Communication

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

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

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Supporting Information Placeholder

ABSTRACT: Here, we report the first highly enantioselective Rh-catalyzed carboacylation of olefins via C–C bond activation of benzocyclobutenones. Good yields and excellent enantioselectivity (92-99% ee, 14 examples) have been 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 carbo-frameworks that are nontrivial to access with conventional methods.

Transition metal-catalyzed carbon–carbon (C–C) bond activation/subsequent functionalization provides a unique strategy to access novel carbo-frameworks and/or chiral all-carbon quaternary centers.[1] These structural motifs are of significant synthetic value and could be challenging to prepare using conventional methods.

Although of significant interest, catalytic asymmetric transformation via C–C activation[2] has been much less explored compared to 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, asymmetric metal-catalyzed C–C cleavage reactions have been mainly achieved via β-carbon elimination of *tert*-cyclobutanolates that are generated either *in situ* from cyclobutanones (by Murakami[4]) or through deprotonation of the corresponding *tert*-cyclobutanols (by Uemura,[5] Trost,[6] and Cramer[7]). Despite elegant work on the asymmetric activation of C–CN bonds,[8] enantioselective transformations mediated by metal insertion into C–C σ bonds are much underdeveloped. In this communication, we describe *the first enantioselective Rh-catalyzed carboacylation of olefins via metal-insertion of benzocyclobutenone C–C bonds*,[9] and also show our efforts to access *chiral saturated tricyclic-fused rings* from the carboacylation products through a catalytic reductive dearomatization reaction (Scheme 1B).

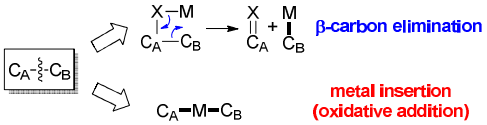
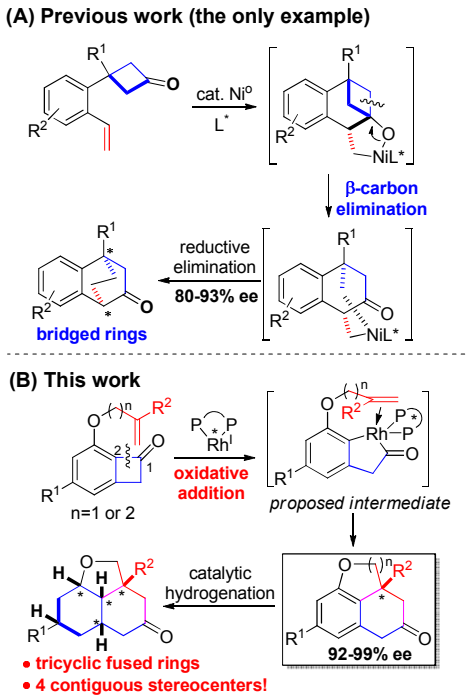


Figure 1. Two major reaction pathways for C–C activation.

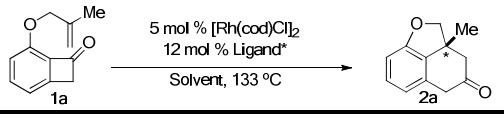
To the best of our knowledge, the work reported earlier this year by Murakami and coworkers is the only example of catalytic enantioselective carboacylation of olefins (Scheme 1A).[4a] In this seminal work, the cyclobutanone C–C bond is cleaved via Ni-mediated cyclometallation/β-carbon elimination to afford bridged-ring products. In search of effective ways to access fused rings, we recently reported a "Cut & Sew" strategy using a Rh-catalyzed intramolecular olefin carboacylation with benzocyclobutanones, where racemic products were obtained using dppb as the ligand.[10] To develop a highly enantioselective reaction for this transformation, two challenges must be addressed. The first is general; a larger energy difference is needed between the diastereomeric transition states at high temperatures 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* $\Delta G^{\ddagger}$=9.1 kJ/mol at rt). The second derives from the sensitivity of this Rh-catalyzed reaction to the ligand employed,[10] where finding conditions that give both high enantioselectivity and high reactivity is nontrivial.

