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Regio- and Stereoselective Rhodium(II)-Catalyzed C–H Functionalization of Cyclobutanes

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SUMMARY

Recent developments in controlled C–H functionalization transformations continue to inspire new retrosynthetic disconnections. One tactic in C–H functionalization is the intermolecular C–H insertion reaction of rhodium bound carbenes. These intermediates can undergo highly selective transformations through the modulation of the ligand framework of the rhodium catalyst. This work describes our continued efforts towards differentiating C–H bonds in the same molecule by judicious catalyst choice. Substituted cyclobutanes which exist as a mixture of interconverting conformers and possess neighboring C–H bonds within a highly strained framework are the targets herein for challenging the current suite of catalysts. While most C–H functionalization tactics focus on generating 1,2-disubstituted cyclobutanes via substrate-controlled directing group methods, the regiodivergent methods in this paper provide access to chiral 1,1-disubstituted and *cis*-1,3-disubstituted cyclobutanes simply by changing the catalyst identity, thus permitting entry to novel chemical space.

Asymmetric, rhodium, cyclobutanes, diazo compound, C–H functionalization

INTRODUCTION

Catalyst-controlled C–H functionalization is of considerable current interest.[1,2] The ability to control which C–H bond in a particular compound is functionalized simply by selecting the right catalyst would offer exciting opportunities in organic synthesis. Considerable effort has been directed towards developing small catalysts[3-5] and evolved enzymes[6-8] that can achieve such selectivity without resorting to well-defined functional groups on substrates. We have been developing the dirhodium-catalyzed reactions of donor/acceptor carbenes as a robust system for site-selective C–H functionalization reactions. [9] The combination of both a donor and acceptor group on the carbene leads to an intermediate that is still sufficiently reactive to functionalize C–H bonds, and due to the modulating effect of the donor group, the system is prone to subtle catalyst control effects. In recent years, we have prepared a series of catalysts that are capable of site-selective functionalization of unactivated C–H bonds (Figure 1A).[10] The catalysts adopt unique geometries that dictate the substrate trajectory towards the rhodium-bound carbene thus enabling single C–H bonds to be transformed. So far, catalysts have been designed to selectively functionalize either primary[11], secondary[12], or tertiary[13] C–H bonds (Figure 1B). Further ligand development has resulted in catalysts that distinguish between benzylic and unactivated methylene C–H bonds,[14] and most recently, we have introduced a catalyst capable of desymmetrizing substituted cyclohexane rings.[15]

The work described in this manuscript details our efforts toward applying this growing suite of catalysts and our understanding of the behavior of C–H bonds for the selective functionalization of arylcyclobutanes, either at C1 or C3, depending on which catalyst is used (Figure 1C). Arylated cyclobutane rings occur frequently in both natural products and pharmaceuticals. Many of the natural products arise directly from photochemical [2+2] dimerization processes of simpler alkene building blocks, as in the truxillic and truxinic acids (from cinnamic acid)[16] and sceptrin (from hymenidin).[17] Beyond these dimeric compounds, arylcyclobutane scaffolds are also observed in monoterpenoids such as cannabicyclol,[18] murrayamine M,[19] rhodonoids A and B,[20] and cochlearol B.[21] Arylcyclobutanes are considered intriguing systems for drug discovery because they place functionality in a defined spacial orientation.[,22] These compounds can exhibit wide-ranging bioactivity, as exemplified by the anti-clotting agent piperaborenine D,[23] the glucocortecoid receptor binding (-)-endiandrin A,[24] and the CYP3 inhibitor dipiperamide A.[25] 1,1-*cis* disubstituted arylcyclobutanes are represented in a number of modern drug candidates. Recently, researchers at Abbvie, inc. have reported on a potent and selective TRPV3 antagonist which is a 1,1-difunctionalized arylcyclobutane.[26,27] In this study, the stereochemistry at the cyclobutane ring was shown to have a significant effect on the bioactivity of the analogs. In light of the significance of these substances, a novel method for preparing chiral 1,1-difunctionalized arylcyclobutanes and 1,3-*cis*-disubstituted arylcyclobutanes could be of significant value to the scientific community.

