Cp*Rh(III)-Catalyzed Enantioselective C(sp^3)–H Amidation of Azine-Linked Cyclobutanes

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ABSTRACT The highly enantioselective desymmetrizing C(sp^3)–H amidation of azine-linked cyclobutanes with dioxazolones, to afford enantioenriched *cis*-configured amido-cyclobutane scaffolds is described. The reaction is catalyzed by an electron-deficient Cp*Rh(III) complex in combination with a newly designed axially chiral carboxylic acid (CCA) that was found to be key in obtaining high levels of enantiocontrol. Computational studies using DFT uncovered the reaction pathway and revealed the presence of multiple non-covalent interactions including inter- and intramolecular *n*–π* interactions and CH–π interactions which contributed to the high enantioselectivity. The methodology was found to be broad in scope with respect to the dioxazolone and could be further extended to larger cycloalkyl derivatives as well as bis-amidated cyclobutane derivatives.

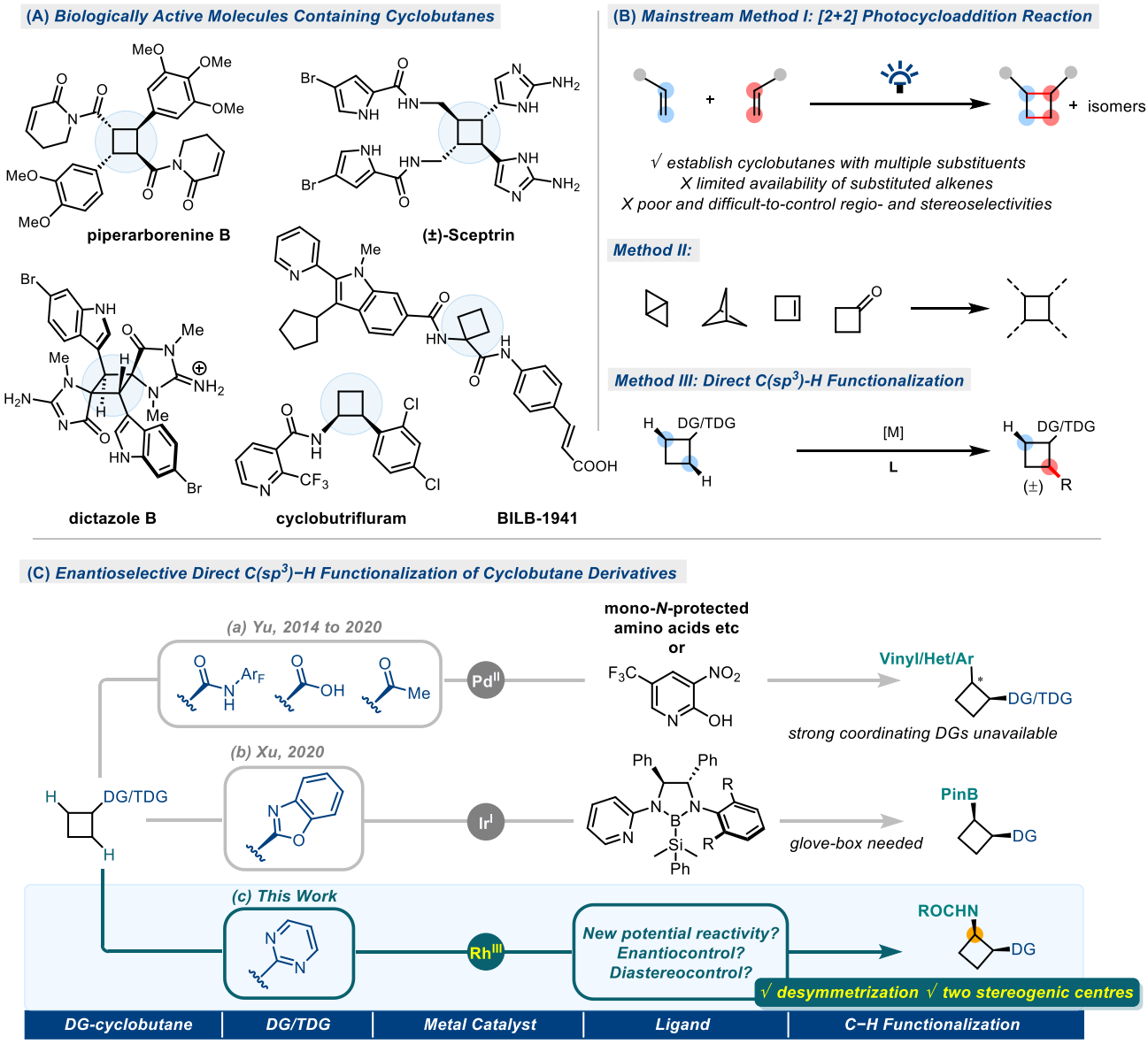
Keywords C–H activation · amidation · cyclobutanes · enantioselective · ligand · rhodium catalysis

