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Copper-Catalyzed Asymmetric Borylative Ring Opening of Diazabicycles

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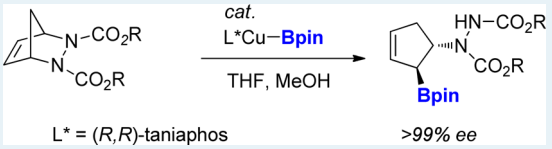
Supporting Information

ABSTRACT: Highly enantioselective, copper-catalyzed ring opening of bicyclic hydrazines using a diboron reagent was accomplished with (*R*,*R*)-taniaphos as a chiral ligand. Desymmetrization of various bicyclic hydrazines by boryl substitution afforded 3-Bpin-4-hydrazino-cyclopentene derivatives with enantioselectivity up to >99% under mild conditions. The resulting allylic boron products were utilized in further organic transformations. Kinetic resolution of a racemic bicyclic oxazine gave useful information about the relative rates of C−O and C−N bond cleavage.



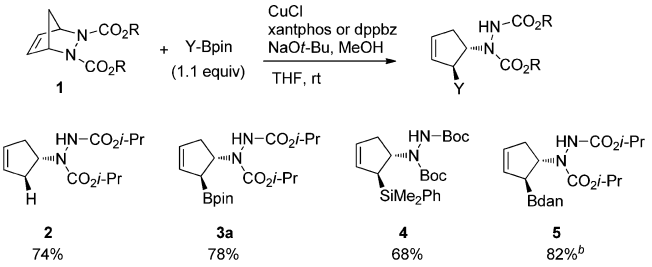
KEYWORDS: *allylboronates, asymmetric ring opening, bicyclic hydrazines, copper, enantioselectivity*

Transition-metal-catalyzed asymmetric ring opening reactions are powerful methods for the construction of chiral organic molecules from cyclic compounds.[1] Symmetric heterobicyclic alkenes are particularly attractive substrates for the asymmetric ring-opening reaction because they can easily produce enantioenriched cyclic compounds with multiple stereogenic centers by allylic fragmentation or carbon−heteroatom cleavage. Palladium[2] and rhodium[3] catalysts have been predominantly used for the ring opening of meso-heterobicyclic alkenes such as oxabicyclic alkenes, azabicyclic alkenes, and diazabicycles, with various nucleophiles. Desymmetrization of such heterobicyclic alkenes by copper catalysts has gradually advanced in recent years as well.[4,5] However, the scope of nucleophiles available with the copper catalysis has been limited compared with the Pd and Rh catalyses: only strong organometallic reagents such as dialkyl zinc,[4b,c] trialkylaluminum,[4d−f] Grignard reagents,[4g−i] and alkyllithium reagents[4j] have been reported as reactive nucleophiles, and no uses of mild heteroatom nucleophiles have been reported.

Interest in the formation of carbon−heteroatom bonds such as C−B, C−O, and C−N has grown significantly for years.[6] Especially, copper-catalyzed boron addition has been extensively developed[7,8] because of the low cost of copper metal and the applicability of C−B bonds to various functional groups such as C−C, C−O, and C−N bonds.[9] Recently, we reported a highly enantioselective Cu-catalyzed hydroboration of bicyclic alkenes with pinacolborane.[10] As a part of our ongoing research to broaden our insight into diverse bicyclic alkenes, we investigated the addition of noncarbon nucleophiles into diazabicycles.

When bicyclic hydrazine **1** was subjected to our previous hydroboration procedure using pinacolborane,[10] ring opening surprisingly occurred instead of addition, thus yielding **2** (Scheme 1). Although the copper−hydride nucleophile (Cu−H) afforded the ring-opened product **2** in good yield, this nucleophile was not qualified for asymmetric study because the product contained a symmetry plane. Therefore, other possible heteronucleophiles were examined for reactivity with the racemic ligands bis(diphenylphosphino)-9,9-dimethylxanthene (xantphos) or 1,2-bis(diphenylphosphino)benzene (dppbz). The diboron reagent B_2pin_2 efficiently produced the ring-opened product **3a** in good isolated yield. A silicon−boron (pinB−$SiMe_2$Ph) reagent was effective in producing the desired product **4** having the silicon moiety, but the ring-opened product **5** of a heterodiboron reagent (pinB−Bdan) (dan = 1,8-diaminonaphthyl) was not stable enough to be isolated by column chromatography, and a high temperature (80 °C) was required for full conversion. Because no examples of highly enantioselective copper-catalyzed ring opening of diazabicycles by mild nucleophiles have been reported previously,[11] we decided to examine the enantioselective ring opening of diazabicycles with B_2pin_2 by screening various chiral bisphosphine ligands (Table 1; Figure 1).

Scheme 1. Ring Opening of Diazabicycles with Non-Carbon Nucleophiles[a]



[a]See the Supporting Information for detailed reaction conditions. [b]NMR yield.