Scheme 1. Catalytic asymmetric carboacylation of olefins.

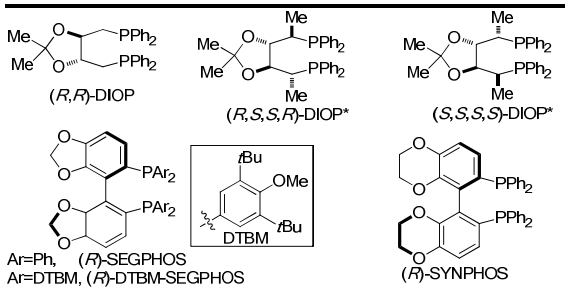


We initiated the study by using benzocyclobutenone **1a** as a model substrate (Table 1). Given the importance of bidentate ligands with wide bite angles in this transformation,[10] chiral bidentate phosphine ligands with a four-carbon linkage were examined first. Although the commonly used BINAP and Tol-BINAP only provided low yield and low enantioselectivity,[10] use of DIOP as the ligand provided good yield (73%) and ee (83%) (entry 1). Aiming to further enhance the enantioselectivity, two bulkier DIOP* ligands, first prepared by Zhang[11a] and RajanBabu[11b], were employed (entries 2 and 3); unfortunately, no improvement of ee was observed.

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 on a 0.1 mmol scale reaction with 20h reaction time. b) Isolated yield; numbers in parentheses are brsm yield. c) ee was determined using chiral HPLC. d) Reaction time was 48h.

Fruitful results were obtained upon surveying other ligands with axial chirality. SYNPHOS gave excellent enantioselectivity (94% ee), albeit only 14% yield (entry 4, Table 1). The yield and ee were further improved by switching to SEGPHOS (entry 5). We hypothesized that the electron-rich ligands would help enhance the catalyst reactivity by promoting oxidative addition of the C–C σ bond.[1b] Indeed, by using the more electron-rich DTBM-SEGPHOS (entry 6), the yield was further improved to 60% (quantitative yield brsm). Furthermore, by optimizing the solvent and reaction time (entries 7-12), the benzo-tricycle (**2a**) was obtained in 81% yield and 97% ee (entry 12). The structure and absolute configuration of tricyclic ketone **2a** was determined through heavy-atom X-ray crystallography of derivative **3** (Figure 2).

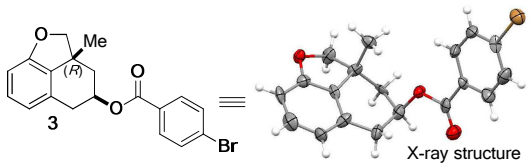


Figure 2. View of compound **3** showing the atom labeling scheme. Displacement ellipsoids are scaled to the 50% probability level.

With the optimal conditions in hand, we sought to explore the substrate scope (Table 2).[12] A number of benzocyclobutenone substrates with different steric and electronic properties were examined; delightedly, high to excellent enantioselectivities were obtained. It was found that changing the electron density of the aromatic ring did not affect the enantioselectivity, and 97-99% ee's were observed (entries 1-4). Not surprisingly, increasing the steric bulk on the olefin substituent from methyl to ethyl, OTBS-methyl, isopropyl or cyclopentyl slowed down the reaction; however, 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, the observed enantioselectivity was generally over 95% ee (entries 9–12) except for substrate **1j** (54% yield, 89% ee with DTBM-SEGPHOS). Interestingly, DIOP was found to be 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, terminal-olefin substrate (***1n***) also afforded excellent enantioselectivity* (94% ee, entry 14), *where a dihydropyran ring was formed*. Overall, many functional groups were compatible to this reaction, such as esters, ketones, ethers, free tertiary alcohols, silyl ethers, trifluoromethyl groups, electron-rich and poor arenes, which shows potential for application in complex molecule synthesis.[14]