INTRODUCTION

The unique properties of the saturated cyclobutane ring make it a valuable structural motif in pharmaceutical chemistry. For instance, its restricted conformational freedom can provide greater spatial complementarity with target proteins, thus improving binding affinity.[1] Additionally, the relatively small size of cyclobutane compared to larger cycloalkyl or aromatic rings can enhance membrane permeability, the pharmacokinetic profile as well as the water solubility of the resulting lead molecule, which are crucial factors in drug design.[2] Accordingly, the cyclobutane ring has emerged as a rising star, which has been increasingly utilized in small-molecule drug candidates in recent years.[3] Despite this, the available methodologies for the synthesis of drug-like molecules containing four-membered rings has lagged behind other carbocyclic homologues (Scheme 1A, selected examples).[4-7] This synthetic challenge is attributed to the strain energy of the cyclobutane ring making it susceptible to ring-opening reactions,[8] while at the same time, the precise synthesis of desired cyclobutane subunits with diverse functionality and stereo-controlled configurations remains a daunting challenge.

Arguably, the most common approach for constructing cyclobutane skeletons is the intermolecular [2+2] photocycloaddition of two olefins reagents (Scheme 1B).[9-13] This strategy generally offers multiple regio- and stereochemical options for forming tri-/tetra-substituted cyclobutanes, however,

the formation of only disubstituted cyclobutanes is rarely reported.[14, 15] Additionally, due to the scarcity and stability of some olefin precursors, it is challenging to directly obtain cyclobutane products specifically disubstituted at the C1/C2 position through cyclization reactions. Another alternative pathway employs cyclobutene or cyclobutanone or bicyclo[1.1.0]butane[8, 16] building blocks to undergo addition or reduction reactions to obtain the targeted cyclobutanes, albeit with increased step count. More recently, the utilization of direct C(sp^3)–H activation presents a viable strategy that has the potential to overcome these limitations and facilitate the efficient synthesis of a broad array of functionalized cyclic scaffolds (Scheme 1B).



Scheme 1 (A) Biologically active molecules containing a cyclobutane motif; (B) General methods to construct cyclobutane skeletons; (C) Enantioselective direct C(sp^3)–H functionalization of cyclobutane derivatives to establish asymmetric four-membered rings.

Between 2014 and 2018, Yu *et al*. reported a series of Pd(II)-catalyzed enantioselective C–H arylation, borylation, and vinylation reactions of cyclobutyl carboxylic acid derivatives with

polyfluorophenyl amides as a *weakly* coordinating monodentate directing group (DG), in the presence of various monoprotected amino acid (MPAA) derivatives as chiral bidentate ligands (Scheme 1C, top).[17-19] Subsequently, the authors further developed the effective and stereoselective C–H arylation of cyclobutyl ketones with chiral transient directing groups (TDGs) (Scheme 1C, top).[20]

In contrast, *strongly* coordinating DGs such as pyridine, pyrimidine, and 8-aminoquinoline, which have proven useful in directing both sp^2 and sp^3 C–H activation reactions, are no longer compatible with the aforementioned palladium(II) catalytic systems. Yu *et al.* found that, when assembled with these strong *N*-heterocycle DGs, the substrate tends to bind to the transition metal center more strongly than the stereeocontrolling chiral ligands, thus resulting in racemic products. Meanwhile, the resulting cyclopalladated intermediate being thermodynamically stable can impede subsequent functionalization steps.[21]

Despite these challenges, in 2020, Davies *et al.*[22] disclosed a unique dirhodium(II)-catalyzed C1/C3-selective C(sp^3)–H desymmetrization with aryldiazoacetates, while in 2023, Yu *et al.*[23] developed an "L-type" free hydroxyl group-directed C3-selective C(sp^3)−H arylation of cyclobutanes using an exquisitely-designed bisanionic pyridine triflamide as the ligand. Moreover, Xu *et al.*[24] reported the iridium(I)-catalyzed borylation of cyclobutanes using benzoxazole as the DG (Scheme 1C, middle), indicating the potential for the development of other transition metal-catalyzed enantioselective C–H functionalization reactions of cyclobutanes. Despite the above reports, broadly applicable methods towards stereo-defined, functionalized azine-linked cyclobutanes remain scarce highlighting the need for new catalytic strategies and methods to expand the chemical toolbox and complement existing literature.

Recently, Matsunaga[25-28], Li,[29] and our group[30, 31] have demonstrated successful unactivated C(sp^3)–H amidation in Cp^xM(III) (M = Co, Rh) catalytic systems, employing a metal-nitrene C–H insertion generated catalytically from the corresponding dioxazolones. These studies imply that the inclusion of a chiral carboxylic acid (CCA) is key to achieving high stereoinduction, which is accomplished by formation of a well-defined chiral environment coordinating with Cp^xM(III) during the stereo-determining step. Motivated by the achievements observed in the Cp^xM/CCA system and leveraging our previous research on C–H amidation reactions, we aimed to develop the first Cp*Rh(III)-catalyzed enantioselective C(sp^3)–H amidation of cyclobutanes in the presence of a strong azine-type DG (Scheme 1c, bottom), and herein we disclose our findings.

