Organic LETTERS
Letter
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Copper(I)−Taniaphos Catalyzed Enantiodivergent Hydroboration of Bicyclic Alkenes

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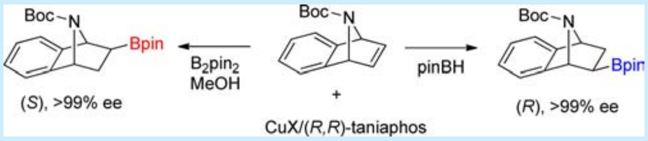
S *Supporting Information*

ABSTRACT: In this study, highly enantioselective copper(I)-catalyzed hydroboration of bicyclic alkenes is reported. Using a copper−taniaphos complex, excellent enantioselectivities up to >99% ee were obtained for bicyclic alkenes including oxa- and azabicyclic alkenes. Furthermore, copper-catalyzed enantiodivergent hydroboration methods with the same chiral ligand−copper precursors were developed using different boron sources based on alternative mechanistic pathways.



The development of enantiodivergent synthetic methods that produce both enantiomers from the same starting material has been receiving increasing attention.[1] Asymmetric catalysis is one of the most effective approaches for the preparation of chiral compounds; however, it mostly relies on the use of both enantiomers of a chiral ligand−catalyst complex to access both enantiomers of a product. Because of the limited availability of both enantiomers of chiral sources, the development of enantiodivergent asymmetric catalysis utilizing the same chiral catalyst (chirality inducer) is scanty, but highly desirable.

Metal-catalyzed hydroboration of unsaturated carbon−carbon bonds provides an easy access to organoboron compounds, which can function as synthons for various functional groups.[2] The reversal of enantioselectivity in the hydroboration was first reported by Micouin and co-workers for *meso*-bicyclic hydrazine substrates using catecholborane reagent by switching the metal from rhodium to iridium.[3] Although the switch in the enantioselectivity was observed in their study, the obtained ee values of the products were low to moderate (16−80% ee). So far, highly enantioselective hydroboration of bicyclic alkenes has been achieved using chiral boranes in a stoichiometric amount,[4] but not with transition-metal catalysts such as rhodium[5] or iridium.[6]

Recently, we reported that chiral phosphine-coordinated copper complexes are efficient catalysts for the enantioselective hydroboration of acyclic alkenes with pinacolborane as the hydroborating reagent.[7] Therefore, we decided to develop an efficient copper-catalytic hydroboration system for bicyclic alkenes. In this study, we report a highly enantioselective copper-catalytic system using the (*R*,*R*)-taniaphos ligand (Figure 1), affording hydroborated products with excellent enantioselectivities (>90% ee). Furthermore, copper-catalyzed enantiodivergent hydroboration using the same chiral ligand−copper precursors is reported by using different boron sources, based on the alternative mechanistic pathways.

In initial experiments, a series of chiral phosphine−copper(I) complexes were screened for the reaction of norbornadiene (**1a**) using pinacolborane (pinBH) as the hydroborating reagent (Table 1). The two representative C_2 symmetric bisphosphines, tol-binap and segphos, were inefficient and afforded disappointingly low yields (entries 1 and 2). Tangphos and josiphos ligands, previously reported as effective ligands for the enantioselective hydroboration of acyclic alkenes,[7] afforded the products with moderate enantioselectivities (entries 3 and 4). In contrast, the taniaphos ligand (**L1**) afforded hydroborated product **2a** in excellent enantioselectivities, but with low conversions (entries 5 and 6). Fortunately, changing the copper precursor to CuTC and increasing the reaction temperature to 40 °C resulted in a good yield of the product without deterioration of the ee in either toluene or THF solvent (entries 7 and 8). The addition of NaO*t*-Bu base was not necessary in this protocol,[8] and the catalytic combination of CuTC and (*R*,*R*)-taniaphos was chosen as the optimal catalyst.

