H, $H^{16b, 18b}$), 2.50 – 2.42 (m, 1H, H^{2a}), 2.33 – 2.21 (m, 2H, $H^{2b, 3a}$), 2.09 (m, J = 11.3, 3.6 Hz, 2H, $H^{3b, 14}$), 1.74 – 1.66 (m, 1H, H^{15a}), 1.63 – 1.58 (m, 1H, H^{19a}), 1.51 – 1.43 (m, 2H, $H^{15b, 19b}$), 1.42 (s, 9H, $H^{24ab, 25ab, 26ab}$).

^{13}C NMR (151 MHz, $CDCl_3$): δ 173.2 (C^{12}), 171.5 (C^{5}), 157.1 ($C^{7, 9}$), 154.8 (C^{20}), 118.9 (C^{8}), 79.7 (C^{23}), 47.7 (C^{1}), 45.6 (C^{4}), 43.3 ($C^{16, 18}$), 42.7 (C^{14}), 29.5 (C^{3}), 28.7 (C^{15}), 28.5 ($C^{24, 25, 26}$), 28.4 (C^{19}), 22.7 (C^{2}).

er: 86:14 [determined by SFC Chiralpak® ID, 1500 psi, 30 °C; flow: 1.0 mL/min; 0% to 70% MeOH over 10 min, then from 70% to 50% MeOH in 0.5 min, then hold 50% MeOH for 2.5 min, λ = 205 nm, $t_{(major)}$ = 5.54 min, $t_{(minor)}$ = 5.32 min].

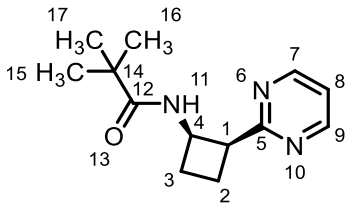
IR (film)/cm^{-1}: 3316, 2945, 1686, 1560, 1427, 1231, 1169, 757.

HRMS (ESI) m/z calcd. for $C_{19}H_{28}N_4O_3{}^{23}Na$ ($[M+Na]^+$) 383.2054, found 383.2054.

$[\alpha]_D{}^{25}$ = +126.91 (c = 1.5, $CHCl_3$).

m.p.: 138-142 °C

***N*-((1*R*,2*S*)-2-(pyrimidin-2-yl)cyclobutyl)pivalamide (476)**



With 2-cyclobutylpyrimidine **332** (0.15 mmol, 20.13 mg), dioxazolone **422** (0.26 mmol, 37.22 mg), the compound **476** was obtained according to the **General Procedure E** as a white solid (27.30 mg, 78 % yield, 88:12 er).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.73 (d, *J* = 4.9 Hz, 2H, $H^{7, 9}$), 7.51 (s, 1H, H^{11}), 7.18 (t, *J* = 4.9 Hz, 1H, H^{8}), 4.98 – 4.84 (m, 1H, H^{4}), 4.11 – 3.99 (m, 1H, H^{1}), 2.57 – 2.43 (m, 1H, H^{2a}), 2.36 – 2.22 (m, 2H, $H^{2b, 3a}$), 2.18 – 2.08 (m, 1H, H^{3b}), 1.05 (s, 9H, $H^{15a, 15b, 15c, 16a, 16b, 16c, 17a, 17b, 17c}$).

^{13}C NMR (101 MHz, $CDCl_3$): δ 177.4 (C^{12}), 171.7 (C^{5}), 157.1 ($C^{7, 9}$), 118.9 (C^{8}), 47.7 (C^{1}), 45.7 (C^{4}), 38.7 (C^{14}), 29.6 (C^{3}), 27.6 ($C^{15, 16, 17}$), 22.7 (C^{2}).

er: 88:12 [determined by SFC Chiralpak® ID, 1500 psi, 30 °C; flow: 1.0 mL/min; 0% to 70% MeOH over 10 min, then from 70% to 50% MeOH in 0.5 min, then hold 50% MeOH for 2.5 min, λ = 205 nm, $t_{(major)}$ = 4.14 min, $t_{(minor)}$ = 4.06 min].

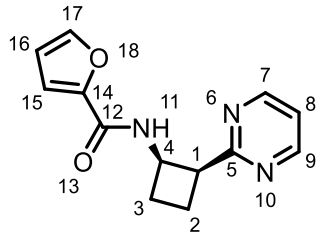
IR (film)/cm^{-1}: 3337, 2966, 1655, 1560, 1519, 1426, 1234, 808, 755.

HRMS (ESI) m/z calcd. for $C_{13}H_{19}N_3O^{23}Na$ ($[M+Na]^+$) 256.1420, found 256.1414.

$[\alpha]_D^{25}$ = +179.55 (c = 0.84, $CHCl_3$).

m.p.: 78-80 °C

***N*-((1*R*,2*S*)-2-(pyrimidin-2-yl)cyclobutyl)furan-2-carboxamide (477)**



With 2-cyclobutylpyrimidine **332** (0.15 mmol, 20.13 mg), dioxazolone **423** (0.26 mmol, 39.80 mg), the compound **477** was obtained according to the **General Procedure E** as a white solid (18.61 mg, 51 % yield, 92:8 er).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.76 (d, *J* = 4.9 Hz, 2H, $H^{7, 9}$), 8.29 (s, 1H, H^{11}), 7.38 (dd, *J* = 1.7, 0.8 Hz, 1H, H^{17}), 7.19 (t, *J* = 4.9 Hz, 1H, H^{8}), 7.02 (dd, *J* = 3.5, 0.9 Hz, 1H, H^{15}), 6.43 (dd, *J* = 3.5, 1.8 Hz, 1H, H^{16}), 5.18 – 5.05 (m, 1H, H^{4}), 4.18 – 4.07 (m, 1H, H^{1}), 2.60 – 2.51 (m, 1H, H^{3a}), 2.50 – 2.25 (m, 2H, $H^{2a, 3b}$), 2.20 – 2.08 (m, 1H, H^{2b}).

^{13}C NMR (101 MHz, $CDCl_3$): δ 171.5 (C^{12}), 157.4 (C^{5}), 157.2 ($C^{7, 9}$), 148.5 (C^{14}), 143.8 (C^{17}), 118.9 (C^{8}), 113.9 (C^{15}), 112.1 (C^{16}), 47.9 (C^{1}), 45.2 (C^{4}), 29.8 (C^{3}), 22.9 (C^{2}).

er: 92:8 [determined by SFC Chiralpak® ID, 1500 psi, 30 °C; flow: 1.0 mL/min; 0% to 70% MeOH over 10 min, then from 70% to 50% MeOH in 0.5 min, then hold 50% MeOH for 2.5 min, λ = 205 nm, $t_{(major)}$ = 5.02 min, $t_{(minor)}$ = 4.90 min].

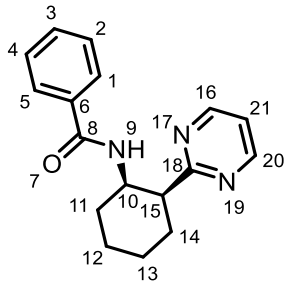
IR (film)/cm^{-1}: 3226, 2989, 2942, 1654, 1562, 1535, 1427, 1302, 1289, 1239, 1191, 825, 758.

HRMS (ESI) m/z calcd. for $C_{13}H_{13}N_3O_2{}^{23}Na$ ($[M+Na]^+$) 266.0900, found 266.0894.

[α]$_D$ ^{25} = +38.96 (c = 1.3, $CHCl_3$).

m.p.: 120-121 °C

***N*-((1*R*,2*S*)-2-(pyrimidin-2-yl)cyclohexyl)benzamide (479)**



With 2-cyclohexylpyrimidine **430** (0.15 mmol, 24.34 mg), dioxazolone **336** (0.26 mmol, 42.41 mg), the compound **479** was obtained according to the **General Procedure E** as a pale yellow solid (29.54 mg, 70 % yield, 85:15 er).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.64 (d, *J* = 4.9 Hz, 2H, $H^{16, 20}$), 7.58 – 7.53 (m, 2H, $H^{1, 5}$), 7.44 – 7.38 (m, 1H, H^{3}), 7.36 – 7.30 (m, 2H, $H^{2, 4}$), 7.09 (t, *J* = 4.9 Hz, 1H, H^{21}), 6.28 (s, 1H, H^{9}), 4.35 – 4.22 (m, 1H, H^{10}), 3.00 – 2.86 (m, 1H, H^{15}), 2.41 – 2.33 (m, 1H, H^{14a}), 2.09 – 2.02 (m, 2H, $H^{11a, 14b}$), 1.91 – 1.83 (m, 2H, $H^{11b, 13a}$), 1.66 – 1.52 (m, 1H, H^{12a}), 1.46 – 1.27 (m, 2H, $H^{12b, 13b}$).

^{13}C NMR (101 MHz, $CDCl_3$): δ 171.7 (C^{8}), 166.5 (C^{18}), 157.1 ($C^{16, 20}$), 135.0 (C^{6}), 131.2 (C^{3}), 128.5 ($C^{2, 4}$), 126.8 ($C^{1, 5}$), 119.2 (C^{21}), 53.2 (C^{10}), 53.2 (C^{15}), 33.8 (C^{14}), 30.8 (C^{11}), 25.5 (C^{13}), 25.2 (C^{12}).

er: 85:15 [determined by HPLC Chiralpak® AD-H, hexane/isopropanol = 85/15, 1 ml/min, λ = 230 nm, $t_{(major)}$ = 11.03 min, $t_{(minor)}$ = 9.23 min].

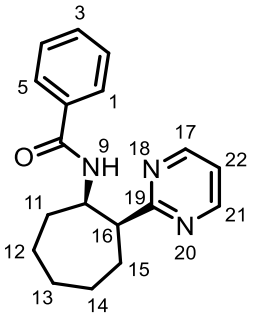
IR (film)/cm^{-1}: 3306, 2934, 2857, 1641, 1562, 1438, 837, 757.

HRMS (ESI) m/z calcd. for $C_{17}H_{20}N_3O$ ($[M+H]^+$) 282.1601, found 282.1603.

$[\alpha]_D^{25}$ = -135.65 (c = 0.7, $CHCl_3$).

m.p.: 180-182 °C

***N*-((1*R*,2*S*)-2-(pyrimidin-2-yl)cycloheptyl)benzamide (480)**



With 2-cycloheptylpyrimidine **432** (0.15 mmol, 26.42 mg), dioxazolone **336** (0.26 mmol, 42.41 mg), the compound **480** was obtained according to the **General Procedure E** as a pale yellow solid (28.33 mg, 64 % yield, 91:9 er).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.64 (d, *J* = 4.9 Hz, 2H, $H^{17, 21}$), 7.60 – 7.52 (m, 2H, $H^{1, 5}$), 7.46 – 7.37 (m, 1H, H^{3}), 7.40 – 7.29 (m, 2H, $H^{2, 4}$), 7.07 (t, *J* = 4.9 Hz, 1H, H^{22}), 6.30 (s, 1H, H^{9}), 4.55 – 4.43 (m, 1H, H^{10}), 3.12 – 3.02 (m, 1H, H^{16}), 2.23 – 2.13 (m, 1H, H^{15a}), 2.12 – 1.99 (m, 1H, H^{11a}), 1.99 – 1.92 (m, 2H, $H^{15b, 11b}$), 1.90 – 1.55 (m, 6H, $H^{12a, 12b, 13a, 13b, 14a, 14b}$).

^{13}C NMR (101 MHz, $CDCl_3$): δ 173.5 (C^{8}), 166.2 (C^{19}), 157.1 ($C^{17, 21}$), 135.0 (C^{6}), 131.2 (C^{3}), 128.5 ($C^{1, 5}$), 126.8 ($C^{2, 4}$), 119.0 (C^{22}), 55.9 (C^{10}), 55.8 (C^{16}), 34.5 (C^{11}), 30.6 (C^{15}), 28.4 (C^{13}), 26.9 (C^{14}), 23.6 (C^{12}).

er: 91:9 [determined by HPLC Chiralpak® AD-H, hexane/isopropanol = 85/15, 1 ml/min, λ = 254 nm, $t_{(major)}$ = 11.53 min, $t_{(minor)}$ = 9.22 min].

IR (film)/cm^{-1}: 3330, 2932, 2857, 1634, 1570, 1562, 1539, 1421, 1329, 757, 694.

HRMS (ESI) m/z calcd. for $C_{18}H_{21}N_3O^{23}Na$ ($[M+Na]^+$) 318.1577, found 318.1580.

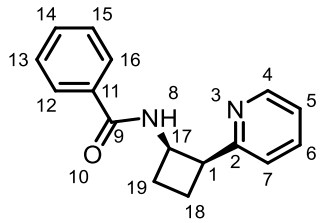
$[\alpha]_D^{25}$ = -96.22 (c = 0.8, $CHCl_3$).

m.p.: 168-170 °C

5.2.3 General Procedure F: Cp*Rh(III)-catalysed enantioselective C(sp^3)–H functionalisation of cyclobutylpyridines

To a small vial was added 2-cyclobutylpyridine **1f** (0.15 mmol, 20 mg), dioxazolone **2a** (0.17 mmol, 1.1 equiv, 27.73 mg), **L27** (16.75 mg, 0.2 equiv), Ag_2CO_3 (2.06 mg, 0.05 equiv), $Cp^*Rh(MeCN)_3(SbF_6)_2$ (12.41 mg, 0.1 equiv) and 1.4-dioxane (0.3 mL, 0.5 M) under air. Then stirred at 80 °C for 2 h. After cooling to room temperature, the mixture was concentrated and purified by silica gel column chromatography (neat pentane to pentane/EtOAc = 1/9 to neat EtOAc) to afford the desired product **3aa**.

