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Highly Enantioselective Rh-Catalyzed Carboacylation of Olefins: Efficient Syntheses of Chiral Poly-Fused Rings

Tao Xu,[†] Haye Min Ko,[†] Nikolas A. Savage, and Guangbin Dong*

Department of Chemistry and Biochemistry, University of Texas at Austin, Austin, Texas 78712, United States

Supporting Information

ABSTRACT: Here we report the first highly enantioselective Rh-catalyzed carboacylation of olefins via C−C bond activation of benzocyclobutenones. Good yields and excellent enantioselectivities (92−99% ee, 14 examples) were obtained for substrates with various steric and electronic properties. In addition, fully saturated poly-fused rings were prepared from the carboacylation products through a challenging catalytic reductive dearomatization approach. These investigations provide a distinct way to prepare chiral carbon frameworks that are nontrivial to access with conventional methods.

Transition-metal-catalyzed C−C bond activation with subsequent functionalization can provide access to novel carbon frameworks and/or chiral all-carbon quaternary centers.[1] These structural motifs have great synthetic value but can be challenging to prepare using conventional methods. Although of significant interest, catalytic asymmetric transformation via C−C activation[2] has been much less explored than the related asymmetric C−H activation.[3] Generally, *β*-carbon elimination and metal insertion into C−C bonds constitute two major reaction pathways for C−C activation (Figure 1).[1b] To date,

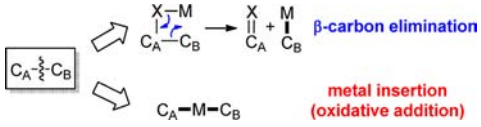
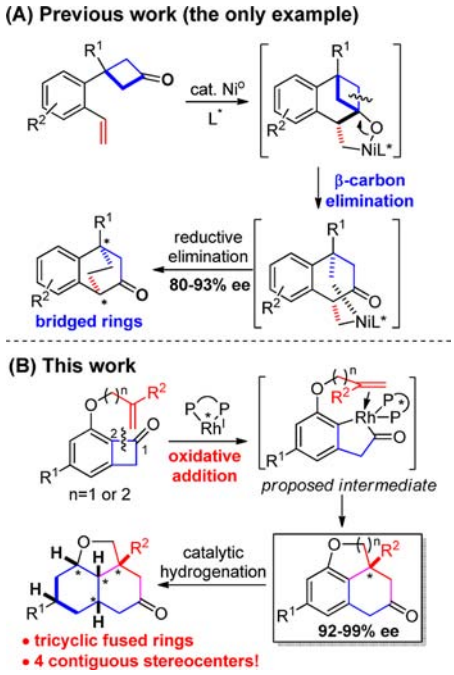


Figure 1. Two major reaction pathways for C−C activation.

asymmetric metal-catalyzed C−C cleavage reactions have mainly been achieved via *β*-carbon elimination of *tert*-cyclobutanolates generated either in situ from cyclobutanones[4] or through deprotonation of the corresponding *tert*-cyclobutanols.[5−7] Despite elegant work on the asymmetric activation of C−CN bonds,[8] enantioselective transformations mediated by metal insertion into C−C *σ* bonds remain underdeveloped. Here we describe *the first enantioselective Rh-catalyzed carboacylation of olefins via metal-insertion of benzocyclobutenone C−C bonds*[9] and our efforts to access *chiral saturated tricyclic-fused rings* from the carboacylation products by catalytic reductive dearomatization (Scheme 1B).