Considerable effort has been expended in generating elaborate cyclobutanes by means of C–H functionalization tactics which rely on the use of directing groups on the substrate to control regiochemistry.[28-34] While these methods have provided elegant entries into complex natural products and access to enantioenriched cyclobutane scaffolds, the methods are restricted to, and primarily successful with, the formation of sp^3-sp^2 carbon-carbon bonds. Additionally, we are aware of only one example of a carbene-induced C–H functionalization of a cyclobutane where a sp^3-sp^3 C-C bond is formed, but this was an intramolecular example.[35]

Even though phenylcyclobutane is a small molecule, it represents an interesting challenge for C–H functionalization (Figure 2). The compound would be expected to exist as two interconverting conformers A and B, with conformer A being favored where the substituent occupies an equatorial position (when R = Br the equatorial isomer is favored by 1 kcal/mol[36]). From previous studies with donor/acceptor carbenes conducted on alkylcyclohexane[15] and acyclic alkanes[11-13], we would not expect the methylene sites adjacent to the substituent to be sterically accessible. Therefore, we would expect carbene insertion to be a competition between C1 (substituted carbon) and C3 (distal) functionalization. We also know from studies on the C–H functionalization of cyclohexane that equatorial sites react about 140 times faster than reactions at axial sites.[15] Hence, we would expect that reaction at C3 would occur at the equatorial site. If the reaction occurs at the major conformer A, the resulting cyclobutane would be *cis* disubstituted, whereas reaction of the minor conformer would give a *trans* disubstituted product. Reaction at C1 is electronically preferred due to the influence of the aryl ring but is sterically encumbered as a tertiary site. The minor conformer B would be expected to be the most reactive because the tertiary C–H bond is equatorial. However, it will not be possible to distinguish whether the tertiary C–H bond functionalization is occurring through A or B because each will generate the same C1 functionalized product. In order to achieve insertion at the C3 position, a sterically bulky catalyst like **2** or **3** would be expected to be required, whereas attack at C1 would be expected to occur with a less bulky catalyst like **4** or **5**.

RESULTS

This study began by surveying dirhodium tetracarboxylate catalysts for functionalizing readily available cyclobutane **6** (Figure 3).[37] The reactions were conducted in refluxing methylene chloride with 2,2,2-trichloroethyl 2-(4-bromophenyl)-2-diazoacetate (**7**)[38] as the carbene precursor. The use of 2,2,2-trihaloethyl ester groups is often advantageous in the dirhodium-catalyzed reactions of donor/acceptor carbenes because they can enhance enantioselectivity.[39] Our analysis above of the current catalyst toolbox and our understanding of selective C–H bond transformations assisted which catalysts were selected for the initial reaction screen. The original prolinate catalyst, Rh_2(S-DOSP)$_4$,[40] is considered to be a relatively uncrowded catalyst, and gave clean reaction at C1 to form **8** with no indication of the C3 product **9**. However, it is well established this catalyst does not give high levels of enantioselectvity in dichloromethane,[41] and this behavior was confirmed in this case, with **8** formed in only 32% ee. Similarly high site selectivities were observed with the phathlimido catalysts **4** and **5**, but now the enantioselectivity was also very high, reaching 98% ee with **4**. The bulky catalysts **2** and **3**, designed for functionalization of primary or secondary C–H bonds,[12,14] caused a dramatic change in selectivity, favoring the C3 product **8** (2:1 for **2** and 5:1 for **3**). Catalyst, **1**, designed for primary C–H functionalization,[11] also preferred attack at C3 (3:1) but did not outperform the site selectivity exhibited by catalyst **3** and also generated a further undefined isomer of the C-H functionalization products. On the basis of these studies, Rh_2(*S*-TCPTAD)$_4$ (**3**) was selected as the optimum catalyst for C1 functionalization and Rh_2(*S*-2-Cl-5-BrTPCP)$_4$ (**3**) was selected for C3 functionalization.