With the enantiomerically enriched benzo-tricyclic compounds in hand, we hypothesized that if a stereoselective reductive dearomatization can be performed, *new types of chiral poly-fused ring structures* with *four contiguous stereocenters* would be afforded (Scheme 2). These saturated structures are found in terpene natural products and often nontrivial to synthesize using conventional methods.[15] Success of this approach would greatly enlarge the scope of the fused-ring scaffolds that can be obtained using the Rh-catalyzed C–C activation method. Moreover, it may be considered as a "reaction surrogate" for using the saturated cyclobutanones as the asymmetric carboacylation substrate (Scheme 2), which is known to be a more difficult reaction.[16]

Scheme 2. Saturated poly-fused rings

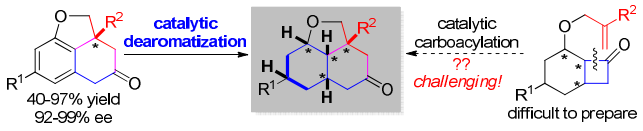
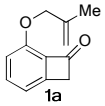
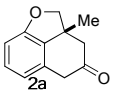
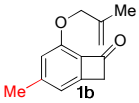
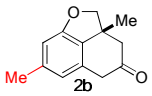
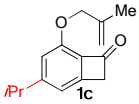
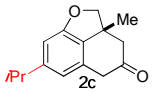
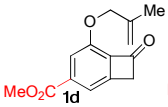
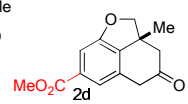
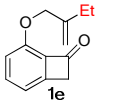
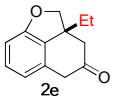
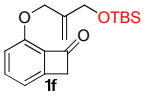
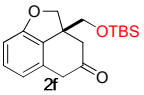
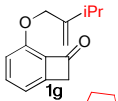
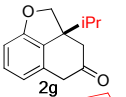
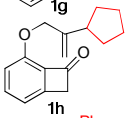
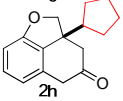
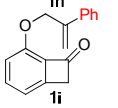
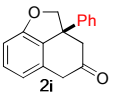
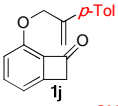
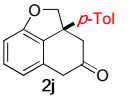
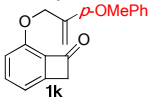
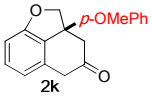
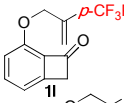
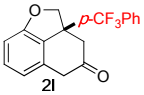
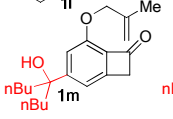
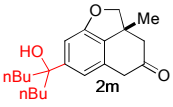
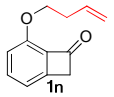
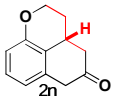


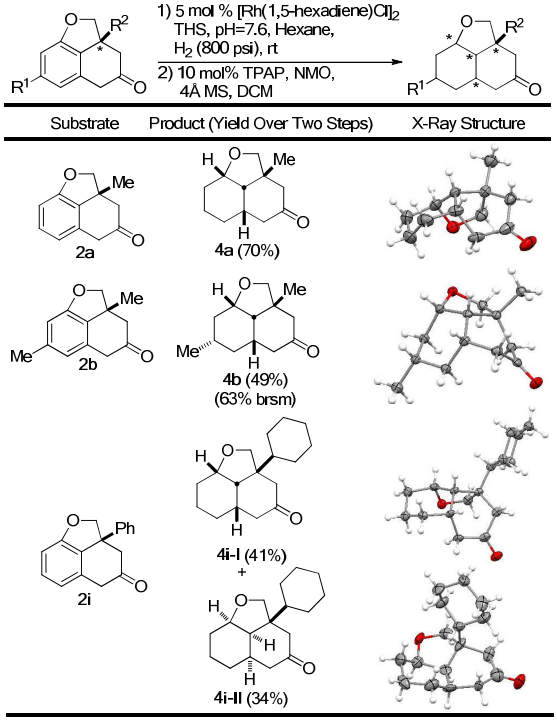
Table 2. Substrate scope[a]

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

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

Despite being an attractive transformation, reduction of poly-substituted (≥ 3) electron-rich benzene rings is very challenging, as in general less hindered and electron-deficient arenes is easier to reduce.[17] However, after extensive experimentations, 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 hydrogen gas with enhanced pressure as no reaction occurred at low pressure.