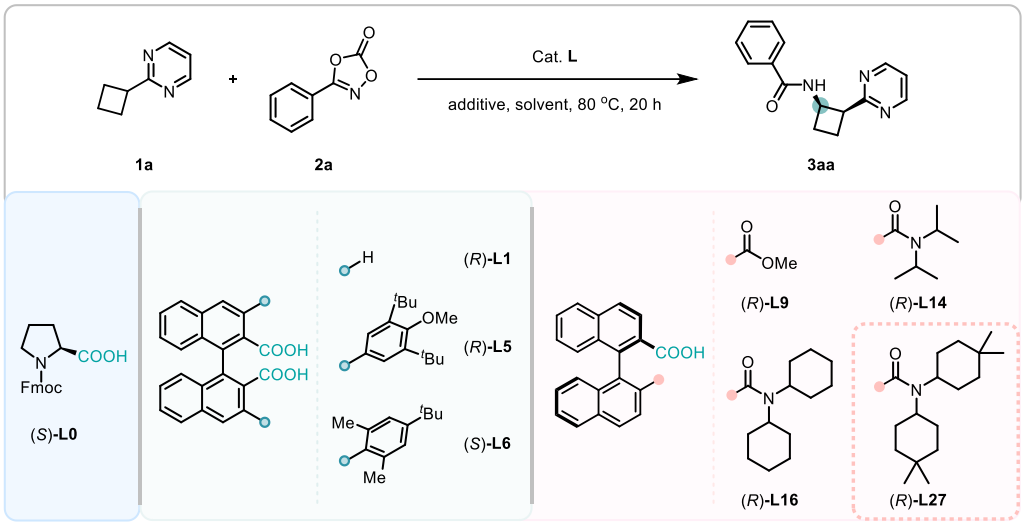
RESULTS AND DISCUSSION

Readily available 2-cyclobutylpyrimidine (**1a**) was selected as a model reaction substrate for reaction investigation, since the strongly coordinating pyrimidyl group has been shown to be an effective directing group in various C–H activation systems.[32] With 2 equivalents of dioxazolone **2a** as the nitrene precursor and amide source, a catalytic amount of $[Cp^*Rh(MeCN)_3](SbF_6)_2$ (10 mol%) and Fmoc-protected prolinate (Fmoc-Pro-OH, (*S*)-**L0** + NaO^{t}Bu as additive) as a ligand in 1,2-dichloroethane (DCE) at 0.1 M concentration at 80 °C (Table 1, entry 1). Pleasingly, this resulted in a 48% NMR yield of mono-amidated product, with no bis-amidated product observed, albeit with low

enantioselectivity (55:45 er). This indicated that the C(sp^3)–H amidation step could indeed proceed smoothly after the metalation step in this Cp*Rh(III)/CCA system.

Due to the symmetric nature of the cyclobutane substrate, we hypothesized that replacing the ligand **L0** with a judicious choice of CCAs containing variously sterically hindered substituents might have a profound effect on establishing an appropriate chiral environment to improve the enantioselectivity.

Table 1 Selected Reaction Optimization.[a]



Entry	2a (eq.)	Cat. (mol%)	Ligand (mol%)	Additive (mol%)	Solvent (M)	Yield (%) [c]	er [d]
1	2	Cp*Rh (10)	(*S*)-**L0** (20)	NaO^{t}Bu (20)	DCE (0.1)	48	55:45
2	2	Cp*Rh (10)	(*R*)-**L1** (10)	NaO^{t}Bu (20)	DCE (0.1)	60	56:44
3	2	Cp*Rh (20)	(*R*)-**L5** (20)	Ag_2CO_3 (10)	1,4-dioxane (0.25)	81	76:24
4	2	Cp*Rh (20)	(*S*)-**L6** (20)	Ag_2CO_3 (10)	1,4-dioxane (0.25)	11	62:38
5	2	Cp*Rh (20)	(*R*)-**L9** (20)	Ag_2CO_3 (10)	1,4-dioxane (0.25)	40	61:39
6	2	Cp*Rh (20)	(*R*)-**L14** (20)	Ag_2CO_3 (10)	1,4-dioxane (0.25)	78	83:17
7	2	Cp*Rh (20)	(*R*)-**L16** (20)	Ag_2CO_3 (10)	1,4-dioxane (0.25)	70	89:11
8	2	Cp*Rh (20)	(*R*)-**L27** (20)	Ag_2CO_3 (10)	1,4-dioxane (0.25)	93	98:2
9	2	-	(*R*)-**L27** (20)	Ag_2CO_3 (10)	1,4-dioxane (0.25)	0	-
10	2	Cp*Co (20)	(*R*)-**L27** (20)	Ag_2CO_3 (10)	1,4-dioxane (0.25)	0	-
11	1.7	Cp*Rh (20)	(*R*)-**L27** (20)	Ag_2CO_3 (10)	1,4-dioxane (0.25)	98	98:2
12	1.7	Cp*Rh (20)	(*R*)-**L27** (20)	Ag_2CO_3 (10)	1,4-dioxane (0.5)	98	99:1
13	1.7	Cp*Rh (5)	(*R*)-**L27** (20)	Ag_2CO_3 (10)	1,4-dioxane (0.5)	57	91:9
14	1.7	Cp*Rh (10)	(*R*)-**L27** (20)	Ag_2CO_3 (10)	1,4-dioxane (0.5)	90	97:3
15 [b]	1.7	Cp*Rh (10)	(*R*)-**L27** (20)	Ag_2CO_3 (5)	1,4-dioxane (0.5)	90	99:1