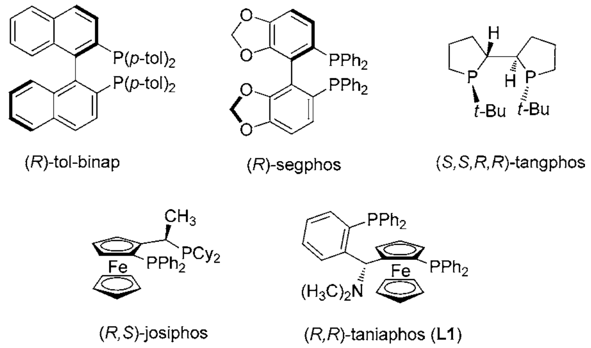


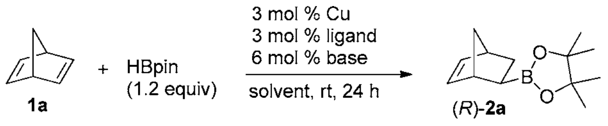
Figure 1. Structure of chiral ligands.

With the optimized reaction conditions, the hydroboration of diverse strained bicyclic alkenes was investigated (Table 2). The reaction of an oxabicyclic alkene (**1b**) and azabicyclic alkenes (**1c** and **1d**) proceeded well to afford the corresponding hydroborated products in excellent enantioselectivities (entries 1−3).[9,10] Benzonorbornadienes (**1e** and **1f**) were also suitable

Received: December 14, 2014
Published: January 20, 2015

DOI: 10.1021/ol503598w
Org. Lett. 2015, 17, 764−766

Table 1. Enantioselective Hydroboration with Various Ligands

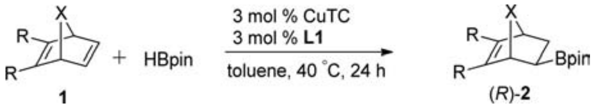


1a **(*R*)-2a**

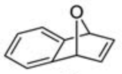
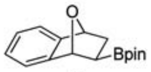
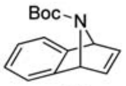
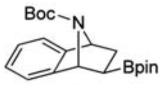
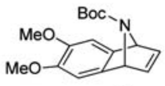
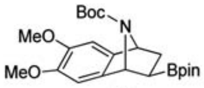
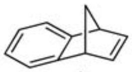
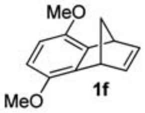
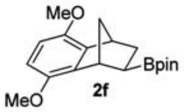
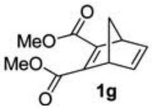
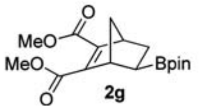
entry	Cu	ligand	base	solvent	yield[a] (%)	ee[b] (%)
1	CuCl	(*R*)-tol-binap	NaO*t*-Bu	toluene	14	–
2	CuCl	(*R*)-segphos	NaO*t*-Bu	toluene	6	–
3	CuCl	(*S*,*S*,*R*,*R*)-tangphos	NaO*t*-Bu	toluene	80	66
4	CuCl	(*R*,*S*)-josiphos	NaO*t*-Bu	toluene	88	62
5	CuCl	(*R*,*R*)-taniaphos	NaO*t*-Bu	toluene	40	97
6	CuTC[c]	(*R*,*R*)-taniaphos	–	toluene	28	98
7[d]	CuTC	(*R*,*R*)-taniaphos	–	toluene	88	98
8[d]	CuTC	(*R*,*R*)-taniaphos	–	THF	84	98

[a]Isolated yield. [b]Determined by chiral HPLC analysis. [c]CuTC = copper(I) thiophene-2-carboxylate. [d]Reaction was perfomed at 40 °C.