Table 3. Catalytic reductive dearomatization



It is interesting to note that, 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, Ley oxidation[20] was carried out subsequently. For substrates **2a** and **2b**, the hydrogenation proceeded stereoselectively on the convex face of the tricycles likely governed by the all-carbon quaternary center, providing ketones **4a** and **4b** as single diastereomers. Note that substrate **2b**, with four electron-donating groups on the benzene ring, still afforded 49% (63% brsm) yield over two steps, and consequently, four new stereocenters are generated. Reaction with substrate **2i** is rather intriguing; under the hydrogenation conditions, the phenyl group (-C_6H_5) is selectively reduced first to the cyclohexyl group,[21] and due to the bulkiness of the cyclohexyl group, the second hydrogenation occurs on both convex and concave faces of the resultant intermediate, giving 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 $^1H/^{13}C$-NMR, IR, HRMS and X-ray crystallography.* Interestingly, as illustrated by the X-ray crystallography, compounds **4a**, **4b** and **4i-I** with all *cis*-fused rings adopted 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. Further, preliminary success to synthesize fully saturated poly-fused rings was demonstrated using a catalytic reductive dearomatization approach, which offers a distinct and atom-economical strategy to prepare chiral "half-cage"-like structures with multiple stereocenters. The highly enantioselective carboacylation reaction, as well as the challenging catalytic hydrogenation of poly-substituted 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. those compatible with Lewis acids) and to further extend the scope of catalytic reductive dearomatization[23] are currently ongoing.

ASSOCIATED CONTENT

Supporting Information. Experimental procedures; spectral data; and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

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Author Contributions

‡These authors contributed equally.

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ABBREVIATIONS

BRSM, based on recovered starting material; TBS, *tert*-butyl dimethyl silyl; rt, room temperature; dppb, 1,1-bis(diphenylphosphino)butane; THS, tetrabutylammonium hydrogen sulfate; DIOP, [(2,2-dimethyl-1,3-dioxolane-4,5-diyl)bis(methylene)]bis(diphenylphosphine); DCE, 1,2-dichloroethane; TPAP, tetrapropylammonium perruthenate; NMO, *N*-methylmorpholine-*N*-oxide.

REFERENCES

(1) For recent reviews of C–C bond activation, see: (a) Rybtchinski, B.; Milstein, D. *Angew. Chem., Int. Ed.* **1999**, *38*, 870. (b) Murakami, M.; Ito, Y. *Top. Organomet. Chem.* **1999**, *3*, 97. (c) van der Boom, M. E.; Milstein, D. *Chem. Rev.* **2003**, *103*, 1759. (d) Jun, C.-H. *Chem. Soc. Rev.* **2004**, *33*, 610. (e) Satoh, T.; Miura, M. *Top. Organomet. Chem.* **2005**, *14*, 1. (f) Jun, C.-H.; Park, J.-W. *Top. Organomet. Chem.* **2007**, *24*, 117. (g) Necas, D.; Kotora, M. *Curr. Org. Chem.* **2007**, *11*, 1566. (h) Korotvicka, A.; Necas, D.; Kotora, M. *Curr. Org. Chem.* **2012**, *16*, 1170. (i) Crabtree, R. H. *Chem. Rev.* **1985**, *85*, 245. (j) Jones, W. D. *Nature* **1993**, *364*, 676. (k) Seiser, T.; Saget, T.; Tran, D. N.; Cramer, N. *Angew. Chem., Int. Ed.* **2011**, *50*, 7740.

(2) For recent highlights on asymmetric transformation via C–C activation, see: (a) Winter, C.; Krause, N. *Angew. Chem., Int. Ed.* **2009**, *48*, 2460. (b) Najera, C.; Sansano, J. M. *Angew. Chem., Int. Ed.* **2009**, *48*, 2452. (c) Seiser, T.; Cramer, N. *Org. Biomol. Chem.* **2009**, *7*, 2835.