***N*-((1*R*,2*S*)-2-(pyridin-2-yl)cyclobutyl)benzamide (481)**



With 2-cyclobutylpyridine **433** (0.15 mmol, 20 mg), dioxazolone **336** (0.17 mmol, 27.73 mg), the compound **481** was obtained according to the **General Procedure F** as a white solid (22.69 mg, 60 % yield, 88:12 er).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.67 (ddd, *J* = 4.9, 1.9, 0.9 Hz, 1H, H^4), 8.26 (d, *J* = 8.3 Hz, 1H, H^8), 7.64 – 7.56 (m, 3H, $H^{6, 13, 15}$), 7.45 – 7.40 (m, 1H, H^{14}), 7.39 – 7.32 (m, 2H, $H^{12, 16}$), 7.17 (ddd, *J* = 7.6, 4.9, 1.2 Hz, 1H, H^7), 7.15 – 7.10 (m, 1H, H^5), 5.11 – 5.02 (m, 1H, H^{17}), 3.98 (tdd, *J* = 7.8, 5.7, 2.3 Hz, 1H, H^1), 2.62 – 2.52 (m, 1H, H^{19a}), 2.41 – 2.24 (m, 3H, $H^{19b, 18a, 18b}$).

^{13}C NMR (101 MHz, $CDCl_3$): δ 166.3 (C^9), 161.9 (C^2), 149.0 (C^4), 136.9 (C^6), 134.9 (C^{11}), 131.2 (C^{14}), 128.5 ($C^{12, 16}$), 126.9 ($C^{13, 15}$), 124.4 (C^5), 121.8 (C^7), 47.5 (C^{17}), 45.7 (C^1), 29.4 (C^{19}), 23.7 (C^{18}).

er: 88:12 [determined by SFC Chiralpak® IC, 1500 psi, 30 °C; flow: 1.0 mL/min; 0% to 70% MeOH over 10 min, then from 70% to 50% MeOH in 0.5 min, then hold 50% MeOH for 2.5 min, λ = 210 nm, $t_{(major)}$ = 7.08 min, $t_{(minor)}$ = 7.27 min].

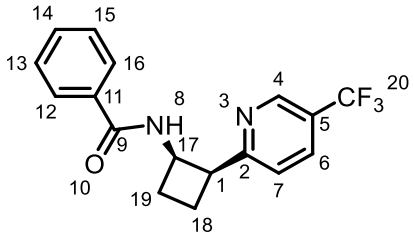
IR (film)/cm^{-1}: 3345, 2948, 1695, 1647, 1531, 1362, 1202, 791, 750, 716.

HRMS (ESI) m/z calcd. for $C_{16}H_{17}N_2O$ ($[M+H]^+$) 253.1335, found 253.1336.

$[\alpha]_D^{25}$ = +59.3846 (c = 1.3, $CHCl_3$).

m.p.: 118-120 °C

***N*-((1*R*,2*S*)-2-(5-(trifluoromethyl)pyridin-2-yl)cyclobutyl)benzamide (482)**



With 2-cyclobutyl-5-(trifluoromethyl)pyridine **435** (0.15 mmol, 30.16 mg), dioxazolone **336** (0.17 mmol, 27.73 mg), stirred for 5 h, the compound **482** was obtained according to the **General Procedure F** as a white solid (26.89 mg, 56 % yield, 89:11 er).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.92 (d, J = 1.9 Hz, 1H, H^{4}), 7.87 – 7.79 (m, 1H, H^{6}), 7.65 (d, J = 7.8 Hz, 1H, H^{8}), 7.59 – 7.50 (m, 2H, $H^{12\&16}$), 7.49 – 7.42 (m, 1H, H^{14}), 7.41 – 7.32 (m, 2H, $H^{13\&15}$), 7.27 (d, J = 8.2 Hz, 1H, H^{7}), 5.13 (p, J = 8.2 Hz, 1H, H^{17}), 4.15 – 4.02 (m, 1H, H^{1}), 2.59 (dtdd, J = 11.5, 8.3, 4.9, 2.1 Hz, 1H, H^{19a}), 2.46 (ddtd, J = 11.1, 10.0, 7.9, 0.8 Hz, 1H, H^{19b}), 2.39 – 2.21 (m, 2H, $H^{18a\&18b}$).

^{13}C NMR (101 MHz, $CDCl_3$): δ 166.5 (C^{9}), 165.8 (C^{2}), 145.8 (C^{4}), 134.6 (C^{11}), 134.1 (C^{6}), 131.5 (C^{14}), 128.6 ($C^{12\&16}$), 126.8 ($C^{13\&15}$), 125.6 (C^{5}), 124.9 (C^{20}), 124.4 (C^{7}), 47.3 (C^{17}), 46.4 (C^{1}), 29.0 (C^{19}), 23.0 (C^{18}).

^{19}F NMR (376 MHz, $CDCl_3$): δ -62.27.

er: 89:11 [determined by SFC Chiralpak® IA, 1500 psi, 30 °C; flow: 1.0 mL/min; 0% to 70% MeOH over 10 min, then from 70% to 50% MeOH in 0.5 min, then hold 50% MeOH for 2.5 min, λ = 210 nm, $t_{(major)}$ = 3.73 min, $t_{(minor)}$ = 4.04 min].

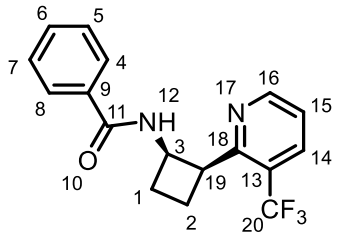
IR (film)/cm^{-1}: 3370, 3006, 1694, 1513, 1363, 1330, 1202, 816, 747.

HRMS (ESI) m/z calcd. for $C_{17}H_{16}F_3N_2O$ ($[M+H]^+$) 321.1209, found 321.1216.

[α]$_D^{25}$ = +11.00 (c = 0.5, $CHCl_3$).

m.p.: 45-47 °C

***N*-((1*R*,2*S*)-2-(3-(trifluoromethyl)pyridin-2-yl)cyclobutyl)benzamide (483)**



With 2-cyclobutyl-3-(trifluoromethyl)pyridine **437** (0.15 mmol, 30.16 mg), dioxazolone **336** (0.17 mmol, 27.73 mg), stirred for 1 h, the compound **483** was obtained according to the **General Procedure F** as a white solid (24.01 mg, 50 % yield, 53:47 er).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.83 (dd, J = 4.8, 1.6 Hz, 1H, H^{16}), 7.89 (dd, J = 8.0, 1.7 Hz, 1H, H^{14}), 7.75 – 7.65 (m, 2H, $H^{4\&8}$), 7.50 – 7.43 (m, 1H, H^6), 7.43 – 7.36 (m, 2H, $H^{5\&7}$), 7.31 – 7.26 (m, 1H, H^{15}), 6.43 (d, J = 7.9 Hz, 1H, H^{12}), 5.04 (p, J = 8.4 Hz, 1H, H^3), 3.91 (q, J = 8.4 Hz, 1H, H^{19}), 2.57 – 2.46 (m, 1H, H^{1a}), 2.42 – 2.28 (m, 1H, H^{2a}), 2.25 – 2.14 (m, 1H, H^{2b}), 2.13 – 2.01 (m, 1H, H^{1b}).

^{13}C NMR (101 MHz, $CDCl_3$): δ 166.9 (C^{11}), 159.0 (C^{18}), 152.2 (C^{16}), 134.6 (C^{14}), 134.1 (C^9), 131.5 (C^6), 128.7 ($C^{5\&7}$), 126.9 ($C^{4\&8}$), 124.6 (C^{20}), 122.7 (C^{13}), 121.3 (C^{15}), 50.5 (C^3), 47.3 (C^{19}), 27.3 (C^1), 22.1 (C^2).

^{19}F NMR (376 MHz, $CDCl_3$): δ -59.54.

er: 53:47 [determined by SFC Chiralpak® IF, 1500 psi, 30 °C; flow: 1.0 mL/min; 0% to 70% MeOH over 10 min, then from 70% to 50% MeOH in 0.5 min, then hold 50% MeOH for 2.5 min, λ = 210 nm, $t_{(major)}$ = 5.21 min, $t_{(minor)}$ = 6.13 min].

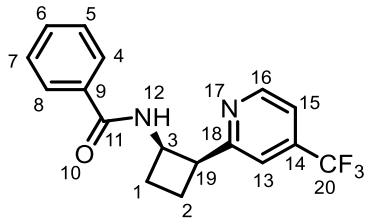
IR (film)/cm^{-1}: 3340, 2947, 1695, 1637, 1322, 1129, 1028, 752.

HRMS (ESI) m/z calcd. for $C_{17}H_{15}F_3N_2O^{23}Na$ ($[M+Na]^+$) 343.1029, found 343.1024.

[α]$_D$ ^{25} = +5.99 (c = 1.1, $CHCl_3$).

m.p.: 138-140 °C

***N*-((1*R*,2*S*)-2-(4-(trifluoromethyl)pyridin-2-yl)cyclobutyl)benzamide (484)**



With 2-cyclobutyl-4-(trifluoromethyl)pyridine **436** (0.15 mmol, 30.16 mg), dioxazolone **336** (0.17 mmol, 27.73 mg), the compound **484** was obtained according to the **General Procedure F** as a white solid (31.77 mg, 66 % yield, 92:8 er).

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.83 (d, J = 5.1 Hz, 1H, H^{16}), 7.76 (d, J = 8.5 Hz, 1H, H^{12}), 7.63 – 7.55 (m, 2H, $H^{4\&8}$), 7.46 – 7.42 (m, 1H, H^6), 7.41 – 7.33 (m, 4H, $H^{5\&7\&13\&15}$), 5.13 (p, J = 8.1 Hz, 1H, H^3), 4.13 – 4.05 (m, 1H, H^{19}), 2.65 – 2.54 (m, 1H, H^{1a}), 2.49 – 2.41 (m, 1H, H^{2a}), 2.38 – 2.27 (m, 2H, $H^{1b\&2b}$).

^{13}C NMR (126 MHz, $CDCl_3$): δ 166.5 (C^{11}), 163.3 (C^{18}), 149.7 (C^{16}), 139.4 (d, J = 33.7 Hz) (C^{14}), 134.6 (C^{9}), 131.4 (C^{6}), 128.6 ($C^{5\&7}$), 126.9 ($C^{4\&8}$), 123.8 (C^{20}), 120.3 (C^{13}), 117.5 (C^{15}), 47.5 (C^{3}), 46.4 (C^{19}), 29.0 (C^{1}), 23.3 (C^{2}).

^{19}F NMR (470 MHz, $CDCl_3$): δ -64.91.

er: 92:8 [determined by SFC Chiralpak® IG, 1500 psi, 30 °C; flow: 1.0 mL/min; 0% to 70% MeOH over 10 min, then from 70% to 50% MeOH in 0.5 min, then hold 50% MeOH for 2.5 min, λ = 210 nm, $t_{(major)}$ = 4.52 min, $t_{(minor)}$ = 4.75 min].

IR (film)/cm^{-1}: 3306, 2948, 1694, 1645, 1324, 1172, 750.

HRMS (ESI) m/z calcd. for $C_{17}H_{16}F_3N_2O$ ($[M+H]^+$) 321.1209, found 321.1216.

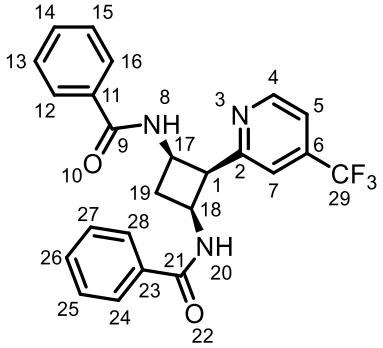
$[\alpha]_D^{25}$ = +172.67 (c = 1.0, $CHCl_3$).

m.p.: 58-60 °C

5.2.4 General Procedure G: Cp*Rh(III)-catalysed enantioselective C(sp^3)–H functionalisation to prepare the bis-amidated product

To a small vial was added *N*-((1*R*,2*S*)-2-(4-(trifluoromethyl)pyridin-2-yl)cyclobutyl)benzamide **484** (0.13 mmol, 40 mg), dioxazolone **336** (0.21 mmol, 1.7 equiv, 34.63 mg), ligand **396** (14.03 mg, 0.2 equiv), Ag_2CO_3 (1.72 mg, 0.05 equiv), $Cp^*Rh(MeCN)_3(SbF_6)_2$ (10.40 mg, 0.1 equiv) and 1.4-dioxane (0.25 mL, 0.5 M) under air. Then stirred at 80 °C for 1 h. After cooling to room temperature, the mixture was concentrated and purified by silica gel column chromatography (pentane to pentane/EtOAc = 1/9 to pure EtOAc) to afford the desired product **495**.

***N*,*N*'-((1*R*,3*S*)-2-(4-(trifluoromethyl)pyridin-2-yl)cyclobutane-1,3-diyl)dibenzamide (495)**



With *N*-((1*R*,2*S*)-2-(4-(trifluoromethyl)pyridin-2-yl)cyclobutyl)benzamide **484** (0.13 mmol, 40 mg), dioxazolone **336** (0.21 mmol, 34.63 mg), **(*S*)-396** (14.03 mg, 0.2 equiv), stirred for 1 h, the compound **495b** was obtained according to the **General Procedure G** as a white solid (48.38 mg, 88% yield).

With *N*-((1*R*,2*S*)-2-(4-(trifluoromethyl)pyridin-2-yl)cyclobutyl)benzamide **484** (0.13 mmol, 40 mg), dioxazolone **336** (0.21 mmol, 34.63 mg), **(*R*)-396** (14.03 mg, 0.2 equiv), stirred for 1 h, the compound **495a** was obtained according to the **General Procedure G** as a white solid (17.05 mg, 31% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.85 (d, J = 5.2 Hz, 1H, H^{4}), 7.55 – 7.48 (m, 4H, $H^{12\&16\&24\&28}$), 7.47 – 7.42 (m, 3H, $H^{5\&14\&26}$), 7.41 (d, J = 1.7 Hz, 1H, H^{7}), 7.35 (dd, J = 8.2, 6.8 Hz, 4H, $H^{13\&15\&25\&27}$), 7.10 (d, 2H, $H^{8\&20}$), 5.10 – 4.99 (m, 2H, $H^{17\&18}$), 4.59 (td, J = 8.1, 2.9 Hz, 1H, H^{1}), 3.09 (dtd, J = 11.2, 8.2, 3.0 Hz, 1H, H^{19a}), 2.68 (q, J = 10.3 Hz, 1H, H^{19b}).