With these regiodivergent methods in place, the substrate scope was evaluated (Figure 5 and 6). The cyclobutane substrates were readily accessed by a 2-step protocol (Grignard addition to cyclobutanone followed by reduction). The functionalization of the benzylic site was first examined using Rh_2(*S*-TCPTAD)$_4$ (**4**) as catalyst (Figure 4). A variety of different arylcyclobutanes were used in this reaction along with a number of aryl diazoacetates to generate the C1 functionalized products **10**-**21**. As the cyclobutane derivatives are the most valuable of the two reagents, these reactions were conducted with 2 equivalents of the diazo compound. Notable examples include the use of heteroaromatic groups in the formation of **18**-**21**. Also notable is the functionalization of the cyclobutane ring in preference to the primary benzylic site as shown for **15**; in this instance, Rh_2(*S*-TCPTAD)$_4$ exhibits complete selectivity for the more substituted benzylic site even though it is more sterically crowded. The absolute configuration of the tertiary substitution was verified by X-ray crystallographic analysis of **8**, and the other examples were tentatively assigned by analogy.

We next investigated the selective functionalization of the distal site, C3, using Rh_2(*S*-2-Cl-5-BrTPCP)$_4$ as catalyst (Figure 5). Despite our initial success, the development of the *cis*-1,3-disubstitued cyclobutane scope would be more challenging because the C1 position is electronically activated. Additionally, the conformational interconversion of different substituted cyclobutanes may lead to varying levels of diastereoselectivity. In fact, a variety of different aryl substituted cyclobutanes and aryldiazoacetates were competent to form the C3 functionalized products **22**-**32**, and the diastereoselectivity for distal functionalization was good for all the examples. Perhaps unsurprisingly, electron-deficient aryl rings on the cyclobutanes lowered the production of the tertiary side-product as seen for **23** *versus* **22**, but importantly, Rh_2(*S*-2-Cl-5-BrTPCP)$_4$ was able to generate the desired *cis*-1,3-disubstituted cyclobutanes as the major product in all instances. The X-ray crystallographic analysis of **27** enabled the unambiguous assignment of the major stereoisomer as *cis,* and this was further verified by nOe analysis wherein the hydrogens on the same face of the cyclobutane were coupled. This validated the hypothesis that the equatorial C–H bonds in conformer A would be most susceptible to functionalization. This reaction was also amenable to heteroaryldiazoacetates and heteroarylcyclobutanes as illustrated in the formation of **29**-**32**.

The successful C-H functionalization of the cyclobutanes is unexpected because the C-H bonds in a cyclobutane ring have greater s character and are stronger than C–H bonds contained in an unstrained system. Therefore, we conducted competition experiments of 4-*tert*-butylphenylcyclobutane with substrates containing unstrained primary, secondary and tertiary benzylic C–H bonds (Figure 6, see supporting information for details). The competition reactions with Rh_2(*S*-TCPTAD)$_4$ revealed that the tertiary benzylic C-H bond on the bicyclobutane is more reactive that the tertiary site in isopropyl benzene. In the reaction with the sterically crowded catalyst Rh_2(*S*-2-Cl-5-BrTPCP)$_4$-catalyzed reaction, the electronically unactivated secondary site of the cyclobutane is more reactive that the secondary benzylic site in ethyl benzene. These results indicate that the cyclobutane C–H bonds are more reactive compared to their unstrained counterparts, presumably because the C–H bonds would be more sterically exposed or possibly because of hyperconjugative effects in the strained ring.

DISCUSSION

C–H functionalization tactics for generating substituted cyclobutanes are dominated by the use of substrate control and directing groups which limits the accessibility of a variety of desirable substituted cyclobutanes. This report details an intermolecular C–H insertion approach to chiral substituted cyclobutanes which can generate both 1,1-disubstituted and 1,3-disubstituted cyclobutanes. The lessons we learned about specific substrate interactions with our growing catalyst toolbox assisted the rapid discovery of reaction conditions which were suitable for generating each set of substituted cyclobutanes. A less bulky dirhodium catalyst favors attack at the tertiary benzylic site, whereas a bulky catalyst favors attack at the sterically most accessible secondary site. These studies illustrate the potential of C–H functionalization strategies to rapidly access novel chiral scaffolds of potential pharmaceutical relevance.