To the best of our knowledge, the seminal work reported earlier this year by Murakami and co-workers,[4a] in which the cyclobutanone C−C bond is cleaved via Ni-mediated cyclometalation/*β*-carbon elimination to afford bridged-ring products (Scheme 1A), is the only example of catalytic enantioselective carboacylation of olefins. In search of effective ways to access

Scheme 1. Catalytic Asymmetric Carboacylation of Olefins



fused rings, we recently reported a "cut and sew" strategy that uses a Rh-catalyzed intramolecular olefin carboacylation with benzocyclobutanones, where racemic products were obtained using 1,1-bis(diphenylphosphino)butane (dppb) as the ligand.[10] To develop a highly enantioselective version of this reaction, two challenges had to be addressed. First, a larger energy difference between the diastereomeric transition states at high temperatures is needed to achieve the same level of enantioselectivity (i.e., to obtain 95% ee, $\Delta G^{\ddagger}$ = 12.3 kJ/mol is needed at 130 °C vs 9.1 kJ/mol at rt). Second, this Rh-catalyzed reaction is sensitive to the ligand employed,[10] so finding conditions that give both high enantioselectivity and high reactivity is nontrivial.

We began by using benzocyclobutenone **1a** as a model substrate (Table 1). In view of the importance of bidentate ligands with wide bite angles in this transformation,[10] chiral bidentate phosphine ligands with a four-carbon linkage were examined first. Although the commonly used BINAP and Tol-BINAP provided only low yields and enantioselectivities,[10] DIOP provided a good yield (73%) and ee (83%) (entry 1). Aiming to

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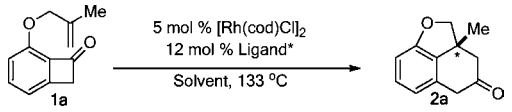
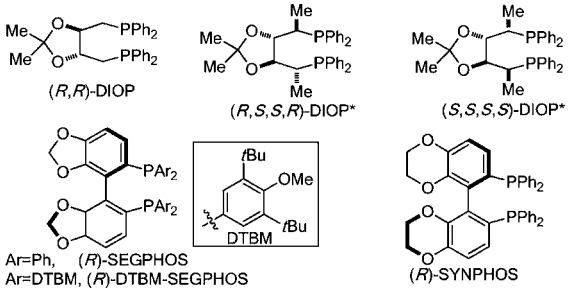
Table 1. Selected Optimization Studies[a]



Entry	Ligand	Solvent	Yield[b]	ee[c]
1	(*R*,*R*)-DIOP	THF	73%	83%
2	(*S*,*S*,*S*,*S*)-DIOP*	THF	10% (37%)	-55%
3	(*R*,*S*,*S*,*R*)-DIOP*	THF	32% (36%)	-83%
4	(*R*)-SYNPHOS	THF	14% (27%)	94%
5	(*R*)-SEGPHOS	THF	20% (28%)	97%
6	(*R*)-DTBM-SEGPHOS	THF	60% (quant.)	98%
7	(*R*)-DTBM-SEGPHOS	Tol	28%	68%
8	(*R*)-DTBM-SEGPHOS	DCE	0	N/A
9	(*R*)-DTBM-SEGPHOS	PhCl	36%	93%
10	(*R*)-DTBM-SEGPHOS	tBuOMe	43%	98%
11	(*R*)-DTBM-SEGPHOS	1,4-dioxane	69%	96%
12	(*R*)-DTBM-SEGPHOS	1,4-dioxane	81%[d]	97%



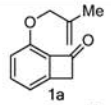
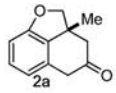
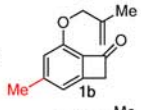
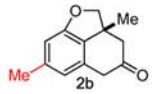
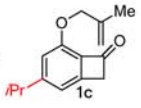
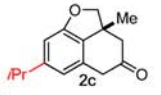
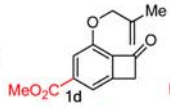
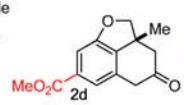
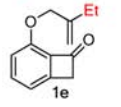
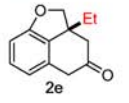
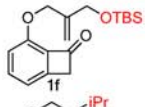
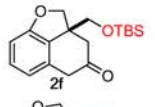
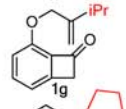
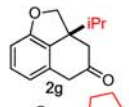
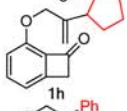
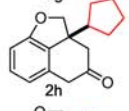
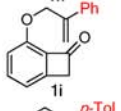
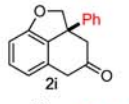
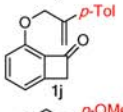
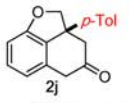
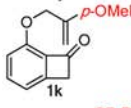
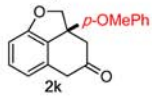
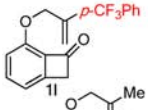
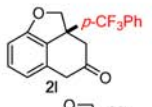
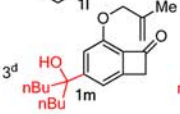
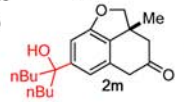
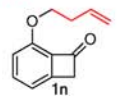
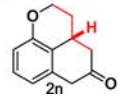
[a]5 mol % Rh precatalyst and 12 mol % ligand were used in a 0.1 mmol scale reaction with a reaction time of 20 h. [b]Isolated yields; values in parentheses are brsm yields. [c]Determined using chiral HPLC. [d]The reaction time was 48 h.