^{13}C NMR (101 MHz, $CDCl_3$): δ 166.8 ($C^{9\&21}$), 134.2 ($C^{11\&23}$), 131.7 ($C^{14\&26}$), 128.7 ($C^{13\&15\&25\&27}$), 126.8 ($C^{12\&16\&24\&28}$), 122.9 (C^{29}), 117.8 (C^{5}), 53.5 (C^{1}), 42.2 ($C^{17\&18}$), 34.1

(C^{19}). Due to the complexity of the aromatic region and overlapping signals, several signals may be missing.

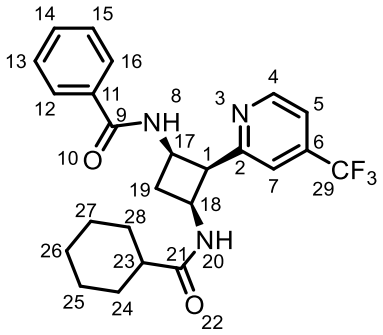
^{19}F NMR (376 MHz, $CDCl_3$): δ -65.02.

IR (film)/cm^{-1}: 3273, 2926, 1655, 1521, 1342, 1034, 695.

HRMS (ESI) m/z calcd. for $C_{24}H_{21}F_3N_3O_2$ ($[M+H]^+$) 440.1580, found 440.1577.

m.p.: 98-104 °C

***N*-((1*R*,2*S*,3*S*)-3-(cyclohexanecarboxamido)-2-(4-(trifluoromethyl)pyridin-2-yl)cyclobutyl)benzamide (496)**



With *N*-((1*R*,2*S*)-2-(4-(trifluoromethyl)pyridin-2-yl)cyclobutyl)benzamide **484** (0.13 mmol, 40 mg), dioxazolone **418** (0.21 mmol, 35.92 mg), **(*S*)-396** (14.03 mg, 0.2 equiv), stirred for 1 h, the compound **496** was obtained according to the **General Procedure G** as a white solid (53.20 mg, 92% yield, >99:1 er).

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.85 (d, J = 5.2 Hz, 1H, H^4), 7.58 – 7.53 (m, 2H, $H^{12\&16}$), 7.48 – 7.38 (m, 3H, $H^{5\&7\&14}$), 7.36 (dd, J = 8.3, 7.0 Hz, 2H, $H^{13\&15}$), 5.96 (s, 1H, H^{20}), 5.09 – 4.98 (m, 1H, H^{17}), 4.74 (dq, J = 9.9, 8.2 Hz, 1H, H^{18}), 4.48 (td, J = 8.0, 2.8 Hz, 1H, H^1),

2.99 (dtd, J = 11.2, 8.2, 2.9 Hz, 1H, H^{19a}), 2.60 (q, J = 10.0 Hz, 1H, H^{19b}), 1.85 – 1.76 (m, 1H, H^{23}), 1.67 – 1.55 (m, 4H, $H^{24a\&24b\&28a\&28b}$), 1.34 – 1.23 (m, 2H, $H^{25a\&27a}$), 1.16 – 1.06 (m, 4H, $H^{25b\&27b\&26a\&26b}$).

^{13}C NMR (126 MHz, $CDCl_3$): δ 175.6 (C^{21}), 166.5 (C^{9}), 160.2 (C^{2}), 148.9 (C^{4}), 134.3 (C^{11}), 131.7 (C^{14}), 128.7 ($C^{13\&15}$), 126.9 ($C^{12\&16}$), 123.6 (C^{29}), 122.9 (C^{7}), 117.8 (C^{5}), 53.5 (C^{1}), 45.0 (C^{23}), 41.9 (C^{18}), 41.7 (C^{17}), 29.7 (C^{19}), 29.3 ($C^{24\&28}$), 25.7 (C^{9}), 25.7 ($C^{25\&27}$), 25.6(C^{26}).

^{19}F NMR (471 MHz, $CDCl_3$): δ -64.97.

er: >99:1 [determined by HPLC Chiralpak® AS-H, hexane/isopropanol = 95/5, 1 ml/min, λ = 254 nm, $t_{(major)}$ = 36.60 min, $t_{(minor)}$ = 46.83 min].

IR (film)/cm^{-1}: 3311, 2932, 1649, 1522, 1325, 1174, 1143, 761.

HRMS (ESI) m/z calcd. for $C_{24}H_{26}F_3N_3O_2{}^{23}Na$ ($[M+Na]^+$) 468.1869, found 468.1877.

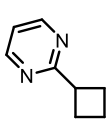
$[\alpha]_D^{25}$ = -41.44 (c = 1.3, $CHCl_3$).

m.p.: 186-190 °C

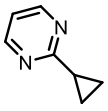
5.2.5 General Procedure H: preparation of racemic compounds for HPLC trace

To a small vial was added 2-cyclobutylpyrimidine **332** (0.15 mmol, 20.13 mg), dioxazolone **336** (0.26 mmol, 42.41 mg), (*rac*)-**396** (16.75 mg, 0.2 equiv), Ag_2CO_3 (2.06 mg, 0.05 equiv), $Cp^*Rh(MeCN)_3(SbF_6)_2$ (12.41 mg, 0.1 equiv) and 1.4-dioxane (0.3 mL, 0.5 M) under air. Then stirred at 80 °C for 20 h. After cooling to room temperature, the mixture was concentrated and purified by silica gel column chromatography (neat pentane to pentane/EtOAc = 1/9 to neat EtOAc) to afford the desired product (*rac*)-**396** for HPLC analysis.

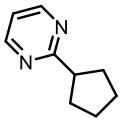
5.2.6 Preparation of starting material alkylpyrimidines (a)



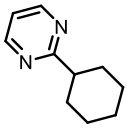
332



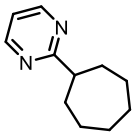
428



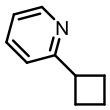
429



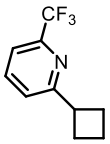
430



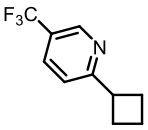
432



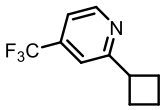
433



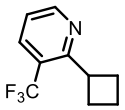
434



435

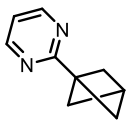


436

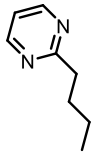


437

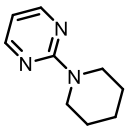
Failed examples for Cp*Rh(III)-Catalysed Enantioselective C-H Amidation



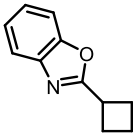
451



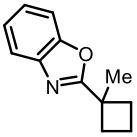
431



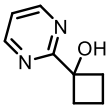
453



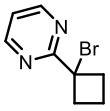
446



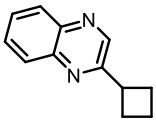
447



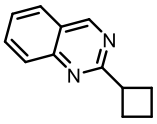
533



534



442



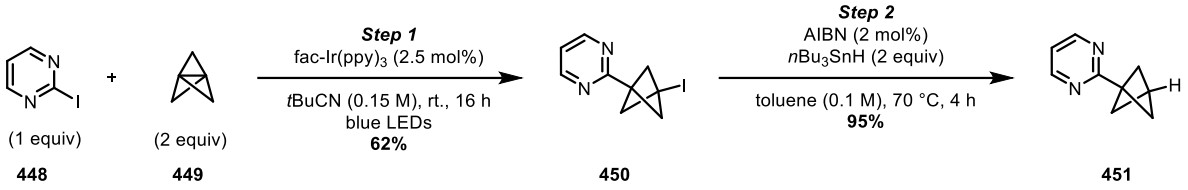
535

Compound **429**,[183] **453**,[184] **446**,[137] **447**[137] were prepared according to the previously reported literature.

Compound **451** was prepared following the **General Procedure I**.

The rest compounds were prepared following the **General Procedure J**.

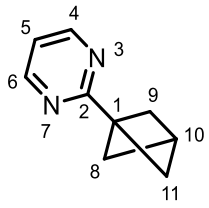
5.2.6.1 General Procedure I: Synthesis of Compound 451



Step 1: the compound 2-(3-iodobicyclo[1.1.1]pentan-1-yl)pyrimidine (**450**) was prepared according to a modified literature procedure.[185] To a screw-capped vial was added fac-Ir(ppy)$_3$ (0.025 equiv, 39.73 mg), the 2-iodopyrimidine (**448**) (2.43 mmol, 1.0 equiv, 500 mg), *t*-BuCN (16 mL) and tricyclo[1.1.1.0^{1,3}]pentane (TCP) (**449**)[186] (2.0 equiv, 0.6 M solution in Et_2O, 8.1 mL,). The vial was sealed and charged with argon, and the solution was degassed *via* freeze-pump-thaw for three times. The reaction was stirred under blue LEDs for 16 h. After the reaction, the solvent was evaporated under reduced pressure, and the residue was purified by column chromatography (Et_2O: Pentane = 1:1) to obtain the product 2-(3-iodobicyclo[1.1.1]pentan-1-yl)pyrimidine (**450**) as a pale yellow solid (409.30 mg, 62% yield).

Step 2: Radical Dehalogenation to prepare the compound 2-(bicyclo[1.1.1]pentan-1-yl)pyrimidine **451**. To a solution of compound 2-(3-iodobicyclo[1.1.1]pentan-1-yl)pyrimidine (**450**) (1.47 mmol, 1.0 equiv, 400 mg) and AIBN (0.12 equiv, 30 mg) in dry toluene (15 mL) was added tributyltin hydride (2 equiv, 0.8 mL) at room temperature. The mixture was stirred for 4 h at 70 °C. After the reaction, the solution was cooled to room temperature and evaporated under reduced pressure. The crude mixture was purified by column chromatography on silica gel (EtOAc/pentane = 1/4) to provide compound **451** (205 mg, 95%) as yellow oil.

2-(bicyclo[1.1.1]pentan-1-yl)pyrimidine (451)



The compound **451** was obtained according to the **General Procedure I** as a colorless oil (59 % yield after two steps).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.66 (d, *J* = 4.9 Hz, 2H, $H^{4, 6}$), 7.11 (t, *J* = 4.9 Hz, 1H, H^{5}), 2.54 (s, 1H, H^{10}), 2.24 (s, 6H, $H^{8a, 8b, 9a, 9b, 11a, 11b}$).

^{13}C NMR (101 MHz, $CDCl_3$): δ 167.9 (C^{2}), 157.1 ($C^{4, 6}$), 118.9 (C^{5}), 52.1 ($C^{1,8, 9, 11}$), 27.3 (C^{10}).

IR (film)/ ν_{max}: 2923, 1571, 1560, 1422 cm^{-1}.

HRMS (ESI) m/z calcd. for $C_9H_{11}N_2$ ($[M+H]^+$) 147.0917, found 147.0916.

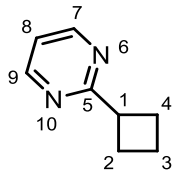
5.2.6.2 General Procedure J: Synthesis of the Starting Material Alkylpyrimidines

Cyclobutylmagnesium bromide Grignard solution (0.3 M in THF) was prepared from cyclobutyl bromide (29.63 mmol, 2.8 mL, 1 equiv) according to a modified literature procedure. To a dry round-bottom flask was added magnesium filings (864.33 mg, 1.2 equiv), and catalytic amounts of iodine (12.78 mg, 0.002 equiv). The reaction vessel was evacuated and back-filled with N_2 three times, and heated up with heat gun until iodine started to subline and create pink vapours. Subsquently, cool the mixture to room temperature and stir for 10 min. To the resulting suspension was added anhydrous THF (98 mL) and cyclobutyl

bromide (0.8 mL) and stirred or sonicated until the Grignard solution was initiated (indicated by the disappearance of the yellow colour). Under the room temperature, the rest portion of cyclobutyl bromide was dropwise added over 20 min. The reaction was stirred at 60 °C for 2 h to get the cyclobutylmagnesium bromide Grignard solution.

Kumada coupling reaction to prepare the cyclobutylpyrimidine (**332**). To a dry round-bottom flask was added 2-bromopyrimidine (3 g, 18.87 mmol, 1 equiv), Ni(dppp)Cl_2 (511.40 mg, 0.05 equiv) and anhydrous THF (63 mL, 0.3 M). The fresh prepared cyclobutylmagnesium bromide Grignard solution was dropwise added and stirred at 60 °C for 1 h. After the reaction, the mixture was quenched with sat. NH_4Cl and extracted with Et_2O for three times, dried over the combined organic layer the $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/pentane = 3/1) to provide compound **332** (2.41 g, 95%) as colorless oil.

2-cyclobutylpyrimidine (332)



The compound **332** was obtained according to the **General Procedure J** as a colorless oil (95 % yield).

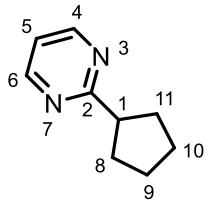
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.65 (d, *J* = 4.9 Hz, 2H, $H^{7, 9}$), 7.07 (t, *J* = 4.9 Hz, 1H, H^8), 3.84 – 3.74 (m, 1H, H^1), 2.48 – 2.32 (m, 4H, $H^{2a, 2b, 4a, 4b}$), 2.14 – 1.98 (m, 1H, H^{3a}), 1.97 – 1.84 (m, 1H, H^{3b}).

^{13}C NMR (101 MHz, $CDCl_3$): δ 173.4 (C^5), 157.0 ($C^{7, 9}$), 118.4 (C^8), 43.0 (C^1), 27.8 ($C^{2, 4}$), 18.3 (C^3).

IR (film)/ ν_{max}: 2985, 1572, 1560, 1430 cm^{-1}.

HRMS (ESI) m/z calcd. for $C_8H_{11}N_2$ ($[M+H]^+$) 135.0917, found 135.0916.

2-cyclopentylpyrimidine (429)



The compound **429** was obtained according to the **General Procedure J** as a colorless oil (87 % yield).

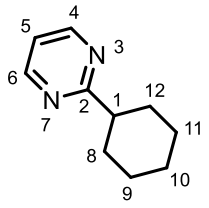
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.64 (d, J = 4.9 Hz, 2H, $H^{4, 6}$), 7.07 (t, J = 4.9 Hz, 1H, H^5), 3.34 (p, J = 8.3 Hz, 1H, H^1), 2.17 – 2.03 (m, 2H, $H^{9a, 10a}$), 1.97 – 1.76 (m, 4H, $H^{8a, 8b, 11a, 11b}$), 1.75 – 1.60 (m, 2H, $H^{9b, 10b}$).