Table 2. Copper-Catalyzed Enantioselective Hydroboration of 1 with Pinacolborane



1 **(*R*)-2**

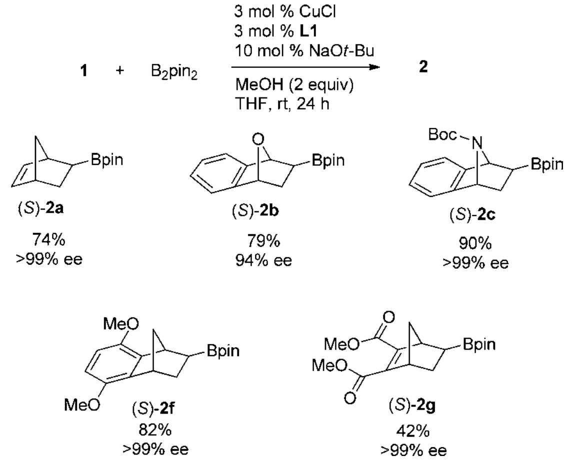
entry	substrate (**1**)	product (**2**)	yield[a] (%)	ee[b] (%)
1	 **1b**	 **2b**	88	97[c]
2	 **1c**	 **2c**	85	>99
3	 **1d**	 **2d**	88	>99
4[d]	 **1e**	 **2e**	88	90
5	 **1f**	 **2f**	84	98
6	 **1g**	 **2g**	20	>99

[a]Isolated yield. [b]Determined by chiral HPLC analysis with **2** or its derivatives. See the Supporting Information for details. [c]The configuration was determined by comparing the optical rotation data reported in the literature. [d]The reaction was performed at 50 °C.

substrates for the reaction and afforded products in good yield and high ee. However, the reaction of norbornadiene (**1g**) containing an ester functional group afforded a low isolated yield of the desired product albeit in high ee, possibly because of side reactions by the additions of copper–hydride species[11] to the conjugate ester moieties.

We then investigated the formal hydroboration of bicyclic alkenes using the same chiral ligand–copper combinations in the presence of bis(pinacolato)diboron (B_2pin_2) and MeOH instead of pinacolborane to test the feasibility of enantiodivergent catalysis. The combination of both the reagents is quite well-known to afford hydroborylated products by the borylcupration and successive protonolysis.[12] However, the protocol has not been applied to the enantioselective formal hydroboration of bicyclic alkenes.[13] We were pleased to find that the **L1**-coordinated copper complex was reactive for the borylation of bicyclic alkenes to afford products in good yields and high enantioselectivities (Scheme 1).[14] The reaction of norbornadiene produced **2a** in >99% ee, with exactly the opposite absolute configuration to that of (*R*)-**2a** obtained by the hydroboration with pinacolborane (Table 1, entries 7 and 8).[15] The other substrates were investigated, and all afforded the opposite enantiomers as the major enantiomer to those obtained in Table 2 with excellent enantioselectivities up to >99% ee. Thus, the reversal of enantioselectivity in the asymmetric hydroboration was achieved using different borylating reagents in the presence of the same copper–ligand complex. These results together establish a good example of highly enantioselective and enantiodivergent catalysis.

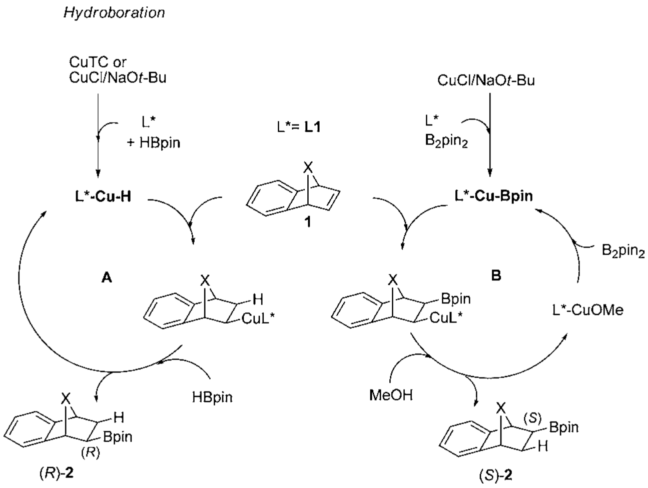
Scheme 1. Enantioselective Borylation of Bicyclic Alkenes (1) Using B_2pin_2 and MeOH