enhance the enantioselectivity further, we tried the bulkier DIOP* ligands reported by Zhang[11a] and RajanBabu,[11b] but no improvement was observed (entries 2 and 3). Fruitful results were obtained when other axially chiral ligands were surveyed. SYNPHOS gave excellent enantioselectivity (94% ee) but only a 14% yield (entry 4). The yield and ee were further improved by switching to SEGPHOS (entry 5). We hypothesized that electron-rich ligands would help enhance the catalyst reactivity by promoting oxidative addition of the C−C σ bond.[1b] Indeed, using more electron-rich DTBM-SEGPHOS further improved the yield to 60% [quantitative yield based on recovered starting material (brsm)] (entry 6). Upon optimization of the solvent and reaction time (entries 7−12), **2a** was obtained in 81% yield with 97% ee (entry 12). Its structure and absolute configuration were determined through heavy-atom X-ray crystallography (XRC) of derivative **3** (Figure 2).

Figure 2. Structure of **3** showing the atom labeling scheme. Displacement ellipsoids are scaled to the 50% probability level.

With the optimal conditions in hand, we sought to explore the substrate scope (Table 2).[12] To our delight, a number of

Table 2. Substrate Scope[a]

Entry	Substrate	Product	Yield[b]	ee[c]
1			81%	97%
2			77%	98%
3			74%	98%
4			61%	99%
5			65%	98%
6			53%	97%
7			44%	97%
8			40%	93%
9			52%	96%
10[d]			76%	92%
11			55%	97%
12			47% (64%)	95%
13[d]			97%	92%
14			44% (85%)	94%

[a]Reaction conditions: $[Rh(cod)Cl]_2$ (5 mol %), (*R*)-DTBM-SEGPHOS (12 mol %), dioxane, 133 °C, 48 h. [b]Isolated yields; values in parentheses are brsm yields. [c]Determined by chiral HPLC. [d](*R*,*R*)-DIOP was used as the chiral ligand and THF as the solvent.

benzocyclobutenone substrates with different steric and electronic properties gave high to excellent enantioselectivities. Changing the electron density of the aromatic ring did not affect the enantioselectivity, and 97−99% ee's were observed

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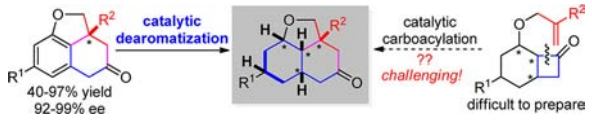
(entries 1−4). Not surprisingly, increasing the steric bulk on the olefin substituent from methyl to ethyl, OTBS-methyl, isopropyl, and cyclopentyl slowed the reaction, but products with high optical purity (93−98% ee) were still isolated in 40−65% yield (entries 5−8).[13] When substrates containing different aryl olefins were subjected to the reaction conditions (entries 9−12), >95% ee was obtained, except for substrate **1j** (54% yield, 89% ee with DTBM-SEGPHOS). Interestingly, DIOP was a more efficient ligand for substrates **1j** and **1m**, as both the yield and ee were enhanced (entries 10 and 13). It is noteworthy that *beyond disubstituted alkenes, a terminal-olefin substrate, which formed a dihydropyran ring, also afforded excellent enantioselectivity* (**1n**, 94% ee; entry 14). Overall, many functional groups were compatible with this reaction, including esters, ketones, ethers, free tertiary alcohols, silyl ethers, CF_3 groups, and electron-rich and -poor arenes, showing the potential for its application in complex-molecule synthesis.[14]