EXPERIMENTAL PROCEDURES

General Procedure for the C–H Functionalization of Cyclobutanes

An oven-dried vial was equipped with magnetic stir bar and sealed with septa and cap. This was cooled under vacuum, and then flame-dried once. After cooling to room temperature, the vial was loaded with rhodium catalyst (0.5-1 mol %), the cyclobutane substrate (1 equiv), and anhydrous dichloromethane (2 mL dichloromethane / 1 mmol cyclobutane). The mixture was allowed to stir under argon (the mixture was heated if heat was applied) while the diazo compound was prepared. A solution of the diazo compound (2 equiv) was prepared by dissolving in the dichloromethane (3 mL dichloromethane / 0.25 mmol diazo compound) and then this mixture was added dropwise by syringe pump over 3 h. Upon completion of the addition, the reaction was stirred an additional 2-4 h. Residual solvent was removed under reduced pressure (if the reaction was heated, it was allowed to come to room temperature before removing residual solvent), and the crude product was purified by silica gel chromatography. The regisomeric ratio (rr) and the diastereomeric ratio (dr) were determined by NMR analysis of the crude reaction mixture. The enantioselectivity (ee, enantiomeric eccess) was determined by HPLC analysis of the material after flash chromatography. Images of the key spectral and analytical data of the compounds generated in this study are included in Figures S1-S138 in the Suplemental Information.

DATA AND SOFTWARE AVAILABILITY

Crystallographic data for compounds **8** and **25** have been submitted to the Cambridge Crystallographic Database under deposition numbers CCDC:1921680-1921681.

SUPPLEMENTAL INFORMATION

Supplemental Information includes detailed experimental data and images of the key spectral and analytical data (Figures S1-S138).

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AUTHOR CONTRIBUTIONS

B.D.W., Z.J.G., and W.L. performed the synthetic experiments; Z.J.G., B.D.W. and H.M.L.D. and E.M.V. designed the experiments; Z.J.G., B.D.W. and H.M.L.D. wrote the manuscript.

DECLARATION OF INTERESTS

H.M.L.D. is a named inventor on a patent entitled 'Dirhodium catalyst compositions and synthetic processes related thereto' (US 8,974,428, issued March 10, 2015).
The other authors declare no competing interests.