Reaction conditions: [a] **1a** (0.05 mmol), catalyst, CCA ligand, additive, solvent, 80 °C, 20 h; [b] **1a** (0.15 mmol); [c] ^{1}H NMR yield; [d] er was determined by HPLC on a chiral stationary phase. Cp*Rh = Cp*Rh(MeCN)$_3$(SbF$_6$)$_2$, Cp*Co = Cp*Co(MeCN)$_3$(SbF$_6$)$_2$, Fmoc = fluorenylmethyloxycarbonyl, DCE = 1,2-dichloroethane; See SI for more details.

The ligand investigation commenced with an unsubstituted axially chiral 2,2'-dicarboxylic acid (*R*)-**L1**, based on the binaphthyl backbone. Although product formation was observed (60% NMR yield), disappointingly, it resulted also in a poor enantiomeric ratio of 56:44 (Table 1, entry 2). Successively, we performed experiments with more ligands bearing increased steric bulk at the C3/C3' positions of the binaphthyl skeleton in addition to many other recently reported ligands, including spirobiindanyl-based CCAs and pseudo-C2-symmetric CCAs (Table 1, entry 3 and 4).[26] Unfortunately, none of these ligands yielded significantly improved results in our test reaction (See SI for details). Having exhausted options with diacids, the monoacid (*R*)-**L9** modified with a methyl ester was then investigated but resulted in worse enantioselectivity (61:39 er) than (*R*)-**L5** and a lower yield (40%)

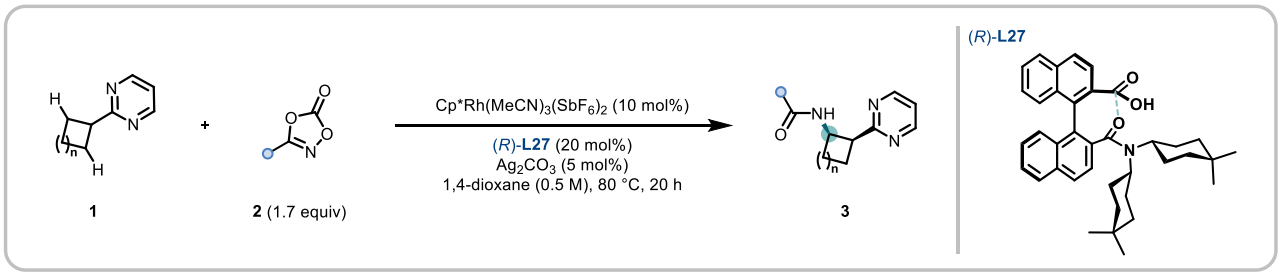
in comparison to the dicarboxylic acid (*R*)-**L1** (Table 1, entry 5). Based on these findings, the effects of the Lewis basic site of the ligand were probed by surrogating the methyl ester substituent in (*R*)-**L9** with a conveniently obtained diisopropyl amide moiety ((*R*)-**L14**). To our delight, this ligand led to a sharp uplift in enantioselectivity, affording **3aa** in 83:17 er (Table 1, entry 6). The er value was then further augmented by the use of an *N*,*N*-dicyclohexyl substituted (*R*)-**L16** (Table 1, entry 7) without compromising reactivity (70% yield, 89:11 er), highlighting an impressive boost to stereocontrol using such amide-bearing ligands. Accordingly, a series of homologous CCAs bearing various amide moieties were tested (See SI for details). Among them, it was interesting to find that the *N*,*N*-4,4-dimethylcyclohexyl analogue (*R*)-**L27**, which possessed additional dimethyl groups on the cyclohexyl rings of the amide skeleton, exhibited a remarkable enantioselectivity enhancement resulting in 93% yield of **3aa** with 98:2 er (Table 1, entry 8).

Given the exceptionally high performance of (*R*)-**L27**, the effects of other variables, including the metal catalyst, stoichiometry, and additives were also investigated (Table 1, entries 10-14). No reaction was detected without a metal catalyst (Table 1, entry 10) or with other trivalent group 9 metal catalysts (Table 1, entry 11). Eventually, 1.7 equivalents of dioxazolone **2a** and 10 mol% of commercial $Cp^*Rh(MeCN)_3(SbF_6)_2$ catalyst in the presence of 10 mol% of (*R*)-**L27** with 5 mol% silver carbonate in 1,4-dioxane (0.5 M) at 80 °C, were found to be the optimal conditions, leading to the target product **3aa** in 90% yield with an excellent enantiomeric ratio (99:1 er) in a slight scale-up of the reaction to 0.15 mmol (Table 1, entry 15). The absolute stereochemical configuration of the amidated product **3aa** was confirmed by single-crystal X-ray diffraction (SCXRD) analysis as (*R*,*S*) (Scheme 2, **3aa**).