With the enantiomerically enriched benzotricyclic compounds in hand, we hypothesized that if a stereoselective reductive dearomatization could be performed, *new types of chiral poly-fused ring structures with four contiguous stereocenters* would be obtained (Scheme 2). These saturated structures are found in terpene

Scheme 2. Saturated Poly-Fused Rings

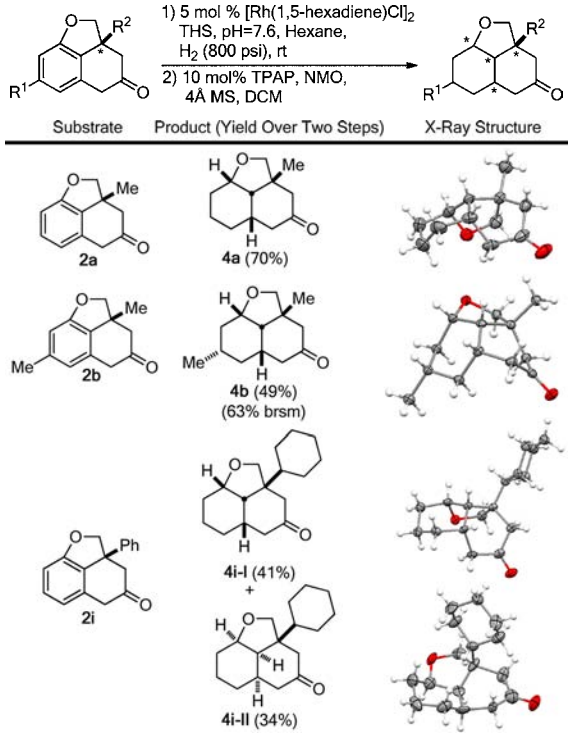


natural products[15] and often are nontrivial to synthesize using conventional methods. The success of this approach would greatly enlarge the scope of fused-ring scaffolds that could be obtained via Rh-catalyzed C−C activation. Moreover, it may be considered as a "reaction surrogate" for the use of saturated cyclobutanones as the asymmetric carboacylation substrate (Scheme 2), which is a more difficult reaction.[16]

Although attractive, the reduction of polysubstituted (≥3) electron-rich benzene rings is very challenging, as less hindered and electron-deficient arenes are generally easier to reduce.[17] However, after extensive experimentation, we were delighted to discover that the benzene rings of tricycles **2a**, **2b**, and **2i** can be effectively reduced to the substituted cyclohexanes via a Rh-catalyzed hydrogenation reaction, a procedure originally reported by Alper[18] (Table 3).[19] These reactions were conducted at room temperature under phase-transfer and near-neutral conditions. We found that it was critical to use H_2 at high pressure, as no reaction occurred at low pressure.

Interestingly, although ketones are generally much easier to reduce than arenes, under these hydrogenation conditions the aryl groups reacted faster, and the ketones were only partially reduced to alcohols. To ensure that the ketones were the sole products isolated, subsequent Ley oxidation[20] was performed. For substrates **2a** and **2b**, the hydrogenation proceeded stereoselectively on the convex face of the tricycle (likely governed by the all-carbon quaternary center), providing ketones **4a** and **4b** as single diastereomers. Notably, substrate **2b**, with four electrondonating groups on the benzene ring, still afforded a 49% yield (63% brsm) over two steps, generating four new stereocenters. The reaction with **2i** was rather intriguing; under the hydrogenation conditions, the phenyl group was selectively reduced first to give a cyclohexyl group,[21] whose bulkiness caused the second hydrogenation to occur on both the convex and

Table 3. Catalytic Reductive Dearomatization[a]



[a]Abbreviations: THS, tetrabutylammonium hydrogen sulfate; TPAP, tetrapropylammonium perruthenate; NMO, *N*-methylmorpholine-*N*-oxide; DCM, dichloromethane.

concave faces of the resultant intermediate, giving the two separable products **4i-I** and **4i-II** in a high overall yield (75%).[22] Structures of all the products described in Table 3 were unambiguously determined by ^1H and ^{13}C NMR, IR, HRMS, and XRC analyses. Interestingly, XRC showed that **4a**, **4b**, and **4i-I** with all cis-fused rings adopt a "half-cage"-like structure.