(3) For recent reviews on: asymmetric C–H activation, see: (a) Morton, D.; Davis, H. M. L. *Chem. Soc. Rev.* **2011**, *40*, 1857. (b) Giri, R.; Shi, B.-F., Engle, K. M.; Maugel, N.; Yu, J.-Q. *Chem. Soc. Rev.* **2009**, *38*, 3242. (b) Davis, H. M. L.; Beckwith, R. E. J. *Chem. Rev.* **2003**, *103*, 2861.

(4) (a) Liu, L.; Ishida, N.; Murakami, M. *Angew. Chem., Int. Ed.* **2012**, *51*, 2485. (b) Matsuda, T.; Shigeno, M.; Makino, M.; Murakami, M. *Org. Lett.* **2006**, *8*, 3379. (c) Matsuda, T.; Shigeno, M.; Murakami, M. *J. Am. Chem. Soc.* **2007**, *129*, 12086. (d) Shigeno, M.; Yamamoto, T.; Murakami, M. *Chem. Eur. J.* **2009**, *15*, 12929.

(5) (a) Nishimura, T.; Matsumura, Y.; Maeda, Y.; Uemura, S. *Chem. Commun.* **2002**, 50. (b) Matsumura, Y.; Maeda, Y.; Nishimura, T.; Uemura, S. *J. Am. Chem. Soc.* **2003**, *125*, 8862. (c) Nishimura, T.; Matsumura, S.; Maeda, Y.; Uemura, S. *Tetrahedron Lett.* **2002**, *43*, 3037.

(6) (a) Trost, B. M.; Yasukata, T. *J. Am. Chem. Soc.* **2001**, *123*, 7162. (b) Trost, B. M.; Xie, J. *J. Am. Chem. Soc.* **2006**, *128*, 6044.

(7) (a) Waibel, M.; Cramer, N. *Chem. Commun.* **2011**, 345. (b) Seiser, T.; Cramer, N. *J. Am. Chem. Soc.* **2010**, *132*, 5340. (c) Seiser, T.; Cramer, N. *Chem. Eur. J.* **2010**, *16*, 3383. (d) Seiser, T.; Cramer, N. *Angew. Chem., Int. Ed.* **2010**, *49*, 10163. (e) Seiser, T.; Roth, O. A.; Cramer, N. *Angew. Chem., Int. Ed.* **2009**, *48*, 6320. (f) Seiser, T.; Cramer, N. *Angew. Chem., Int. Ed.* **2008**, *47*, 9294.

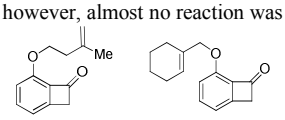
(8) For Ni-catalyzed asymmetric carbocyanation of olefins, see: (a) Watson, M. P.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2008**, *130*, 12594. (b) Nakao, Y.; Ebata, S.; Yada, A.; Hiyama, T.; Ikawa, M.; Ogoshi, S. *J. Am. Chem. Soc.* **2008**, *130*, 12874. (c) Yasui, Y.; Kamisaki, H.; Takemoto, Y. *Org. Lett.* **2008**, *10*, 3303.

(9) For seminal work of studying the mechanism of Rh insertion into benzocyclobutanones, see: (a) Huffman, M. A.; Liebeskind, L. S.; Pennington, W. T. *Organometallics* **1990**, *9*, 2194. (b) Huffman, M. A.; Liebeskind, L. S.; Pennington, W. T. *Organometallics* **1992**, *11*, 255. For recent synthesis and utilization of benzocyclobutenones, see: (c) Alvarez-Bercedo, P.; Flores-Gaspar, A.; Martin, R. *J. Am. Chem. Soc.* **2010**, *132*, 466. (d) Flores-Gaspar, A.; Gutierrez-Bonet, A.; Martin, R. *Org. Lett.* **2012**, *14*, 5234. (e) Hosoya, T.; Hasegawa, T.; Kuriyama, Y.; Matsumoto, T.; Suzuki, K. *Synlett* **1995**, 177. (f) Stevens, R. V.; Bisacchi, G. S. *J. Org. Chem.* **1982**, *47*, 2393. (g) Aidhen, I. S.; Ahuja, J. R. *Tetrahedron Lett.* **1992**, *33*, 5431.