^{13}C NMR (101 MHz, $CDCl_3$): δ 174.9 (C^2), 157.0 ($C^{4, 6}$), 118.4 (C^5), 49.0 (C^1), 33.1 ($C^{8, 11}$), 26.2 ($C^{9, 10}$).

IR (film)/ ν_{max}: 2958, 1572, 1560, 1426 cm^{-1}.

HRMS (ESI) m/z calcd. for $C_9H_{13}N_2$ ($[M+H]^+$) 149.1073, found 149.1074.

2-cyclohexylpyrimidine (430)



The compound **430** was obtained according to the **General Procedure J** as a colorless oil (68 % yield).

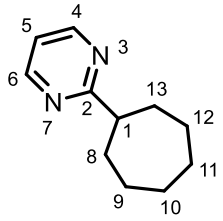
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.63 (d, *J* = 4.9 Hz, 2H, $H^{4, 6}$), 7.07 (t, *J* = 4.9 Hz, 1H, H^{5}), 2.85 (tt, *J* = 11.8, 3.5 Hz, 1H, H^{1}), 1.96 (dq, *J* = 3.8, 1.7 Hz, 2H, $H^{8a, 12a}$), 1.82 (ddd, *J* = 13.5, 4.2, 2.2 Hz, 2H, $H^{9a, 11a}$), 1.71 (dddd, *J* = 12.6, 4.9, 3.1, 1.6 Hz, 1H, H^{10a}), 1.66 – 1.52 (m, 2H, $H^{8b, 12b}$), 1.39 (qt, *J* = 12.5, 3.3 Hz, 2H, $H^{9b, 11b}$), 1.27 (d, *J* = 12.5 Hz, 1H, H^{10b}).

^{13}C NMR (101 MHz, $CDCl_3$): δ 174.8 (C^{2}), 157.1 ($C^{4, 6}$), 118.5 (C^{5}), 47.7 (C^{1}), 32.0 ($C^{8, 12}$), 26.3 ($C^{9, 11}$), 26.1 (C^{10}).

IR (film)/ ν_{max}: 2930, 1572, 1560, 1424 cm^{-1}.

HRMS (ESI) m/z calcd. for $C_{10}H_{15}N_2$ ($[M+H]^+$) 163.1230, found 163.1235.

2-cycloheptylpyrimidine (432)



The compound **432** was obtained according to the **General Procedure J** as a colorless oil (89 % yield).

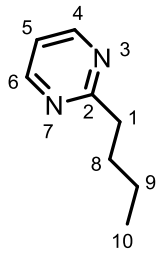
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.63 (d, *J* = 4.9 Hz, 2H, $H^{4, 6}$), 7.06 (t, *J* = 4.9 Hz, 1H, H^{5}), 3.04 (tt, *J* = 10.2, 3.8 Hz, 1H, H^{1}), 2.07 – 1.95 (m, 2H, $H^{8a, 13a}$), 1.88 – 1.73 (m, 4H, $H^{9a, 9b, 12a, 12b}$), 1.73 – 1.48 (m, 6H, $H^{8b, 13b, 10a, 10b, 11a, 11b}$).

^{13}C NMR (101 MHz, $CDCl_3$): δ 176.2 (C^{2}), 157.1 ($C^{4,6}$), 118.3 (C^{5}), 49.7 (C^{1}), 34.1 ($C^{8, 13}$), 28.2 ($C^{9, 12}$), 27.2 ($C^{10, 11}$).

IR (film)/ ν_{max}: 1572, 1560, 1420 cm^{-1}.

HRMS (ESI) m/z calcd. for $C_{11}H_{17}N_2$ ($[M+H]^+$) 177.1386, found 177.1378.

2-butylpyrimidine (431)



The compound **1g** was obtained according to the **General Procedure J** as a colorless oil (93 % yield).

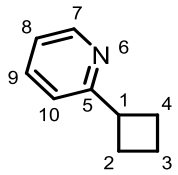
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.62 (d, *J* = 4.9 Hz, 2H, $H^{4, 6}$), 7.07 (t, *J* = 4.9 Hz, 1H, H^{5}), 2.96 – 2.88 (m, 2H, $H^{1a, 1b}$), 1.83 – 1.71 (m, 2H, $H^{8a, 8b}$), 1.37 (dq, *J* = 14.7, 7.4 Hz, 2H, $H^{9a, 9b}$), 0.91 (t, *J* = 7.4 Hz, 3H, $H^{10a, 10b, 10c}$).

^{13}C NMR (101 MHz, $CDCl_3$): δ 171.8 (C^2), 157.1 ($C^{4, 6}$), 118.3 (C^5), 39.4 (C^1), 30.9 (C^8), 22.6 (C^9), 13.9 (C^{10}).

IR (film)/ ν_{max}: 2977, 1560, 1443 cm^{-1}.

HRMS (ESI) m/z calcd. for $C_8H_{13}N_2$ ($[M+H]^+$) 137.1073, found 137.1074.

2-cyclobutylpyridine (433)



The compound **433** was obtained according to the **General Procedure J** as a colorless oil (86 % yield).

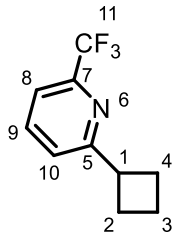
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.54 (ddd, *J* = 4.9, 1.9, 0.9 Hz, 1H, H^7), 7.56 (td, *J* = 7.7, 1.9 Hz, 1H, H^9), 7.17 – 7.09 (m, 1H, H^8), 7.06 (ddd, *J* = 7.5, 4.9, 1.2 Hz, 1H, H^{10}), 3.72 – 3.59 (m, 1H, H^1), 2.39 – 2.26 (m, 4H, $H^{2a, 2b, 4a, 4b}$), 2.12 – 1.96 (m, 1H, H^{3a}), 1.95 – 1.80 (m, 1H, H^{3b}).

^{13}C NMR (101 MHz, $CDCl_3$): δ 164.8 (C^5), 149.3 (C^7), 136.2 (C^9), 120.9 ($C^{8, 10}$), 42.1 (C^1), 28.6 ($C^{2, 4}$), 18.3 (C^3).

IR (film)/ ν_{max}: 2934, 1571, 1559, 1423 cm^{-1}.

HRMS (ESI) m/z calcd. for $C_9H_{12}N$ ($[M+H]^+$) 134.0964, found 134.0968.

2-cyclobutyl-6-(trifluoromethyl)pyridine (434)



The compound **434** was obtained according to the **General Procedure J** as a colorless oil (64 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75 (t, *J* = 7.8 Hz, 1H, H^{8}), 7.47 (dd, *J* = 7.7, 0.8 Hz, 1H, H^{9}), 7.35 (d, *J* = 7.9 Hz, 1H, H^{10}), 3.73 (p, *J* = 8.7 Hz, 1H, H^{1}), 2.37 (tt, *J* = 9.0, 1.6 Hz, 4H, $H^{2a, 2b, 4a, 4b}$), 2.13 – 2.00 (m, 1H, H^{3a}), 1.93 (dddd, *J* = 13.5, 11.0, 5.6, 2.2 Hz, 1H, H^{3b}).

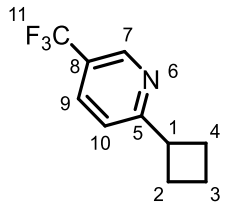
^{13}C NMR (101 MHz, $CDCl_3$): δ 165.8 (C^{5}), 147.9 (C^{7}), 137.4 (C^{9}), 123.9 (C^{10}), 120.5 (C^{11}), 117.6 (C^{8}), 42.1(C^{1}), 28.6 ($C^{2, 4}$), 18.3 (C^{3}).

^{19}F NMR (376 MHz, $CDCl_3$): δ -68.04.

IR (film)/ ν_{max}: 2980, 1590, 1568, 1474, 1434, 747 cm^{-1}.

HRMS (ESI) m/z calcd. for $C_{10}H_{11}F_3N$ ($[M+H]^+$) 202.0838, found 202.0837.

2-cyclobutyl-5-(trifluoromethyl)pyridine (435)



The compound **435** was obtained according to the **General Procedure J** as a colorless oil (50% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.81 (dt, *J* = 2.1, 1.0 Hz, 1H, H^{7}), 7.81 (ddd, *J* = 8.2, 2.4, 0.8 Hz, 1H, H^{9}), 7.26 (dd, *J* = 8.1, 0.9 Hz, 1H, H^{10}), 3.73 (p, *J* = 8.7 Hz, 1H, H^{1}), 2.43 – 2.29 (m, 4H, $H^{2a, 2b, 4a, 4b}$), 2.09 (dddd, *J* = 18.1, 11.0, 9.6, 8.5 Hz, 1H, H^{3a}), 1.99 – 1.86 (m, 1H, H^{3b}).

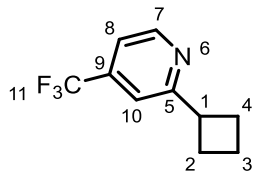
^{13}C NMR (101 MHz, $CDCl_3$): δ 168.7 (C^{5}), 146.2 (C^{7}), 133.2 (C^{9}), 125.2 (C^{8}), 122.5 (C^{11}), 120.7 (C^{10}), 41.9 (C^{1}), 28.3 ($C^{2,4}$), 18.2 (C^{3}).

^{19}F NMR (376 MHz, $CDCl_3$): δ -62.22.

IR (film)/ ν_{max}: 2977, 1560, 1443, 1208 cm^{-1}.

HRMS (ESI) m/z calcd. for $C_{10}H_{11}F_3N$ ($[M+H]^+$) 202.0838, found 202.0835.

2-cyclobutyl-4-(trifluoromethyl)pyridine (436)



The compound **436** was obtained according to the **General Procedure J** as a colorless oil (68 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.72 (d, *J* = 5.1 Hz, 1H, H^{7}), 7.34 (dq, *J* = 1.5, 0.8 Hz, 1H, H^{8}), 7.32 – 7.28 (m, 1H, H^{10}), 3.81 – 3.67 (m, 1H, H^{1}), 2.46 – 2.27 (m, 4H, $H^{2a, 2b, 4a, 4b}$), 2.09 (dddd, *J* = 18.2, 11.0, 9.6, 8.4 Hz, 1H, H^{3a}), 1.99 – 1.85 (m, 1H, H^{3b}).

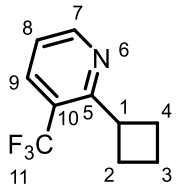
^{13}C NMR (101 MHz, $CDCl_3$): δ 166.5 (C^5), 150.3 (C^7), 138.7 (C^9), 116.8 (C^{10}), 116.3 (C^{11}), 42.1 (C^1), 28.5 ($C^{2,4}$), 18.3 (C^3).

^{19}F NMR (376 MHz, $CDCl_3$): δ -64.84.

IR (film)/ ν_{max}: 2934, 1586, 1506 cm^{-1}.

HRMS (ESI) m/z calcd. for $C_{10}H_{11}F_3N$ ($[M+H]^+$) 202.0838, found 202.0837.

2-cyclobutyl-3-(trifluoromethyl)pyridine (437)



The compound **437** was obtained according to the **General Procedure J** as a colorless oil (58 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.77 (dd, *J* = 4.8, 1.7 Hz, 1H, H^7), 7.85 (ddd, *J* = 7.9, 1.7, 0.7 Hz, 1H, H^9), 7.21 (ddt, *J* = 7.7, 4.8, 0.9 Hz, 1H, H^8), 3.99 (ttt, *J* = 9.4, 8.0, 1.4 Hz, 1H, H^1), 2.54 (pd, *J* = 9.2, 2.5 Hz, 2H, $H^{2a, 4a}$), 2.27 (qt, *J* = 8.3, 2.7 Hz, 2H, $H^{2b, 4b}$), 2.13 – 1.99 (m, 1H, H^{3a}), 1.92 (tddt, *J* = 10.9, 8.1, 2.9, 1.4 Hz, 1H, H^{3b}).

^{13}C NMR (101 MHz, $CDCl_3$): δ 162.3 (C^5), 152.2 (C^7), 133.7 (q, *J* = 5.5 Hz) (C^9), 124.1 – 123.3 (m) (C^{10}), 122.8 (C^{11}), 120.6 (C^8), 38.9 (q, *J* = 2.0 Hz) (C^1), 28.3 ($C^{2,4}$), 18.2 (C^3).

^{19}F NMR (376 MHz, $CDCl_3$): δ -60.82.

IR (film)/ ν_{max}: 2959, 1561, 1425 cm^{-1}.

HRMS (ESI) m/z calcd. for $C_{10}H_{11}F_3N$ ($[M+H]^+$) 202.0838, found 202.0834.

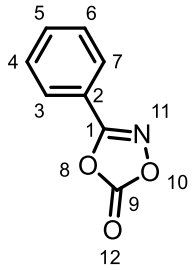
5.2.7 General Procedure K: preparation of starting material dioxazolones (b)

A flask was charged with hydroxylamine hydrochloride (1 equiv), potassium carbonate (1 equiv) and solvent (diethyl ether/water = 7.5:1). The reaction was cooled to 0 °C with vigourous stirring before addition of acid chloride (1 equiv) dropwise. The reaction was stirred overnight, diluted with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated in vacuo. The crude hydroxamic acid product was purified by trituration with pentane/diethyl ether if necessary.

To a slurry of hydroxamic acid (1 equiv) in dichloromethane was added carbonyl diimidazole (CDI, 1.5 equiv). The reaction was stirred for 30 minutes, diluted with 1M aqueous HCl and extracted with dichloromethane. The combined organic layers were dried over sodium sulfate, and concentrated in vacuo to give dioxazolone **336**. Purification by dissolving in toluene and filtration was performed in necessary.

Analytical data for the isolated compound were identical with reported values.

3-phenyl-1,4,2-dioxazol-5-one (336)



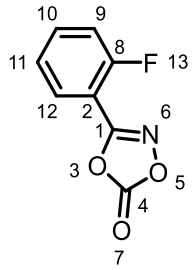
The compound **336** was obtained according to the **General Procedure K** as a white solid in 90 % yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89 – 7.84 (m, 2H, $H^{3, 7}$), 7.69 – 7.62 (m, 1H, H^{5}), 7.59 – 7.52 (m, 2H, $H^{4, 6}$).