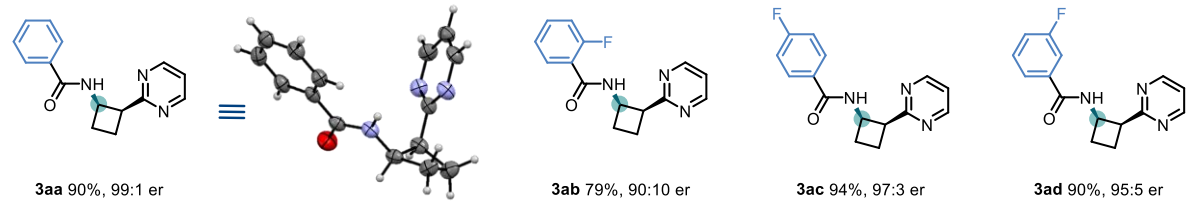
With the optimal reaction conditions in hand, we initially investigated the substrate scope with respect to the dioxazolone coupling partner using 2-cyclobutylpyrimidine (Table 2). First, dioxazolones bearing a variety of aromatic substituents were examined (**3aa**-**3ak**). It was found that with *ortho*-, *para*-, and *meta*-F substituents on the aromatic ring, the amidated product was afforded in excellent yield and enantioselectivity (**3ab**-**3ac**: 79-94% yield, 90:10-97:3 er). Aromatic dioxazolones bearing other halogen atoms (**3ae**-**3ag**) reacted smoothly, providing amidated products in excellent yields and enantioselectivities. Other aryl substituents, including an electron-withdrawing *para*-nitro group (**3ah**) and weakly electron-donating *para*-trifluoromethoxy group (**3ai**), were compatible with our catalytic system, affording the desired products in good to excellent yields and enantioselectivities (51%, 90:10 er & 82%, 94:6 er, respectively). Biphenyl-derived dioxazolone furnished **3aj** in 45% yield and 85:15 er, while bis-3,5-methoxy substituted phenyl dioxazolone afforded **3ak** 93:7 er in 70% yield.

Subsequently, acyclic alkyl-substituted dioxazolones were tested and found to be compatible with the methodology (**3al**-**3ax**). Simple methyl-substituted dioxazolone (**2l**) afforded the desired product **3al** in 65% yield and 93:7 er, while dioxazolone bearing a longer *n*-heptyl chain (**2o**) gave similar enantioselectivity (94:6 er) in a higher product yield (90%) (**3ao**). Importantly, branched sp^3-rich scope examples demonstrated good compatibility giving **3am** and **3an** with similar results. However, *tert*-butyl-substituted carboxamide **3ax** was obtained in a slightly lower yield of 78% with 88:12 er. Dioxazolone bearing a bulky triphenylethyl group (**2u**) was then tested and gave a 93% yield with

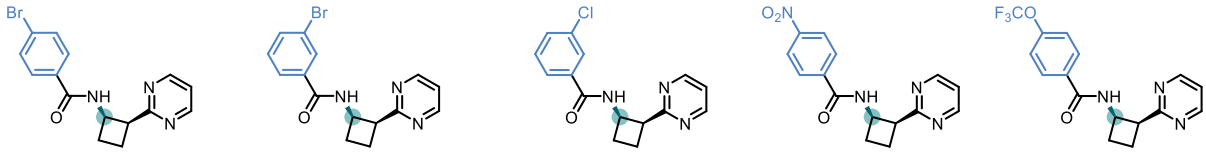
Table 2 Reaction Scope with Respect to the Dioxazolone and Cycloalkylpyrimidine.[a]



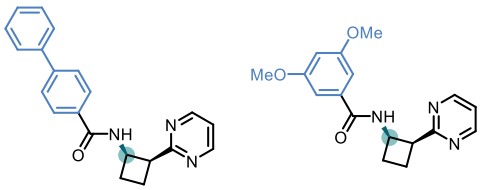
aryl-substituted dioxazolones



3aa 90%, 99:1 er | **3ab** 79%, 90:10 er | **3ac** 94%, 97:3 er | **3ad** 90%, 95:5 er

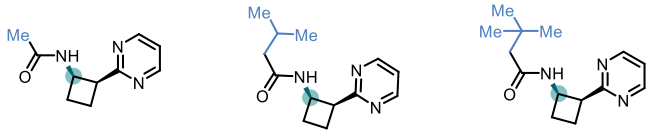


3ae 91%, 95:5 er | **3af** 93%, 97:3 er | **3ag** 92%, 96:4 er | **3ah** 51%, 90:10 er | **3ai** 82%, 94:6 er