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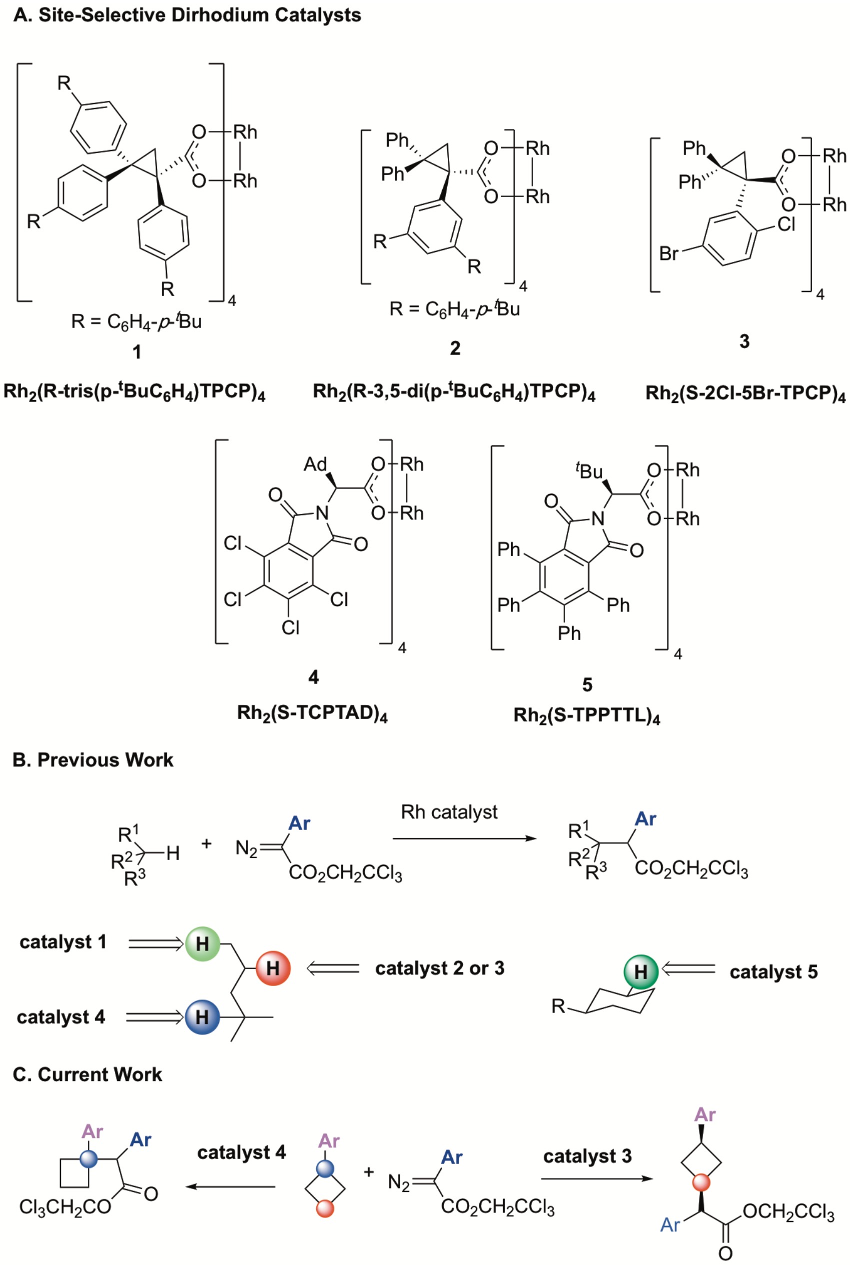


Figure 1. Site-Selective C–H Functionalization by Carbenoid Insertion Reactions

(A) Dirhodium tetracarboxylate catalysts possess structural diversity which enables functionalization of specific C–H bonds.

(B) Primary, secondary, and tertiary C–H bonds can be selectively functionalized by judicious catalyst choice.

(C) The work outlined herein showcases a regioselective C–H insertion reaction which permits access to new chemical space.

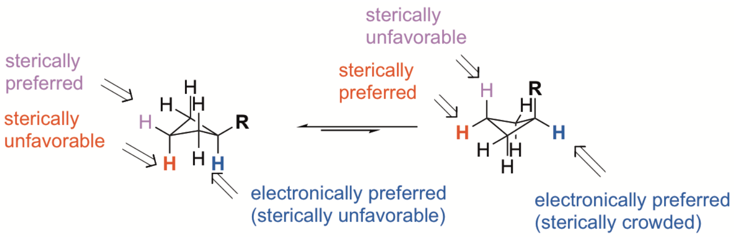
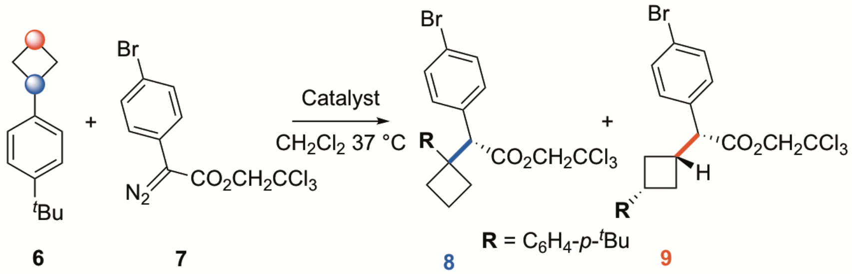


Figure 2. Analysis of Cyclobutane C–H Functionalization

Selective intermolecular C–H functionalization of cyclobutanes poses significant challenges. Potential functionalization can occur at three carbon sites. On the basis of our understanding of donor/acceptor carbene-induced C-H functionalization, we would expect the equatorial C-H bonds at C1 and C3 to be prefered and distinguished by appropriate choice of catalyst.