(10) Xu, T.; Dong, G. *Angew. Chem., Int. Ed.* **2012**, *51*, 7567.

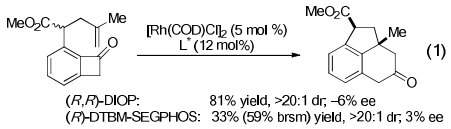
(11) (a) Li, W.; Zhang, X. *J. Org. Chem.* **2000**, *65*, 5871. (b) Yan, Y.-Y.; RajanBabu, T. V. *J. Org. Chem.* **2000**, *65*, 900.

(12) Unfortunately, $ZnCl_2$ is not compatible with these enantioselective conditions, because both SEGPHOS and DIOP ligands were found decomposed by heating together with $ZnCl_2$, which is likely due to the acid-labile ketal groups of both ligands. Thus, when more challenging substrates (i.e. trisubstituted olefins, see ref 10) were used, low reactivity was observed under current asymmetric conditions. For example, the following two substrates have been attempted under the optimized conditions with DTBM-SEGPHOS; however, almost no reaction was observed.



(13) The yields with substrates **2d-2f** were higher (92-94%) when dppb ligand was used (see ref 10), which is likely attributed to the structural difference between SEGPHOS ligands and dppb ligands. We further found that shorter reaction time and higher yields were generally observed with DIOP, a dppb-like ligand. For a detailed report and comparison of the results between DTBM-SEGPHOS and DIOP ligands, see SI (Table S1).

(14) A carbon-tethered substrate has also been attempted (eq 1): excellent diastereoselectivity was observed albeit in an almost racemic form (the dr with dppb ligand is only 1.3:1, see ref 10). The cause for such selectivity with this substrate is unclear.



(15) For a recent book on terpene natural products, see: Breitmaier, E. *Terpenes: flavors, fragrances, pharmaca, pheromones*, WILEY-VCH, Weinheim, Germany: 2006.

(16) (a) Murakami, M.; Amii, H.; Ito, Y. *Nature* **1994**, *370*, 540. (b) Murakami, M.; Itahashi, T.; Ito, Y. *J. Am. Chem. Soc.* **2002**, *124*, 13976.

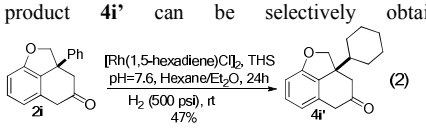
(17) (a) For a review of Birch reduction, see: Rabideau, P. W.; Marcinow, Z. *Org. React.* **1992**, *42*, 1. (b) For transition metal-catalyzed hydrogenative dearomatization, see: Rylander, P. N. in *Catalytic Hydrogenation in Organic Synthesis,* Academic Press, New York, **1979**, p.175.

(18) Januszklewicz, K. R.; Alper, H. *Organometallics*, **1983**, *2*, 1055. For a review of biphasic homogeneous catalysis, see: Kalck, P.; Monteil, F. *Adv. Organomet. Chem.* **1992**, *34*, 219.

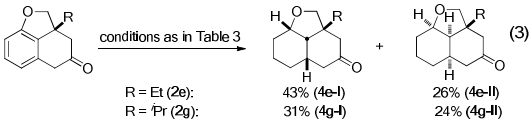
(19) Attempts to combine the Rh-catalyzed carboacylation and hydrogenation into a one-pot reaction were unsuccessful so far.

(20) Griffith, W. P.; Ley, S. V.; Whitcombe, G. P.; White, A. D. *J. Soc. Chem., Chem. Commun.* **1987**, 1625.

(21) By controlling the reaction time and H_2 pressure, partially reduced product **4i'** can be selectively obtained (eq 2).



(22) Reductive dearomatization of ethyl and *i*-propyl substituted substrates (**2e** and **2g**) has been attempted (eq 3). The selectivity for the "concave-face addition" products increases with raising the steric hindrance from the methyl to ethyl to *i*-propyl.



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