^{13}C NMR (101 MHz, $CDCl_3$): δ 163.7 (C^{1}), 153.9 (C^{9}), 133.9 (C^{5}), 129.5 ($C^{3, 7}$), 126.8 ($C^{4, 6}$), 120.3 (C^{2}).

The spectra data are consistent with reported literature.[149]

3-(2-fluorophenyl)-1,4,2-dioxazol-5-one (400)



The compound **400** was obtained according to the **General Procedure K** as a white solid in 73 % yield.

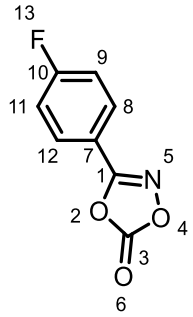
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80 (ddd, *J* = 8.2, 6.8, 1.8 Hz, 1H, H^{12}), 7.66 (dddd, *J* = 8.4, 7.5, 5.1, 1.8 Hz, 1H, H^{11}), 7.39 – 7.28 (m, 2H, $H^{9, 10}$).

^{13}C NMR (101 MHz, $CDCl_3$): δ 161.8 (C^{1}), 159.2 (C^{8}), 153.4 (C^{4}), 135.6 (d, *J* = 8.7 Hz) (C^{11}), 129.1 (C^{12}), 125.0 (C^{10}), 117.3 (C^{9}), 108.8 (C^{2}).

^{19}F NMR (376 MHz, $CDCl_3$): δ -105.7 (ddd, *J* = 10.6, 7.1, 5.1 Hz) (F^{13}).

The spectra data are consistent with reported literature.[187]

3-(4-fluorophenyl)-1,4,2-dioxazol-5-one (401)



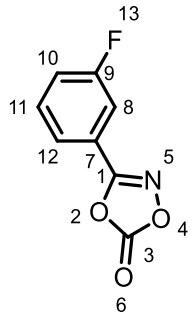
The compound **401** was obtained according to the **General Procedure K** as a white solid in 79 % yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.87 (d, J = 8.0 Hz, 2H, $H^{8, 12}$), 7.24 (d, J = 8.4 Hz, 2H, $H^{9, 11}$).

^{13}C NMR (101 MHz, $CDCl_3$): δ 165.8 (C^{1}), 162.5 (C^{10}), 153.6 (C^{3}), 129.1 ($C^{8, 12}$), 117.10 (C^{7}), 116.6 ($C^{9, 11}$).

The spectra data are consistent with reported literature.[187]

3-(3-fluorophenyl)-1,4,2-dioxazol-5-one (402)



The compound **402** was obtained according to the **General Procedure K** as a white solid in 59 % yield.

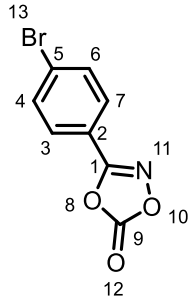
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67 (d, J = 7.8 Hz, 1H, H^{8}), 7.68 – 7.59 (m, 2H, $H^{11, 12}$), 7.42 – 7.35 (m, 1H, H^{10}).

^{13}C NMR (101 MHz, $CDCl_3$): δ 162.9 (C^{1}), 162.8 (C^{9}), 153.4 (C^{3}), 131.5 (C^{7}), 122.6 (C^{11}), 122.4 (C^{12}), 121.1 (C^{10}), 113.7 (C^{8}).

^{19}F NMR (376 MHz, $CDCl_3$): δ -106.9 (m) (F^{13}).

The spectra data are consistent with reported literature.[188]

3-(4-bromophenyl)-1,4,2-dioxazol-5-one (403)



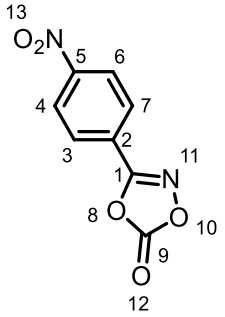
The compound **403** was obtained according to the **General Procedure K** as a white solid in 68 % yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 – 7.71 (m, 4H, $H^{3, 4, 5, 6}$).

^{13}C NMR (101 MHz, $CDCl_3$): δ 163.1 (C^{1}), 153.6 (C^{9}), 133.0 ($C^{3, 7}$), 129.3 (C^{5}), 128.1 ($C^{4, 6}$), 119.3 (C^{2}).

The spectra data are consistent with reported literature.[189]

3-(4-nitrophenyl)-1,4,2-dioxazol-5-one (406)



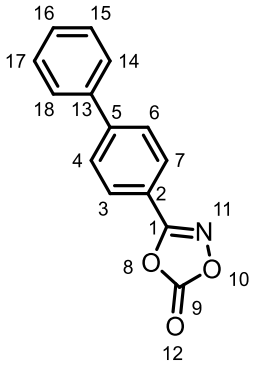
The compound **406** was obtained according to the **General Procedure K** as a pale-yellow solid in 56 % yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.43 – 8.41 (m, 2H, $H^{4, 6}$), 8.10 – 8.08 (m, 2H, $H^{3,7}$).

^{13}C NMR (101 MHz, $CDCl_3$): δ 162.1 (C^{1}), 153.1 (C^{9}), 150.9 (C^{5}), 128.0 (C^{2}), 125.8 ($C^{3, 7}$), 124.7 ($C^{4, 6}$).

The spectra data are consistent with reported literature.[190]

3-([1,1'-biphenyl]-4-yl)-1,4,2-dioxazol-5-one (408)



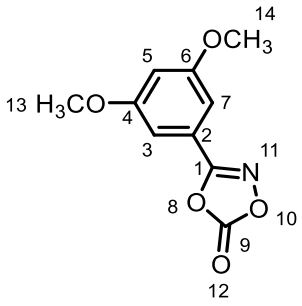
The compound **408** was obtained according to the **General Procedure K** as a white solid in 51 % yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93 (d, J = 8.6 Hz, 2H, H, $H^{4, 6}$), 7.76 (d, J = 8.6 Hz, 2H, $H^{14, 18}$), 7.63 (d, J = 7.3 Hz, 2H, $H^{3, 7}$), 7.50 (t, J = 7.3 Hz, 2H, $H^{15, 17}$), 7.44 (t, J = 7.3 Hz, 1H, H^{16}).

^{13}C NMR (101 MHz, $CDCl_3$): δ 163.4 (C^{1}), 153.7 (C^{9}), 146.6 (C^{5}), 139.1 (C^{13}), 129.1 ($C^{3, 7}$), 128.7 ($C^{15, 17}$), 127.9 (C^{2}), 127.2 ($C^{4, 6}$), 127.2 ($C^{14, 18}$), 118.6(C^{16}).

The spectra data are consistent with reported literature.[187]

3-(3,5-dimethoxyphenyl)-1,4,2-dioxazol-5-one (409)



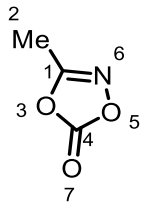
The compound **409** was obtained according to the **General Procedure K** as a white solid in 78 % yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.96 (d, J = 2.3 Hz, 2H, $H^{3, 7}$), 6.69 (t, J = 2.3 Hz, 1H, H^{5}), 3.84 (s, 6H, $H^{13a, 13b, 13c, 14a, 14b, 14c}$).

^{13}C NMR (101 MHz, $CDCl_3$): δ 163.7 (C^{1}), 161.3 (C^{9}), 153.8 ($C^{4, 6}$), 121.7 (C^{2}), 106.3 (C^{5}), 104.5 ($C^{3, 7}$), 55.9 ($C^{13, 14}$).

The spectra data are consistent with reported literature.[149]

3-methyl-1,4,2-dioxazol-5-one (410)



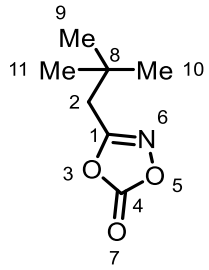
The compound **410** was obtained according to the **General Procedure K** as colorless oil in 91% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.35 (s, 3H, $H^{2a, 2b, 2c}$).

^{13}C NMR (101 MHz, $CDCl_3$): δ 163.8 (C^{1}), 154.3 (C^{4}), 10.4 (C^{2}).

The spectra data are consistent with reported literature.[189]

3-neopentyl-1,4,2-dioxazol-5-one (412)



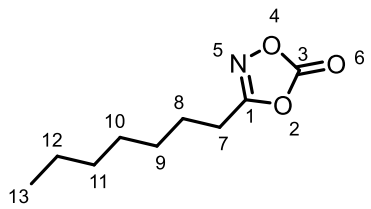
The compound **412** was obtained according to the **General Procedure K** as colorless oil in 70% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.50 (s, 2H, $H^{2a, 2b}$), 1.04 (s, 9H, $H^{9a, 9b, 9c, 10a, 10b, 10c, 11a, 11b, 11c}$).

^{13}C NMR (101 MHz, $CDCl_3$): δ 164.9 (C^{1}), 153.6 (C^{4}), 37.8 (C^{2}), 31.2 (C^{8}), 29.3 ($C^{9, 10, 11}$).

The spectra data are consistent with reported literature.[149]

3-heptyl-1,4,2-dioxazol-5-one (413)



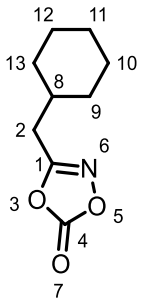
The compound **413** was obtained according to the **General Procedure K** as colorless oil in 67% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.62 (t, J = 7.5 Hz, 2H, $H^{7a, 7b}$), 1.77 – 1.60 (m, 2H, $H^{8a, 8b}$), 1.46 – 1.20 (m, 8H, $H^{9a, 10a, 11a, 12a, 9b, 10b, 11b, 12b}$), 0.89 (t, J = 6.8 Hz, 3H, $H^{13a, 13b, 13c}$).

^{13}C NMR (101 MHz, $CDCl_3$): δ 166.9 (C^1), 154.3 (C^3), 31.5 (C^1), 28.7 (C^1), 28.7 (C^1), 24.9 (C^1), 24.7 (C^1), 22.7 (C^1), 14.1 (C^1).

The spectra data are consistent with reported literature.[189]

3-(cyclohexylmethyl)-1,4,2-dioxazol-5-one (414)



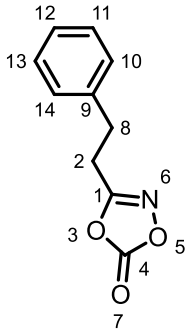
The compound **414** was obtained according to the **General Procedure K** as colorless oil in 69% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.50 (d, J = 6.7 Hz, 2H, $H^{2a, 2b}$), 1.84 – 1.65 (m, 6H, $H^{9a, 10a, 12a, 12b, 13a, 13b}$), 1.37 – 1.11 (m, 3H, $H^{8, 9b, 10b}$), 1.05 (qd, J = 11.4, 5.6 Hz, 2H, $H^{11a, 11b}$).

^{13}C NMR (101 MHz, $CDCl_3$): δ 166.1 (C^1), 154.4 (C^4), 34.7 (C^8), 32.9 ($C^{9, 13}$), 32.2 (C^2), 25.9 (C^{11}), 25.8 ($C^{12, 10}$).

The spectra data are consistent with reported literature.[149]

3-phenethyl-1,4,2-dioxazol-5-one (415)



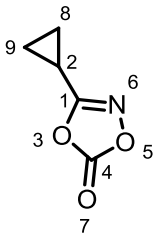
The compound **415** was obtained according to the **General Procedure K** as a white solid in 72 % yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 – 7.32 (m, 2H, $H^{11, 13}$), 7.32 – 7.26 (m, 1H, H^{12}), 7.24 – 7.21 (m, 2H, $H^{10, 14}$), 3.09 – 3.02 (m, 2H, $H^{2a, 2b}$), 2.98 – 2.90 (m, 2H, $H^{8a, 8b}$)

^{13}C NMR (101 MHz, $CDCl_3$): δ 166.0 (C^{1}), 154.1 (C^{4}), 138.2 (C^{9}), 129.0 ($C^{11, 13}$), 128.2 ($C^{10, 14}$), 127.3 (C^{12}), 30.6 (C^{2}), 26.8 (C^{8}).

The spectra data are consistent with reported literature.[149]

3-cyclopropyl-1,4,2-dioxazol-5-one (416)



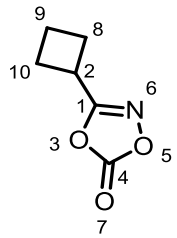
The compound **416** was obtained according to the **General Procedure K** as colorless oil in 68% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.91 (tt, *J* = 8.3, 5.1 Hz, 1H, H^{2}), 1.22 – 1.17 (m, 2H, $H^{9a, 9b}$), 1.16 – 1.12 (m, 2H, $H^{8a, 8b}$).

^{13}C NMR (101 MHz, $CDCl_3$): δ 167.9 (C^{1}), 154.1 (C^{4}), 7.5 ($C^{8, 9}$), 5.6 (C^{2}).

The spectra data are consistent with reported literature.[149]

3-cyclobutyl-1,4,2-dioxazol-5-one (417)



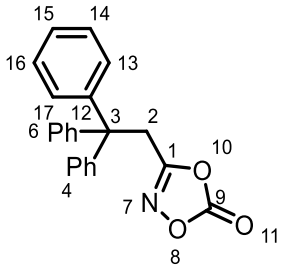
The compound **417** was obtained according to the **General Procedure K** as colorless oil in 43% yield.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.47 (pd, J = 8.4, 1.1 Hz, 1H, H^{2}), 2.38 (td, J = 8.8, 7.1 Hz, 4H, $H^{8a, 8b, 10a, 10b}$), 2.21 – 2.00 (m, 2H, $H^{9a, 9b}$).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 168.5 (C^{1}), 154.5 (C^{4}), 29.7 (C^{2}), 25.3 ($C^{8, 10}$), 19.1 (C^{9}).

The spectra data are consistent with reported literature.[149]

3-(3,3,3-triphenylpropyl)-1,4,2-dioxazol-5-one (419)



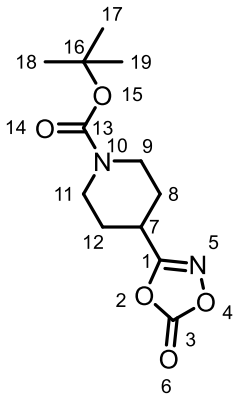
The compound **419** was obtained according to the **General Procedure K** as a white solid in 59 % yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 – 7.14 (m, 15H, H^{Ph}), 3.97 (s, 2H, $H^{2a, 2b}$).