6 **7** **8** **9**

Entry	Catalyst	Yield, %	**8** : **9**	**8** ee / **9** ee, %
1	Rh_2(*S*-DOSP)$_4$	94	>95 : 5	32 / n/a
2	Rh_2(*S*-TPPTTL)$_4$ **(5)**	71	>95 : 5	94 / n/a
3	Rh_2(*S*-TCPTAD)$_4$ **(4)**	65	**>95 : 5**	**98** / na
4	Rh_2(*R*-3,5-di(*p*-^{t}BuC_6H_4)TPCP)$_4$ **(2)**	71	33 : 67	3 / 96
5	Rh_2(*S*-2Cl-5Br-TPCP)$_4$ **(3)**	63	**17 : 83**	34 / **91**
6	Rh_2(R-tris(p-^{t}BuC_6H_4)TPCP)$_4$ **(1)**	83	25 : 75	3 / 96

Figure 3. Optimization of C–H Functionalization of Substituted Cyclobutanes

The reaction conditions were the following: the diazo compound **6** (0.25 mmol) in 1.5 mL solvent was added over 3 h to a solution of the cyclobutane substrate **7** (0.75 mmol, 3.0 equiv.) and catalyst (1.0 mol %) in 3.0 mL dichloromethane at room temperature. The reaction was allowed to stir an additional 2 h. All yields are isolated yields (98% of unreacted **6** was recovered). The enantiomeric excess (ee) was determined by chiral HPLC analysis of the isolated product.