(*S*)-**2a** 74% >99% ee; (*S*)-**2b** 79% 94% ee; (*S*)-**2c** 90% >99% ee; (*S*)-**2f** 82% >99% ee; (*S*)-**2g** 42% >99% ee

In Micouin and co-workers' report,[3] the reversal of the enantioselectivity was achieved by switching the catalytic metal from rhodium to iridium. Favored Ir–B and Rh–H insertion pathways over Ir–H and Rh–B were proposed for the switch in the enantioselectivity (regioselectivity) of *meso*-hydrazines. In our study, the results could be explained by following mechanisms including catalytically active Cu–H or Cu–B species, generated *in situ* from the copper precursors with different boron reagents (Scheme 2).[12b,16] The insertion of a bicyclic alkene into either the Cu–H or Cu–B bond generates two different organocopper intermediates, and the subsequent steps such as transmetalation with pinBH (**A**-cycle) and protonolysis with MeOH (**B**-cycle) afforded both enantiomers of a chiral product.

Scheme 2. Proposed Mechanisms



In summary, we successfully developed a copper(I)-catalyzed highly enantioselective hydroboration of bicyclic alkenes under mild reaction conditions. Using pinacolborane as the hydroborating reagent, we found that the (*R,R*)-taniaphos ligand is extremely selective for the hydroboration of bicyclic alkenes including oxa- and azabicyclic alkenes with enantioselectivities up to >99%. Furthermore, copper-catalyzed enantiodivergent hydroboration with the same chiral ligand−copper precursors was demonstrated by using different boron sources based on alternative mechanistic pathways.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and characterization of products and copies of the ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This research was supported by the Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education, Science, and Technology (NRF-2013R1A1A2058160).

■ REFERENCES

(1) (a) Zanoni, G.; Castronovo, F.; Franzini, M.; Vidari, G.; Giannini, E. *Chem. Soc. Rev.* **2003**, *32*, 115−129. (b) Bartók, M. *Chem. Rev.* **2010**, *110*, 1663−1705. (c) Stymiest, J. L.; Bagutski, V.; French, R. M.; Aggarwal, V. K. *Nature* **2008**, *456*, 778−782. (d) Kim, Y. H. *Acc. Chem. Res.* **2001**, *34*, 955−962.

(2) For reviews, see: (a) Beletskaya, I.; Pelter, A. *Tetrahedron* **1997**, *53*, 4957−5026. (b) Crudden, C. M.; Edwards, D. *Eur. J. Org. Chem.* **2003**, 4695−4712. (c) Carroll, A.-M.; O'Sullivan, T. P.; Guiry, P. J. *Adv. Synth. Catal.* **2005**, *347*, 609−631.

(3) Luna, A. P.; Bonin, M.; Micouin, L.; Husson, H.-P. *J. Am. Chem. Soc.* **2002**, *124*, 12098−12099.

(4) (a) Brown, H. C.; Vara Prasad, J. V. N. *J. Am. Chem. Soc.* **1986**, *108*, 2049−2054. (b) Brown, H. C.; Vara Prasad, J. V. N.; Zaidlewicz, M. *J. Org. Chem.* **1988**, *53*, 2911−2916. (c) Brown, H. C.; Ramachandran, P. V. *J. Organomet. Chem.* **1995**, *500*, 1−19.