^{13}C NMR (101 MHz, $CDCl_3$): δ 165.0 (C^{1}), 153.8 (C^{9}), 144.6 (C^{12}), 128.9 (C^{13}), 128.4 (C^{14}), 127.2 (C^{15}), 56.3 (C^{5}), 37.1 (C^{2}).

The spectra data are consistent with reported literature.[149]

***tert*-butyl 4-(5-oxo-1,4,2-dioxazol-3-yl)piperidine-1-carboxylate (421)**



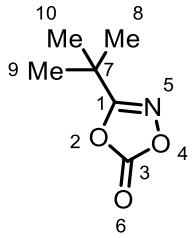
The compound **421** was obtained according to the **General Procedure K** as colorless oil in 50% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.10 (d, J = 13.5 Hz, 2H, $H^{9a, 11a}$), 2.98 – 2.74 (m, 3H, $H^{9b, 11b, 7}$), 2.01 – 1.89 (m, 2H, $H^{8a, 12a}$),1.75 – 1.61 (m, 2H, $H^{8b, 12b}$), 1.43 (s, 9H, $H^{17a, 17b, 17c, 18a, 18b, 18c, 19a, 19b, 19c}$).

^{13}C NMR (101 MHz, $CDCl_3$): δ 168.1 (C^{1}), 154.5 (C^{13}), 154.1 (C^{3}), 80.2 (C^{16}), 33.1 ($C^{11, 9}$), 28.4 (C^{7}), 28.4 ($C^{17, 18, 19}$), 27.2 ($C^{8, 12}$).

The spectra data are consistent with reported literature.[191]

3-(*tert*-butyl)-1,4,2-dioxazol-5-one (422)



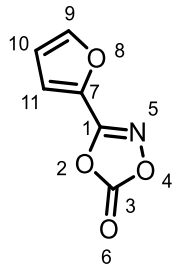
The compound **422** was obtained according to the **General Procedure K** as colorless oil in 67% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.32 (s, 9H, $H^{8a, 8b, 8c, 9a, 9b, 9c, 10a, 10b, 10c}$);

^{13}C NMR (101 MHz, $CDCl_3$): δ 172.4 (C^{1}), 154.5 (C^{3}), 32.5 (C^{7}), 26.3 ($C^{8, 9, 10}$).

The spectra data are consistent with reported literature.[190]

3-(furan-2-yl)-1,4,2-dioxazol-5-one (423)



The compound **423** was obtained according to the **General Procedure K** as a white solid in 29 % yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72 (dd, J = 1.8, 0.8 Hz, 1H, H^{11}), 7.18 (dd, J = 3.6, 0.8 Hz, 1H, H^{9}), 6.66 (dd, J = 3.6, 1.8 Hz, 1H, H^{10}).

^{13}C NMR (101 MHz, $CDCl_3$): δ 156.7 (C^{1}), 153.2 (C^{3}), 147.9 (C^{11}), 135.1 (C^{7}), 117.9 (C^{9}), 112.7 (C^{10}).

The spectra data are consistent with reported literature.[149]

5.2.8 Computational studies

a) Computational Methods and Main Findings

Employ state-of-the-art density functional theory (DFT) computations that account for solvation and dispersion interactions, to evaluate the total electronic and Gibbs free energies associated with the proposed mechanism for the enantioselective C−H amidation of cyclobutanes.

All calculations reported in this paper were performed using the Gaussian 16 (G16) program.[192] Geometry optimizations and frequency calculations for all reported structures were performed using the B3LYP functional[193, 194] with the 6-31G(d) basis set for C, H, N, O atoms and the Lanl2dz effective core potential (ECP) for Rh.[195, 196] Dispersion interactions were included using Grimme's DFT-D3 correction.[197, 198] SMD solvent effects were incorporated into all calculations with 1,4-dioxane as the solvent.[199] This level is referred to as SMD(1,4-dioxane)/B3LYP-D3/Lanl2dz(Rh)-6-31G(d). Each reported minimum has zero imaginary frequency and each transition state (TS) has only one imaginary frequency. Energy changes were shown by the use of Gibbs free energies (T = 298.15 K and P = 1 atm). Optimized structures were illustrated using CYLview20.[200] Potential energies were refined by means of single point calculations using the B3LYP functional[193, 194] with the 6-311+G(d,p) basis set for C, H, N, O atoms and the SDD effective core potential (ECP) for Rh.[201-203] Dispersion interactions were included using Grimme's DFT-D3 correction with Becke–Johnson damping. This level is denoted SMD(1,4-dioxane)/B3LYP-D3(BJ)/SDD(Rh)-6-311+G(d,p)//SMD(1,4-dioxane)/B3LYP-D3/Lanl2dz(Rh)-6-31G(d).

b) Computational Results and Discussion

To elucidate and understand the role of axially chiral acid ligand for the rhodium(III)-catalysed enantioselective C−H amidation reaction, a density functional theory (DFT) study was performed (Figure 1). The reaction begins when the pyrimidine substrate **1a** and the chiral acid co-catalyst (*R*)-**396** coordinate to the Cp*Rh(III) moiety, and then the adjacent C–H on the cyclobutyl ring is activated by the ambiphilic metal-ligand activation/concerted metalation deprotonation (AMLA/CMD) mechanism.[25] The computed C–H activation transition state (TS) structures that lead to the formation of two enantiomers are **TS1-(*R*)** and **TS1-(*S*)**, and the reaction preferably proceeds through **TS1-(*S*)** that forms the *S*-configured product which agrees with the experimentally confirmed absolute stereochemical outcome of the reaction ($\Delta\Delta G^{\ddagger}$ = 4.5 kcal mol^{-1}). An interesting feature that can be seen in these TSs is that the amide oxygen atom of the ligand contributes to the stabilization of TS conformations by both inter- and intramolecular n–π* interaction. The empty π* orbital of the carboxylate group accepts the lone-pair electron density of the amide nucleophile, resulting in acceleration of the AMLA/CMD process. In addition, the methyl group on cyclohexyl ring interacts with one of the naphthyl ring by an intramolecular CH–π interaction that contributes for an increased rigidity of the axially chiral acid ligand. The origin of the stereoselectivity for this transformation is that the cyclobutane moiety clashes with the Cp* ring in the unfavored transition state **TS1-(*R*)**, and thus the less sterically demanding **TS1-(*S*)** has a lower energy barrier. Therefore, the fine tuning of catalytic system enabled a realization of high degree of enantioselectivity by multiple stabilizing interactions and the steric repulsion between the substrate and the catalyst.

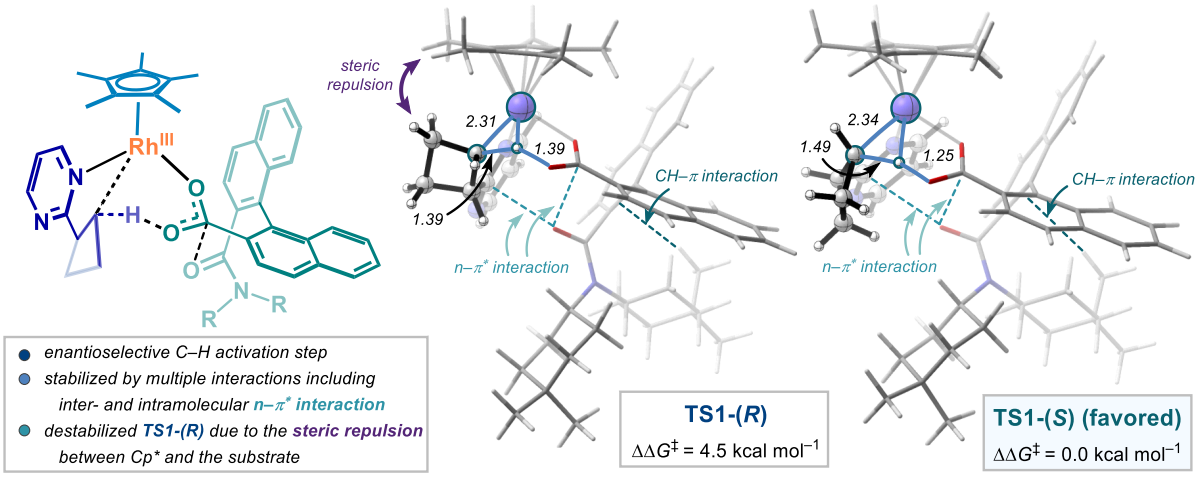


Figure 1 The key C–H activation transition state structures for the formation of (*R*)-product and (*S*)-product (Δ*G* [kcal mol^{-1}])) computed at the SMD(1,4-dioxane)/B3LYP-D3(BJ)/SDD(Rh)-6-311+G(d,p)//SMD(1,4-dioxane)/B3LYP-D3/Lanl2dz(Rh)-6-31G(d) level of theory. Energies (kcal mol^{-1}) and forming bond lengths (Å) of the TS geometries are provided in the insert.

c) Computational Details

Table S1. Cartesian coordinates (in Å), energies (in Hartrees), and number of imaginary frequencies of all stationary points, computed at SMD(1,4-dioxane)/B3LYP-D3(BJ)/SDD(Rh)-6-311+G(d,p)//SMD(1,4-dioxane)/B3LYP-D3/Lanl2dz(Rh)-6-31G(d) level of theory. Energies (in Hartrees) at SMD(1,4-dioxane)/B3LYP-D3/Lanl2dz(Rh)-6-31G(d) level of theory are also provided.

TS1-(*R*)

B3LYP-D3/Lanl2dz(Rh)-6-31G(d) SCF energy in solution: -2673.89564356 a.u.

B3LYP-D3/Lanl2dz(Rh)-6-31G(d) enthalpy in solution: -2672.717180 a.u.

B3LYP-D3/Lanl2dz(Rh)-6-31G(d) free energy in solution: -2672.867824 a.u.

B3LYP-D3(BJ)/SDD(Rh)-6-311+G(d,p) SCF energy in solution: -2675.80506876 a.u.

B3LYP-D3(BJ)/SDD(Rh)-6-311+G(d,p) enthalpy in solution: -2674.626605 a.u.

B3LYP-D3(BJ)/SDD(Rh)-6-311+G(d,p) free energy in solution: -2674.77725 a.u.

N_{imag} = 1, 1317.09*i* cm^{-1}

H	4.27385600	0.31884400	3.59658600
H	3.42784600	-1.18565400	3.21411800
H	5.14094800	-1.22555200	3.66122900
N	2.50880500	1.02209300	-1.65177800
C	1.99868500	3.14051700	-0.52245500
C	3.00216200	2.64868100	0.54338300
C	2.96846100	4.33239100	-0.79852500
H	0.98597100	3.37843500	-0.19194600
H	7.48754700	0.50629400	-1.47840400
H	2.78179500	3.17075000	1.48561700
H	2.52928000	1.62009400	1.34221200
H	6.44707900	2.50340400	1.20962200

H	5.42686600	2.07855600	2.59548700
H	7.02294100	1.34363800	2.41458100
H	4.36575900	-3.44977600	1.53413900
C	1.14414500	1.87603600	-3.83625300
H	6.01848800	1.11000400	-2.25460700
Rh	3.53409100	0.43207900	0.14759700
C	1.71693500	0.60584200	-3.85920300
H	6.77262900	2.03196600	-0.94567400
N	1.22464600	2.67414000	-2.77034500
C	2.39276800	0.20943100	-2.71595700
H	2.84165000	-0.77174500	-2.63259200
O	1.50096300	1.21406800	2.18657500
C	1.06310400	0.15506200	1.64543600
O	1.67906900	-0.43295400	0.69436200
H	1.63200000	-0.05149100	-4.71666900
H	0.59980000	2.26489700	-4.69432500
H	2.68676300	5.20751400	-0.20621000

C	4.11126100	3.51482800	-0.13983900
C	1.89347500	2.22915100	-1.70441500
H	3.09439400	4.63139500	-1.84341700
C	5.72094300	0.26075600	-0.29917100
C	5.10517600	-1.03454900	-0.56481800
C	5.56501200	0.53647500	1.09889000
C	4.76667900	-0.51481100	1.67472300
C	4.54458200	-1.51843800	0.64700400
C	6.53734400	1.02470700	-1.29416500
C	5.16585500	-1.75757000	-1.87179000
C	6.13767400	1.68638200	1.86261600
C	4.37882300	-0.65536000	3.11347200
C	3.79731700	-2.79152700	0.86478900
H	5.16534100	-1.06411800	-2.71754200
H	6.09647500	-2.33779700	-1.92909700
H	4.33428300	-2.45809800	-1.99024700
H	2.82853200	-2.59095800	1.33002500

H	3.61230900	-3.32835900	-0.06738700
H	4.69208800	2.97671900	-0.89071900
H	4.79443600	4.04689400	0.52642600
C	-0.63617500	-1.73327500	0.06890600
C	-1.00688500	-0.80803700	-0.90385000
C	-0.73555600	-1.07129600	-2.27060400
C	-0.13885800	-2.24322900	-2.66772800
C	1.31151200	-5.32985600	-1.14264000
C	1.06836300	-5.07876800	0.22956700
C	0.43420100	-3.92309600	0.62782700
C	0.00316000	-2.95493500	-0.32220000
C	0.25410600	-3.21163100	-1.70946400
C	0.91153600	-4.41375700	-2.08894400
C	-1.42546000	0.60229800	-0.53087200
H	-0.98462900	-0.31530600	-3.00731100
H	0.05315300	-2.43334700	-3.72103100
H	1.80949500	-6.24716500	-1.44446200

H	1.38763800	-5.80329300	0.97358600
H	0.25856000	-3.74196300	1.68273700
H	1.08871300	-4.59917600	-3.14596500
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C	-0.52327300	-0.11419500	3.53414900
C	-1.57423600	-0.71871300	4.17296300
C	-4.04523300	-3.45419200	3.59746600
C	-3.68401300	-3.86329100	2.29132000
C	-2.66951600	-3.22694700	1.61384500
C	-1.95002200	-2.14718500	2.20335100
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H	-4.62361300	-3.28956900	-3.59233700
H	-4.75942300	-4.00719900	-1.97924000
O	-0.48947200	1.36857100	-0.24862900
N	-2.72274900	1.01114000	-0.51348200
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C	-3.91278400	0.24702300	-0.96523200
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H	-6.58627000	4.99438100	-0.09350000
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TS1-(*S*)

B3LYP-D3/Lanl2dz(Rh)-6-31G(d) SCF energy in solution: -2673.90265380 a.u.