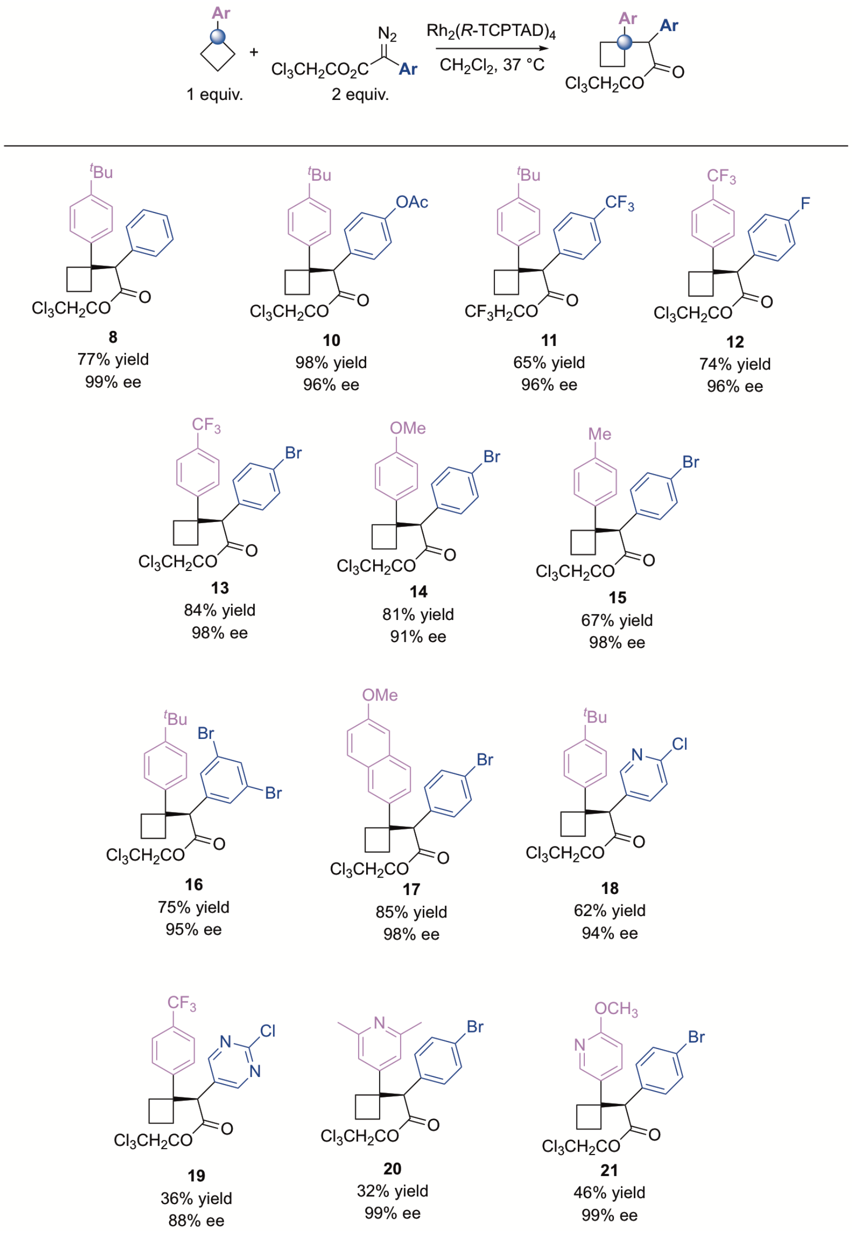
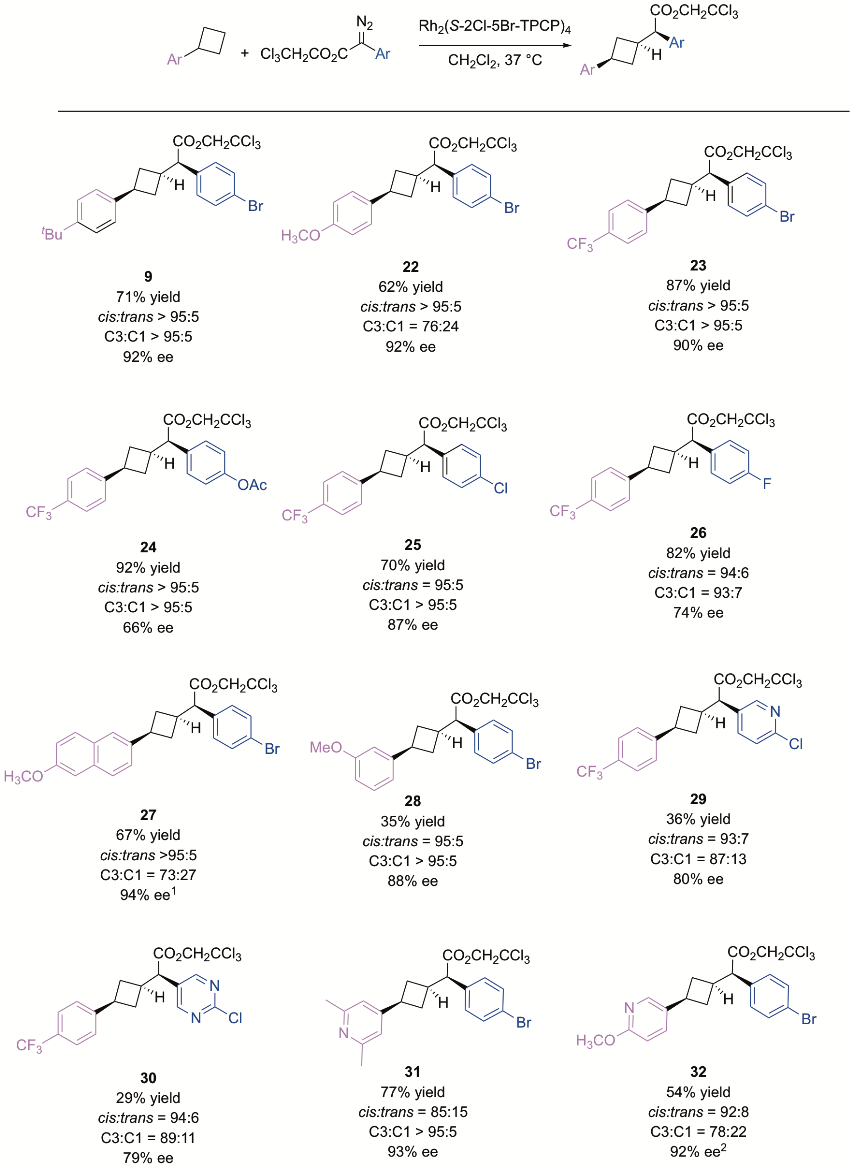