(5) (a) Burgess, K.; Ohlmeyer, M. J. *J. Org. Chem.* **1988**, *53*, 5179−5181. (b) Luna, A. P.; Ceschi, M.-A.; Bonin, M.; Micouin, L.; Husson, H.-P. *J. Org. Chem.* **2002**, *67*, 3522−3524. (c) Renaud, P.; Ollivier, C.; Weber, V. *J. Org. Chem.* **2003**, *68*, 5769−5772.

(6) Alexakis, A.; Polet, D.; Bournaud, C.; Bonin, M.; Micouin, L. *Tetrahedron: Asymmetry* **2005**, *16*, 3672−3675.

(7) (a) Noh, D.; Chea, H.; Ju, J.; Yun, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 6062−6064. (b) Feng, X.; Jeon, H.; Yun, J. *Angew. Chem., Int. Ed.* **2013**, *52*, 3989−3992.

(8) For the activation of copper precursors with pinacolborane in the absence of NaO*t*-Bu, see: Kim, H.; Yun, J. *Adv. Synth. Catal.* **2010**, *352*, 1881−1885.

(9) For ring-opening reactions of oxabicyclic and azabicyclic alkenes, see: (a) Bos, P. H.; Rudolph, A.; Pérez, M.; Fãnanás-Mastral, M.; Harutyunyan, S. R.; Feringa, B. L. *Chem. Commun.* **2012**, *48*, 1748−1750. (b) Millet, R.; Bernardez, T.; Palais, L.; Alexakis, A. *Tetrahedron Lett.* **2009**, *50*, 3474−3477. (c) Cabrera, S.; Arrayás, R. G.; Alonso, I.; Carretero, J. C. *J. Am. Chem. Soc.* **2005**, *127*, 17938−17947. (d) Cho, Y.-h.; Zunic, V.; Senboku, H.; Olsen, M.; Lautens, M. *J. Am. Chem. Soc.* **2006**, *128*, 6837−6846.

(10) The absolute configuration of the products **2a** and **2b** was assigned as R by comparison with the optical rotation data reported in the literature. The configuration of the other products (**2c**−**2g**) was established by analogy. See ref 4b.

(11) (a) Mahoney, W. S.; Brestensky, D. M.; Stryker, J. M. *J. Am. Chem. Soc.* **1988**, *110*, 291−293. (b) Appella, D. H.; Moritani, Y.; Shintani, R.; Ferreira, E. M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9473−9474. (c) Lipshutz, B. H.; Papa, P. *Angew. Chem., Int. Ed.* **2002**, *41*, 4580−4582. (d) Kim, H.; Yun, J. *Adv. Synth. Catal.* **2010**, *352*, 1881−1885.

(12) (a) Mun, S.; Lee, J.-E.; Yun, J. *Org. Lett.* **2006**, *8*, 4887−4889. (b) Lee, Y.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2009**, *131*, 3160−3161. (c) Sasaki, Y.; Horita, Y.; Zhong, C.; Sawamura, M.; Ito, H. *Angew. Chem., Int. Ed.* **2011**, *50*, 2778−2782.

(13) Ondrusek, B. A.; Opalka, S. M.; Hietsoi, O.; Shatruk, M.; McQuade, D. T. *Synlett* **2013**, *24*, 1211−1214.

(14) The use of CuTC as the copper precursor in the borylation resulted in low yields of products. For example, the reaction of **1b** with CuTC afforded **2b** in 60% yield under otherwise the same conditions, and only 30% conversion was observed in the absence of NaO*t*-Bu.

(15) The chiral HPLC data of both enantiomers of the compounds **2** are included in the Supporting Information.

(16) (a) Dang, L.; Lin, Z.; Marder, T. B. *Organometallics* **2008**, *27*, 4443−4454. (b) Won, J.; Noh, D.; Yun, J.; Lee, J. Y. *J. Phys. Chem. A* **2010**, *114*, 12112−12115. (c) Noh, D.; Yoon, S. K.; Won, J.; Lee, J. Y.; Yun, J. *Chem.—Asian J.* **2011**, *6*, 1967−1969.