B3LYP-D3/Lanl2dz(Rh)-6-31G(d) enthalpy in solution: -2672.725048 a.u.

B3LYP-D3/Lanl2dz(Rh)-6-31G(d) free energy in solution: -2672.877426 a.u.

B3LYP-D3(BJ)/SDD(Rh)-6-311+G(d,p) SCF energy in solution: -2675.80960117 a.u.

B3LYP-D3(BJ)/SDD(Rh)-6-311+G(d,p) enthalpy in solution: -2674.631995 a.u.

B3LYP-D3(BJ)/SDD(Rh)-6-311+G(d,p) free energy in solution: -2674.784373 a.u.

N_{imag} = 1, 1551.90*i* cm^{-1}

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H	6.66506200	-1.32079700	-2.16218300

C	2.32605800	3.88867800	0.88633100
H	2.25104800	1.81439800	1.12275500
H	6.49741600	1.87081000	-1.12961500
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C	-3.38291900	3.84411300	1.79056800
C	-3.46447400	2.41223900	1.23783400
C	-3.03453900	3.32289000	-1.10125200

C	-2.97183000	4.74580200	-0.52529000
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C	-5.34871300	-0.52555100	-2.82467400

C	-5.75019000	-1.79187900	-2.02969700
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H	-3.74831400	0.93928400	-3.00345500
H	-5.38879100	-0.73468700	-3.90187400
H	-6.09599000	0.25864100	-2.63257000
C	-4.85498500	-2.98691500	-2.41412500
H	-5.60615300	5.62496200	-0.24323100
H	-5.89484000	4.99155500	1.38569000
H	-5.60219800	3.88206000	0.04329000
H	-3.77252700	7.11653900	0.66167200
H	0.68847800	3.34736500	-0.47707600
H	1.40654700	4.92612200	-0.91320600

H	2.98492100	4.75157500	1.03805900
H	1.70908000	3.75803100	1.77670300

5.2.9 Single Crystal X-Ray Structures for Compound 341

Low temperature[152] single crystal X-ray diffraction data were collected using a Rigaku Oxford Diffraction SuperNova diffractometer. Raw frame data were reduced using CrysAlisPro and the structures were solved using 'Superflip'[204] before refinement with CRYSTALS[205, 206] as per the SI (CIF). Full refinement details are given in the Supporting Information (CIF); Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre (CCDC 2097043-44) and can be obtained via www. ccdc.cam.ac.uk/data_request/cif.

Compound 341

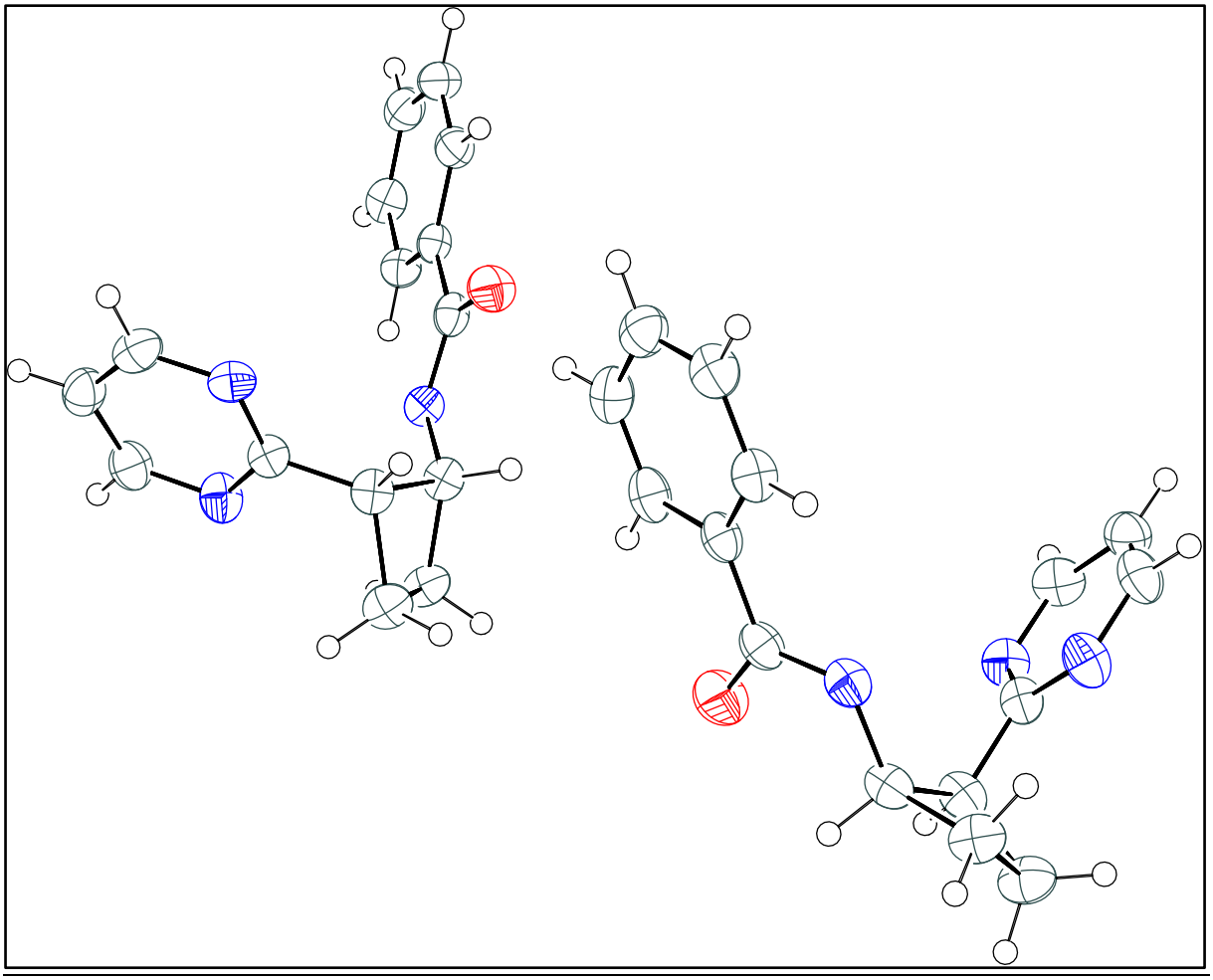


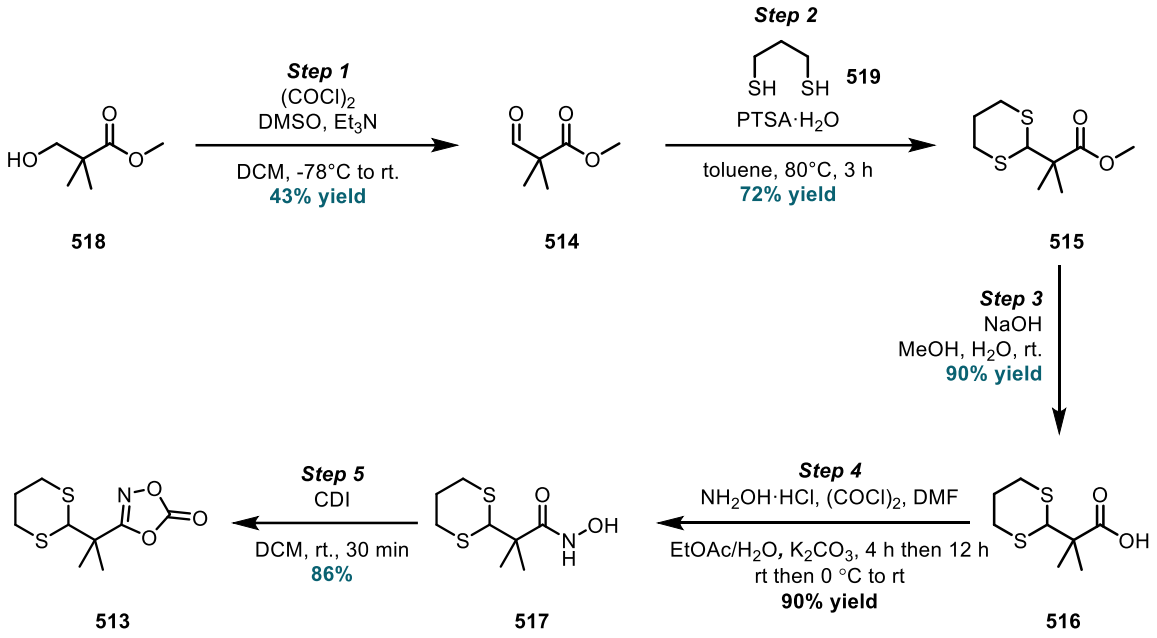
Table S2. Crystal data and structure refinement for **341**.

Identification code	2363673	
Empirical formula	$C_{15}H_{14}N_3O$	
Formula weight	252.30	
Temperature	150 K	
Wavelength	1.54184 Å	
Crystal system	Monoclinic	
Space group	P 2_1	
Unit cell dimensions	a = 5.50450(10) Å	α = 90°.
	b = 14.1222(4) Å	β = 99.187(2)°.
	c = 16.7621(5) Å	γ = 90°.
Volume	1286.30(6) $Å^3$	
Z	4	
Density (calculated)	1.303 Mg/m^3	
Absorption coefficient	0.678 mm^{-1}	
F(000)	532	
Crystal size	0.04 x 0.11 x 0.12 mm^3	
Theta range for data collection	4.116 to 76.348°.	
Index ranges	-5<=h<=6, -17<=k<=17, -21<=l<=20	

Reflections collected	17179
Independent reflections	5330
Completeness to theta = 76.348°	99.6 %
Absorption correction	multi-scan
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5329 / 1 / 344
Goodness-of-fit on F2	1.0145
Final R indices [I>2sigma(I)]	R1 = 0.0459, wR2 = 0.1175
R indices (all data)	R1 = 0.0532, wR2 = 0.1271
Absolute structure parameter	-0.2(3)
Index ranges	-5<=h<=6, -17<=k<=17, -21<=l<=20

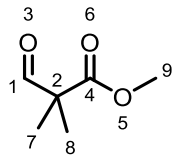
5.3 Experimental Details for Chapter 3

5.3.1 Synthesis of 3-(2-(1,3-dithian-2-yl)propan-2-yl)-1,4,2-dioxazol-5-one (513)



Scheme 1 Synthesis of model substrate (**513**).

Methyl 2,2-dimethyl-3-oxopropanoate (514)



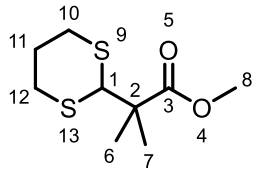
Step 1: A solution of oxalyl chloride (15.75 g, 124.05 mmol) in dichloromethane (60 mL) was prepared at -78 °C. Subsequently, a solution of DMSO (18 mL, 253.5 mmol) in DCM (60 mL) was added dropwise. The resultant reaction mixture was stirred for 10 minutes at -78°C, after which a solution of methyl 3-hydroxy-2,2-dimethylpropionate (**518**) (15 g, 113.4 mmol) in DCM (60 mL) was introduced. Next, triethylamine (80 mL, 567 mmol) was added portion-wise and stirred for another 10 min. The reaction mixture was then allowed to warm up to ambient temperature, and water was added to quench the reaction. The organic layer was extracted with DCM, washed with water and brine successively, and dried over anhydrous sodium sulfate. After filtration and solvent evaporation, the crude product was purified by distillation to afford methyl 2,2-dimethyl-3-oxopropionate (**514**) (6.34 g, 43%) as a colorless oil.[175]

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.65 (s, 1H, H^{1}), 3.74 (s, 3H, $H^{9a, 9b, 9c}$), 1.34 (s, 6H, $H^{7a, 7b, 7c, 8a, 8b, 8c}$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 199.1 (C^{1}), 173.3 (C^{4}), 53.9 (C^{2}), 52.7 (C^{9}), 19.8 ($C^{7, 8}$).

HRMS (ESI) m/z calcd. for $C_6H_{11}O_3$ $[M+H]^+$ 131.0708, found 131.0712.

Methyl 2-(1,3-dithian-2-yl)-2-methylpropanoate (515)



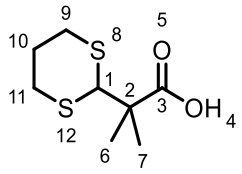
Step 2: To a solution of methyl 2,2-dimethyl-3-oxopropionate (**514**) (5.99 g, 46 mmol) in toluene (1 M), was added *p*TSA·H_2O (0.879 g, 4.62 mmol) and propane dithiol (5.10 mL, 50.71 mmol) respectively. The reaction was purged with nitrogen and warmed up to 80 °C until full consumption of the aldehyde. The reaction was diluted with diethyl ether and washed twice with 1 M aqueous KOH. The organic layers were dried over anhydrous sodium sulfate and concentrated in vacuo. The crude product was purified by flash column chromatography (Et_2O/pantane = 1:10) to give desired methyl 2-(1,3-dithian-2-yl)-2-methylpropanoate (**515**) (7.30 g, 72%) as a pale-yellow oil.[149]

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.44 (s, 1H, H^1), 3.71 (s, 3H, $H^{8a, 8b, 8c}$), 3.00 – 2.82 (m, 4H, $H^{10a, 10b, 12a, 12b}$), 2.09 (dtt, *J* = 14.0, 4.3, 2.7 Hz, 1H, H^{11a}), 1.84 (dtt, *J* = 14.1, 11.8, 3.8 Hz, 1H, H^{11b}), 1.34 (s, 6H, $H^{6a, 6b, 6c, 7a, 7b, 7c}$).