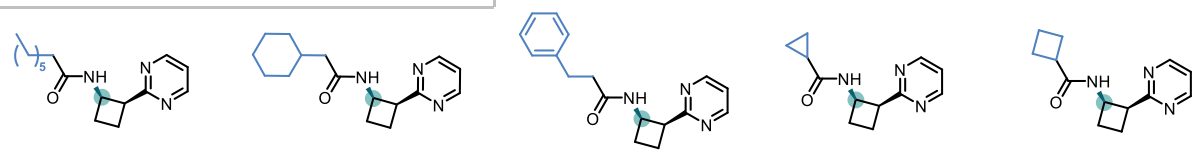


3aj 48%, 85:15 er | **3ak** 70%, 93:7 er

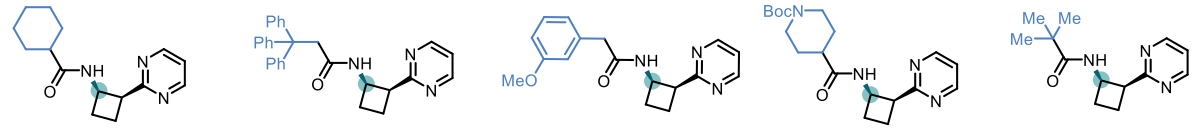
alkyl-substituents dioxazolones



3al 65%, 93:7 er | **3am** 87%, 95:5 er | **3an** 87%, 94:6 er

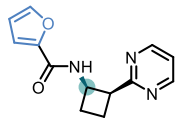


3ao 90%, 94:6 er | **3ap** 88%, 90:10 er | **3aq** 89%, 94:6 er | **3ar** 80%, 92:8 er | **3as** 69%, 92:8 er



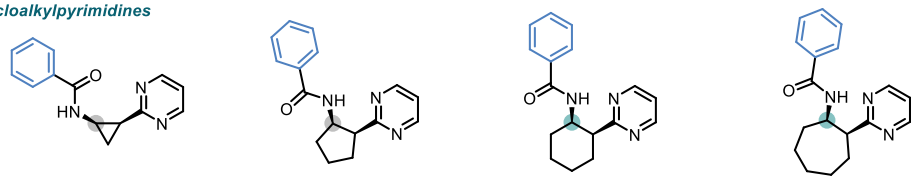
3at 92%, 95:5 er | **3au** 93%, 89:11 er | **3av** 73%, 93:7 er | **3aw** 87%, 86:14 er | **3ax** 78%, 88:12 er

heteroaromatic-substituents dioxazolones



3ay 51%, 92:8 er

cycloalkylpyrimidines

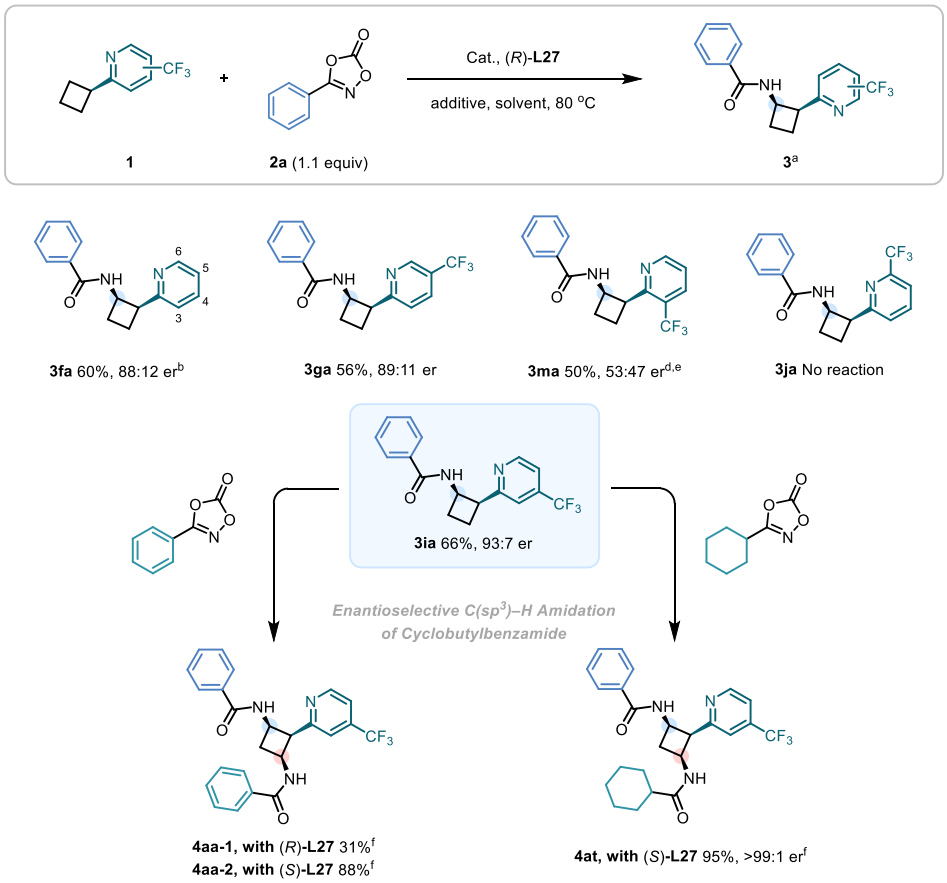


3ba 0% | **3ca** trace | **3da** 70%, 85:15 er | **3ea** 64%, 91:9 er

Reaction conditions: [a] **1** (0.15 mmol), **2** (0.26 mmol, 1.7 equiv), $[Cp^*Rh(MeCN)_3](SbF_6)_2$ (10 mol%), (*R*)-**L27** (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. See SI for more details.