Figure 4. Reaction Scope for C–H Functionalization of Arylcyclobutanes at C1

The $Rh_2(S\text{-}TCPTAD)_4$ (**4**)-catalyzed reactions of aryldiazoacetates results in the selective C–H functionalization of the tertiary benzylic site of the arylcyclobutane. The catalyst is relatively uncrowded and reacts at the electronically preferred site. ee (enantiomeric excess).



9
71% yield
cis:trans > 95:5
C3:C1 > 95:5
92% ee

22
62% yield
cis:trans > 95:5
C3:C1 = 76:24
92% ee

23
87% yield
cis:trans > 95:5
C3:C1 > 95:5
90% ee

24
92% yield
cis:trans > 95:5
C3:C1 > 95:5
66% ee

25
70% yield
cis:trans = 95:5
C3:C1 > 95:5
87% ee

26
82% yield
cis:trans = 94:6
C3:C1 = 93:7
74% ee

27
67% yield
cis:trans >95:5
C3:C1 = 73:27
94% ee[1]

28
35% yield
cis:trans = 95:5
C3:C1 > 95:5
88% ee

29
36% yield
cis:trans = 93:7
C3:C1 = 87:13
80% ee

30
29% yield
cis:trans = 94:6
C3:C1 = 89:11
79% ee

31
77% yield
cis:trans = 85:15
C3:C1 > 95:5
93% ee

32
54% yield
cis:trans = 92:8
C3:C1 = 78:22
92% ee[2]

Figure 5. Reaction Scope for C–H Functionalization of Arylcyclobutanes at C3

The Rh_2(S-2-Cl-5-BrTPCP)$_4$ (**3**)-catalyzed reactions of aryldiazoacetates results in the selective C–H functionalization of the C3 secondary site of the arylcyclobutanes. The catalyst is sterically demanding and reacts at the sterically most accessible secondary site. *ee* (enantiomeric excess). [1]The tertiary substituted product was obtained in 84% ee. [2]The tertiary substituted product was obtained in 90% ee.

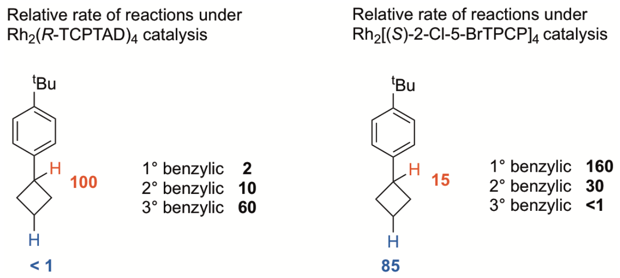


Figure 6. Competition studies for site-selective C-H functionalization

The relative rates of functionalization of the cyclobutane C-H bonds versus the unstrained benzylic C-H bonds in isopropyl-, ethyl- and methylbenzene The tertiary benzylic site of cyclobutane (marked in red) is more reactive than the tertiary benzylic site is an unstrained system for both the Rh_2(*S*-TCPTAD)$_4$ and Rh_2(S-2-Cl-5-BrTPCP)$_4$ catalyzed reactions (1.7 times and >15 times more reactive, respectively). The electronically unactivated secondary site of the cyclobutane (marked in blue) is 2.8 times more reactive in the Rh_2(*S*-2-Cl-5-BrTPCP)$_4$-catalyzed reaction and >10 times more reactive in the Rh_2(*S*-TCPTAD)$_4$-catalyzed reaction.

TOC graphic