^{13}C NMR (101 MHz, $CDCl_3$): δ 175.9 (C^3), 57.7 (C^1), 52.4 (C^8), 47.9 (C^2), 31.4 ($C^{10, 12}$), 26.1 (C^{11}), 22.9 ($C^{6, 7}$).

HRMS (ESI) m/z calcd. for $C_9H_{16}O_2{}^{23}Na^{32}S_2$ $[M+Na]^+$ 243.0484, found 243.0484.

2-(1,3-dithian-2-yl)-2-methylpropanoic acid (516)

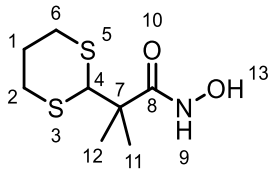


Step 3: Following **General Procedure C** starting from methyl 2-(1,3-dithian-2-yl)-2-methylpropanoate (**515**) (6.4 g, 29.04 mmol) and gave desired 2-(1,3-dithian-2-yl)-2-methylpropanoic acid (**516**) (5.39 g, 90%) as an oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.47 (s, 1H, H^{1}), 3.01 – 2.85 (m, 4H, $H^{9a, 9b, 11a, 11b}$), 2.11 (dtt, *J* = 14.0, 4.3, 2.7 Hz, 1H, H^{10a}), 1.85 (dtt, *J* = 14.1, 11.8, 3.8 Hz, 1H, H^{10b}), 1.37 (s, 6H, $H^{6a, 6b, 6c, 7a, 7b, 7c}$).

^{13}C NMR (101 MHz, $CDCl_3$): δ 180.6 (C^{3}), 57.1 (C^{1}), 47.8 (C^{2}), 31.5 ($C^{9, 11}$), 26.1 (C^{10}), 22.8 ($C^{6, 7}$).

2-(1,3-dithian-2-yl)-N-hydroxy-2-methylpropanamide (517)



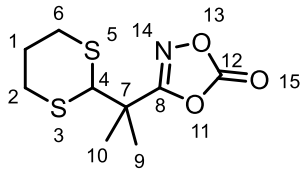
Step 4: To a solution of the 2-(1,3-dithian-2-yl)-2-methylpropanoic acid (**516**) (4.50 g, 21.81 mmol) in DCM (0.1 M) at 0 °C was dropwise added oxalyl chloride (2.8 mL, 32.72 mmol) and then added catalytic amount of DMF (0.1 mL). The mixture was allowed to stir at room temperature for 2.5 h, the solvent was removed under reduced pressure to provide

corresponding crude acid chloride, which was used directly in the following step. A solution of the crude acid chloride dissolving in small amount of EtOAc (25 mL) was added dropwise to a solution of NH_2OH•HCl (2.27 g, 32.72 mmol) and K_2CO_3(6.03 g, 43.62 mmol) in EtOAc/H_2O (0.1 M, 2/1). The resulting solution was cooled to 0 °C followed by dropwise addition of the unpurified acid chloride dissolved in a minimum amount of EtOAc under air. The flask containing the acid chloride was then rinsed with additional EtOAc. The reaction was warmed to room temperature for stirring additional 12 h. The phases were separated, and the aqueous phase was extracted twice with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by recrystallization (DCM + few drops of methanol/*n*-pentane) or silica chromatography (eluent: DCM/methanol = 30:1 ~ 10:1) to afford the desired 2-(1,3-dithian-2-yl)-N-hydroxy-2-methylpropanamide (**517**) (4.34 g, 90%) as an oil.[207]

^{1}H NMR (400 MHz, Acetone-d6): δ 10.12 (s, 1H, H^9), 7.91 (s, 1H, H^{13}), 4.54 (s, 1H, H^4), 2.96 (m, 2H, $H^{2a, 6a}$), 2.89 – 2.80 (m, 2H, $H^{2b, 6b}$), 2.13 – 2.07 (m, 1H, H^{1a}), 1.71 (m, 1H, H^{1b}), 1.29 (s, 6H, $H^{11a, 11b, 11c, 12a, 12b, 12c}$).

^{13}C NMR (101 MHz, Acetone-d6): δ 179.8 (C^8), 58.2 (C^4), 46.8 (C^7), 31.7 ($C^{2, 6}$), 27.0 (C^1), 22.9 ($C^{11, 12}$).

3-(2-(1,3-dithian-2-yl)propan-2-yl)-1,4,2-dioxazol-5-one (513)

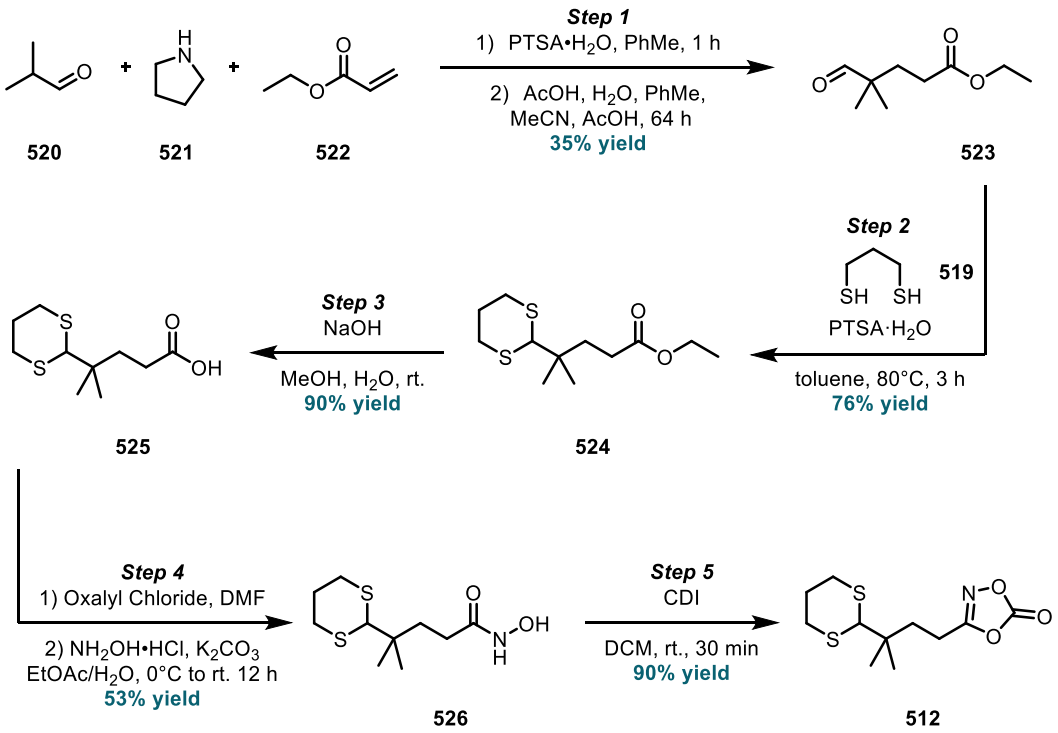


Step 3: Following **General Procedure J** starting from 2-(1,3-dithian-2-yl)-N-hydroxy-2-methylpropanamide (**517**) (3.5 g, 15.81 mmol) and gave desired 3-(2-(1,3-dithian-2-yl)propan-2-yl)-1,4,2-dioxazol-5-one (**513**) (3.52 g, 90%) as an oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.31 (s, 1H, H^{4}), 2.96 – 2.93 (m, 2H, $H^{2a, 6a}$), 2.93 – 2.91 (m, 2H, $H^{2b, 6b}$), 2.18 – 2.08 (m, 1H, H^{1a}), 1.91 – 1.78 (m, 1H, H^{1b}), 1.50 (s, 6H, $H^{9a, 9b, 9c, 10a, 10b, 10c}$).

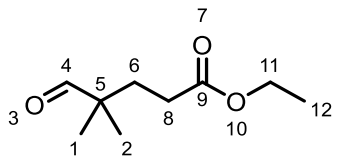
^{13}C NMR (101 MHz, $CDCl_3$): δ 169.6 (C^{8}), 154.2(C^{12}), 55.9 (C^{4}), 45.1 (C^{7}), 31.4 ($C^{2, 6}$), 25.7 (C^{1}), 21.8 ($C^{9, 10}$).

5.3.1 Synthesis of 3-(3-(1,3-dithian-2-yl)-3-methylbutyl)-1,4,2-dioxazol-5-one (512)



Scheme 2 Synthesis of model substrate (**512**).

Ethyl 4,4-dimethyl-5-oxopentanoate (523)



2-Methylpropanal (16.4 mL, 180 mmol), pyrrolidine (16.0 mL, 180 mmol), *p*-toluene sulfonic acid (0.4 g, 2.3 mmol) and dry toluene (150 mL) were refluxed using a Dean and Stark head for 1 h. The mixture was then distilled until the temperature of the distillate

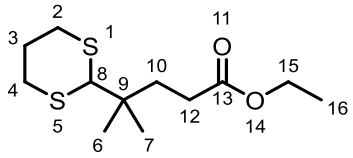
reached 108-110 °C. The residual solution of the enamine was used without further purification. Subsequently, ethyl acrylate (22.5 g, 225 mmol) in dry MeCN (180 mL) was added over 30 min to a solution of 2-methyl-1-pyrrolidinoprop-1-ene at 0 °C. The mixture was stirred for 30 min, then refluxed for 64 h. Acetic acid (100 mL) and water (100 mL) were added and the mixture refluxed for a another 6 h. Brine was added, the layers separated, the organics washed with saturated sodium bicarbonate solution (200 mL), dried (MgSO4), and concentrated under reduced pressure. The crude product was purified by flash column chromatography (EtOAc/pantane = 1/20) to give desired ethyl 4,4-dimethyl-5-oxopentanoate (**523**) (10.85 g, 35%) as a pale-yellow oil. Rf (EtOAc-hexane, 20:80) = 0.37.[208]

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.43 (s, 1H, H^{4}), 4.10 (qd, *J* = 7.1, 0.6 Hz, 2H, $H^{11a, 11b}$), 2.27 – 2.19 (m, 2H, $H^{8a, 8b}$), 1.87 – 1.78 (m, 2H, $H^{6a, 6b}$), 1.23 (t, *J* = 0.8 Hz, 3H, $H^{12a, 12b, 12c}$), 1.05 (d, *J* = 0.6 Hz, 6H, $H^{1a, 1b, 1c, 2a, 2b, 2c}$).

^{13}C NMR (101 MHz, $CDCl_3$): δ 205.2 (C^{4}), 173.2 (C^{9}), 60.5 (C^{11}), 45.3 (C^{5}), 31.6 (C^{8}), 29.5 (C^{6}), 21.2 ($C^{1, 2}$), 14.2 (C^{12}).

Compounds **524**, **525**, **526**, and **512** were synthesised according to the ***Step 2-5*** of the procedure to synthesize compound (**513**).

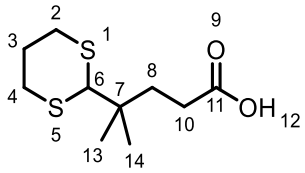
Ethyl 4-(1,3-dithian-2-yl)-4-methylpentanoate (524)



^{1}H NMR (400 MHz, $CDCl_3$): δ 4.13 (q, *J* = 7.1 Hz, 2H, H^{15}), 3.98 (s, 1H, H^{8}), 2.92 – 2.84 (m, 4H, $H^{2a, 2b, 4a, 4b}$), 2.37 – 2.29 (m, 2H, $H^{12a, 12b}$), 2.13 – 2.02 (m, 1H, H^{3a}), 1.87 – 1.76 (m, 3H, $H^{10a, 10b, 3b}$), 1.26 (t, *J* = 7.1 Hz, 3H, $H^{16a, 16b, 16c}$), 1.09 (s, 6H, $H^{6a, 6b, 6c, 7a, 7b, 7c}$).

^{13}C NMR (101 MHz, $CDCl_3$): δ 173.9 (C^{13}), 60.6 (C^{15}), 60.4 (C^{8}), 37.9 (C^{9}), 35.3 (C^{10}), 31.6 ($C^{2, 4}$), 29.5 (C^{12}), 26.2 (C^{3}), 25.3 ($C^{6, 7}$), 14.4 (C^{16}).

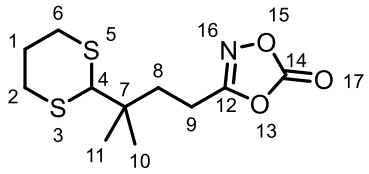
4-(1,3-dithian-2-yl)-4-methylpentanoic acid (525)



^{1}H NMR (400 MHz, $CDCl_3$): δ 3.98 (s, 1H, H^{6}), 2.94 – 2.81 (m, 4H, $H^{2a, 2b, 4a, 4b}$), 2.44 – 2.35 (m, 2H, $H^{10a, 10b}$), 2.14 – 2.02 (m, 2H, $H^{3a, 3b}$), 1.88 – 1.82 (m, 2H, $H^{8a, 8b}$), 1.10 (s, 6H, $H^{13a, 13b, 13c, 14a, 14b, 14c}$).

^{13}C NMR (101 MHz, $CDCl_3$): δ 179.4 (C^{11}), 60.3 (C^{6}), 37.9 (C^{7}), 35.1 (C^{8}), 31.6 ($C^{2, 4}$), 29.1 (C^{10}), 26.2 (C^{3}), 25.3 ($C^{13, 14}$).

3-(3-(1,3-dithian-2-yl)-3-methylbutyl)-1,4,2-dioxazol-5-one (512)



^{1}H NMR (400 MHz, $CDCl_3$): δ 4.00 (s, 1H, H^{4}), 2.91 – 2.86 (m, 4H, $H^{2a, 2b, 6a, 6b}$), 2.71 – 2.65 (m, 2H, $H^{9a, 9b}$), 2.13 – 2.05 (m, 1H, H^{1a}), 1.93 – 1.84 (m, 2H, $H^{8a, 8b}$), 1.84 – 1.74 (m, 1H, H^{1b}), 1.15 (s, 6H, $H^{11a, 11b, 11c, 10a, 10b, 10c}$).

^{13}C NMR (101 MHz, $CDCl_3$): δ 167.1 (C^{12}), 154.2 (C^{14}), 59.5 (C^{4}), 38.2 (C^{7}), 34.7 (C^{8}), 31.5 ($C^{2, 6}$), 26.0 (C^{9}), 25.4 ($C^{10, 11}$), 20.4 (C^{1}).

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