diminished 89:11 er (**3au**). Additionally, examples bearing small medicinally-relevant ring systems were also evaluated. Cyclobutyl-substituted dioxazolone provided the corresponding product **3as** in 69% yield and 92:8 er. Intriguingly, the cyclopropyl-substituted example did not suffer C−C insertion by rhodium,[33] and instead gave the desired product **3ar** in 80% yield and 92:8 er. In addition, the introduction of a furan moiety was successfully achieved, and the corresponding product was obtained in 51% yield and 92:8 er (**3ay**). During our investigation of the reaction scope, we observed that a small fraction of the dioxazolones underwent decomposition to the corresponding amide (detected within the reaction mixtures). The amides could also bind to the rhodium catalyst, serving as ligands to continue the catalytic circle. This process introduced the possibility of a competitive dynamic exchange process with **L27** during the reaction and thus a competitive non-enantioselective pathway. It suggested that the distinct enantioselectivities in different amidated products were a consequence of the kinetic difference in the decomposition rates of diverse dioxazolones (See SI for details).

Table 3 Investigation of Cyclobutanes Modified with Other Azine DGs.[a]



Standard reaction conditions: [a] **1** (0.15 mmol), **2a** (0.17 mmol, 1.1 equiv), $[Cp^*Rh(MeCN)_3](SbF_6)_2$ (10 mol%), (*R*)-**L27** (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; [f] **2** (0.26 mol, 1.7 equiv), 1 h.

Moreover, we are able to extend this reaction to other cycloalkylpyrimidines (**1b**-**1e**) in the presence of dioxazolone **2a**. Notably, it was found that both 2-cyclohexylpyrimidine and 2-cycloheptylpyrimidine gave corresponding products in moderate to good isolated yields and

enantioselectivities, respectively (70% yield with 85:15 er (**3da**) and 64% yield with 91:9 er (**3ea**)). However, under the standard conditions, 2-cyclopentylpyrimidine (**1c**) afforded only traces of product **3ca**, and the anticipated product derived from 2-cyclopropylpyrimidine (**1b**) was entirely undetectable following the reaction (See SI for details).

Turning our attention to other *N*-containing azine directing groups, we observed that the pyridyl cyclobutane (**1f**) provided the corresponding mono-amidated product **3fa** in 60% with 88:12 er in only 2 h, indicating the higher reactivity of the pyridine DG compared to the pyrimidine DG. In contrast to the use of pyrimidine as the DG, when pyridine was employed, the presence of significant quantities of bis-amidated products was observed upon exceeding a 2 hour reaction time. To better understand the influence of the electronic and steric effects shown by DGs, a trifluoromethyl group was introduced at different positions on the pyridine ring. A CF_3 group attached to the C5 position of the pyridine ring gave a similar result to **1f** after 5 h, while cyclobutane **1j** with the CF_3 in the C6 position showed no conversion what-so-ever. Likely the CF_3 group in the C6 position hindered its necessary binding of the pyridyl nitrogen with the rhodium center. When the reaction time was shortened to 1 h, the mono-amidated product **3ma** was obtained as the main product in 50% yield with very low enantioselectivity (53:47 er). C4-CF_3-sustituted pyridinyl-cyclobutane (**1i**) illustrated an increase in reactivity with full conversion after 1.5 h, transforming into 18% bis-amidated cyclobutane product **4aa** and the corresponding mono-amidated product **3ia**. Notably, simply restricting the reaction time to 1 h enabled substrate **1i** to predominantly transform into the corresponding mono-amidated product **3ia** 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 unreacted).

Based on the outcomes above, we envisaged the possibility of achieving a highly selective secondary amidation of cyclobutylbenzamide to establish the four-membered ring containing three contiguous stereogenic centres within the same methodology. Encouragingly, in the presence of 1.7 equivalents of dioxazolones **2a**, we successfully obtained the desired bis-amidated product **4aa-1**, albeit in a modest 31% yield after two amidating steps, using only (*R*)-**L27** as the ligand. Ideally, we found that replacing (*R*)-**L27** with (*S*)-**L27** in the second amidation process led to an 88% yield of the same symmetrical product after two steps. Similarly, employing the favored (*R*)-**L27** in the first amidating step and (*S*)-**L27** in the second amidating step, the asymmetric disubstituted product **4at** was readily synthesized as well, showing exceptional efficiency; product **4at** was obtained in 95% yield and with an excellent enantiomeric ratio of 99:1. These results clearly demonstrate the precise enantiocontrol that can be imparted by the specific chiral ligand **L27** in the amidation reaction with this catalytic system.