In summary, we have developed the first enantioselective Rh-catalyzed carboacylation of olefins via C−C bond activation of benzocyclobutenones. We have also achieved preliminary success in synthesizing fully saturated poly-fused rings using a catalytic reductive dearomatization approach, which offers a distinct and atom-economical strategy for preparing chiral "half-cage"-like structures with multiple stereocenters. The highly enantioselective carboacylation reaction and the challenging catalytic hydrogenation of polysubstituted electron-rich arenes described here should have broad implications beyond this work, such as new strategy design for terpenoid synthesis. Efforts to discover more efficient chiral catalysts (i.e., ones compatible with Lewis acids) and to extend further the scope of catalytic reductive dearomatization[23] are currently ongoing.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Procedures and additional data. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

gbdong@cm.utexas.edu

Author Contributions

†T.X. and H.M.K. contributed equally.

Notes

The authors declare no competing financial interest.

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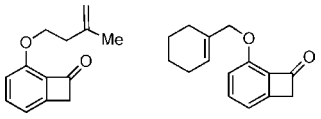
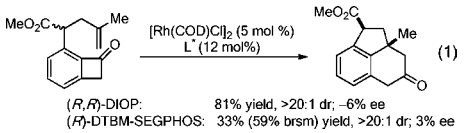
(12) $ZnCl_2$ is not compatible with these enantioselective conditions. Both SEGPHOS and DIOP decomposed when heated with $ZnCl_2$, likely because of their acid-labile ketal groups. Thus, more challenging substrates (i.e., trisubstituted olefins[10]), showed low reactivity under the current asymmetric conditions. For example, almost no reaction was observed under the optimized conditions with DTBM-SEGPHOS when the two substrates shown below were used:



(13) The yields with substrates **2d−f** were higher (92−94%) when dppb was used,[10] likely because of the structural difference between SEGPHOS and dppb. We further found that shorter reaction times and higher yields were generally observed with DIOP, a dppb-like ligand. For a comparison of the results obtained using DTBM-SEGPHOS and DIOP, see Table S1 in the Supporting Information.

(14) A carbon-tethered substrate was also tried (eq 1). Excellent diastereoselectivity was observed, albeit in an almost racemic form (the dr with dppb was only 1.3:1[10]). The cause for such selectivity with this substrate is unclear.



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(19) Attempts to combine the Rh-catalyzed carboacylation and the hydrogenation into a one-pot process have been unsuccessful to date.

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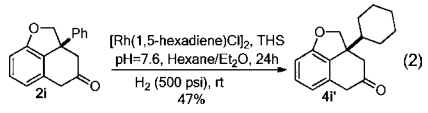
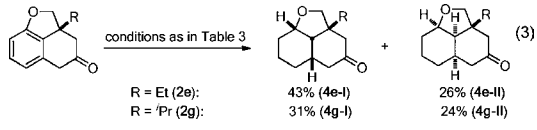
(21) By control of the reaction time and H_2 pressure, the partially reduced product **4i′** could be obtained selectively (eq 2).



(22) Reductive dearomatization of ethyl- and isopropyl-substituted substrates (**2e** and **2g**) was attempted (eq 3). The selectivity for the "concave-face addition" products increased with increasing steric hindrance (Me < Et < ^{i}Pr).



(23) Reductive dearomatization of substrates **2d** and **2l** was also attempted. Unfortunately, only deposition and starting material recovery (ca. 40%) were observed for **2d**, and a complex mixture of partially hydrogenated products was obtained for **2l**.