COMPUTATIONAL STUDY

In order to elucidate the origin of enantioselectivity, a relationship between the enantiopurities of CCA and the obtained product was studied (see the SI for details). A clear linear correlation between the enantiomeric excess of the product **3aa** and **L27** was observed, thus indicating that there were no high-order aggregates of the catalyst operating in the reaction. To further understand the role of

axially chiral acid ligand for the rhodium(III)-catalyzed 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*)-**L27** coordinates 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.[34] The computed C–H activation transition structures (TS) that lead to the formation of the two enantiomeric products are **TS1-(*R*)** and **TS1-(*S*)**, and the reaction preferably proceeds through **TS1-(*S*)** that forms the *S*-configured product in agreement 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* interactions.[35] 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 the cyclohexyl ring interacts with one of the naphthyl rings by an intramolecular CH–π interaction that leads 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 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.

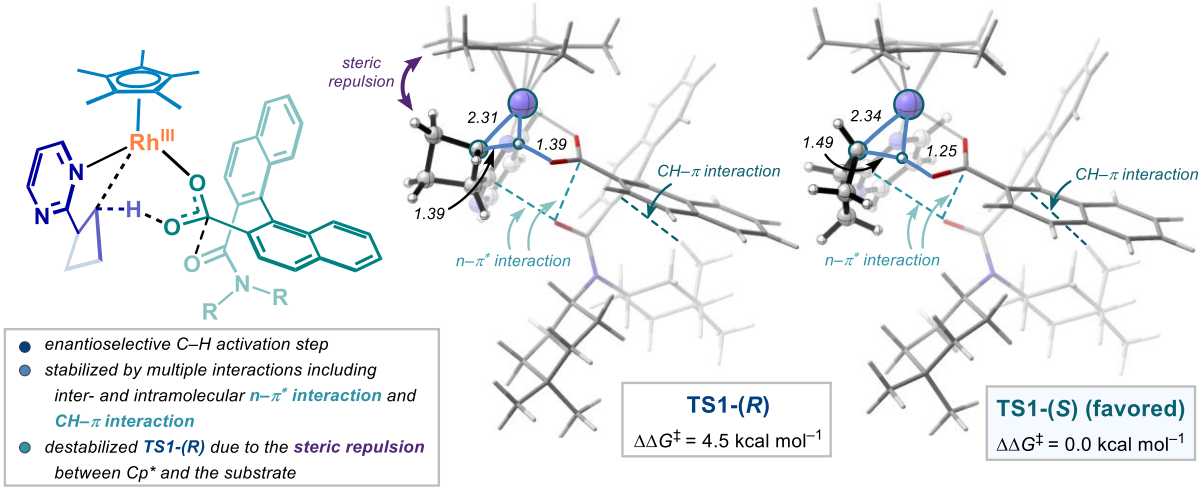


Figure 1 The key C−H activation transition state structures for the formation of (*R*)-product and (*S*)-product (ΔG [kcal mol^{-1}]) computed at the SMD(1,4-dioxane)/B3LYP-D3(BJ)/SDD(Rh)-6-311+G(d,p)//SMD(1,4-dioxane)/B3LYP-D3/Lanl2dz(Rh)-6-31G(d) level of theory. Energies (kcal mol^{-1}) and forming bond lengths (Å) of the TS geometries are provided in the insert.

CONCLUSION

In summary, we have developed an efficient azine-directed Cp*Rh(III)-catalyzed C(sp^3)–H amidation of cyclobutanes. The introduction of a binapthyl-based CCA modified with *N*,*N*-4,4-dimethylcyclohexyl amide was shown to be key for the highly-enantioselective desymmetrization process. A wide range of substituted dioxazolones were amenable to this transformation with

moderate to excellent enantioselectivity and yield. Furthermore, various amidated cycloalkylpyrimidines and cyclobutanes with other *N*-containing azine DGs could also be prepared using this catalytic system. With simple modifications to the general reaction conditions, enantioenriched bis-amidated cyclobutanes were also accessible. Detailed computational mechanistic studies suggest that the $n{-}\pi^*$ interaction with pyrimidine and the amide on the ligand, in combination with additional CH$-\pi$ interactions with one of the methyl groups of the dimethylated ligand, contribute to the rigidity of the conformation. We anticipate this reaction will serve to stimulate the further development of new asymmetric reactions to enantioenriched four-membered ring-containing drug-like molecules, and the unique chiral carboxylic acid controller herein reported could be applied to other related stereoselective reactions in the future.

SUPPLEMENTAL INFORMATION

Supplemental Information can be found online at xxxxxxxxxxxxxxxxxxxxxxxxxxxxxx

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AUTHOR CONTRIBUTIONS

X.X., H.S., and D.J.D. conceived the project. X.X. conducted the ligand design, experimental work and analyzed the data. X.X., H.S. P.B. and A.J.M.F. performed preliminary investigations at various stages of the project, with directional input on the initial non-asymmetric reaction from C.G. K.Y. conducted the computational work. The manuscript was written by X.X., K.Y. and D.J.D. with contributions and proof-reading from all authors. D.J.D. directed the project.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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