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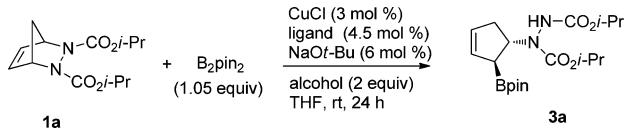
Table 1. Ligand Screening Conditions



1a 3a

entry	catalyst	ligand	alcohol	conv (%)[a]	yield (%)[b]	ee (%)[c]
1	–	–	MeOH	9	–[d]	–
2	CuCl	xantphos	none	20	–[d]	–
3	CuCl	–	MeOH	100	65	–
4	CuCl	**L1**	MeOH	100	60	37
5	CuCl	**L2**	MeOH	73	–[d]	46
6	CuCl	**L3**	MeOH	100	44	62
7	CuCl	**L4**	MeOH	100	85	5
8	CuCl	**L5**	MeOH	100	62	32
9	CuCl	**L6**	MeOH	100	61	62
10	CuCl	**L7**	MeOH	80	–[d]	>99
11[e]	CuCl	**L7**	MeOH	100	83	97
12	CuCl	**L7**	*i*-PrOH	50	–[d]	98

[a]Determined by GC analysis. [b]Isolated yield. [c]Determined by chiral HPLC analysis with its derivatives; see the Supporting Information for details. [d]Not isolated. [e]10 mol % NaO*t*-Bu was used.

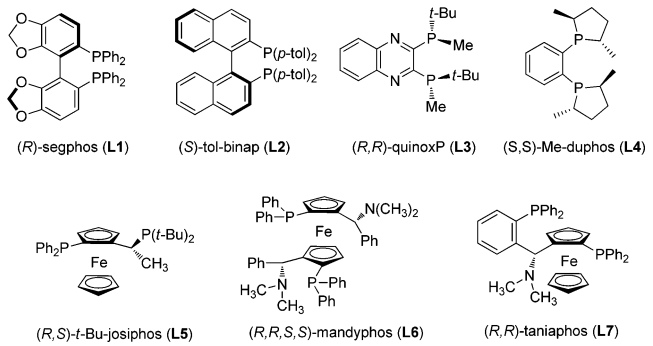
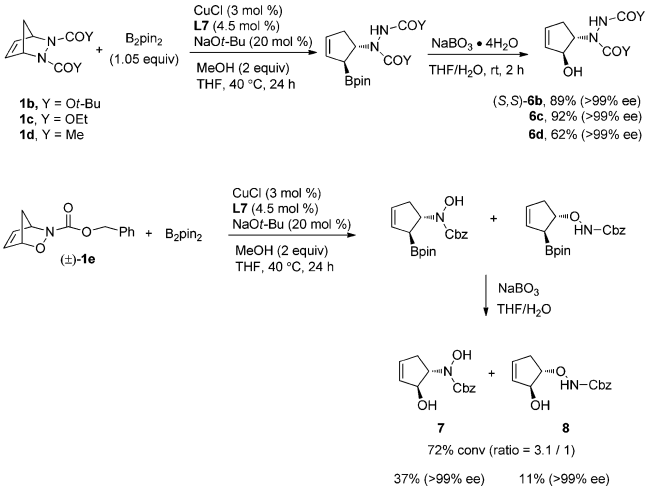


Figure 1. Chiral ligands.

Initially, we assessed the extent of background reaction in the desymmetrization reaction of **1a**. Both copper catalyst and MeOH are essential reagents for the ring opening (entries 1 and 2), but the reaction reached full conversion without the ligand (entry 3). Due to this severe background reaction occurring in the absence of ligand, we used the 1.5:1 ratio of ligand to copper for screening to minimize the possible deleterious effect of the nonselective background reaction on the enantioselectivity. Next, we focused on screening a series of copper–chiral phosphine complexes for the reaction. Reactions employing the C_2 symmetric atropisomeric bisphosphine ligands, (*R*)-segphos (**L1**), and (*S*)-tol-binap (**L2**) displayed moderate to good reactivity but poor enantioselectivity (entries 4 and 5). **L3**–**L6** showed good reactivity but with disappointing enantioselectivities (entries 6–9). Lastly, (*R,R*)-taniaphos (**L7**) led the reaction to only 80% conversion under the screening conditions but with surprisingly excellent enantioselectivity (entry 10). Further optimization by increasing the amount of base to 10 mol % led to full conversion while maintaining high enantioselectivity (entry 11). Changing the alcohol additive from methanol to isopropanol, however, resulted in low reactivity (entry 12).

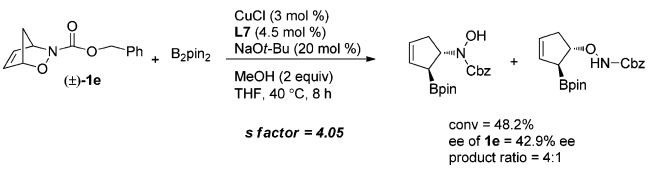
We chose CuCl and taniaphos as the optimal catalyst–ligand combination for the asymmetric ring opening of bicyclic hydrazines **1b**–**1d** with B_2pin_2 (Scheme 2); compounds **6b**, **6c**, and **6d** were obtained in good yield and with excellent enantioselectivity after oxidation. Desymmetrization of racemic substrate **1e** was also investigated using the copper–**L7** catalyst. Interestingly, both C–O bond cleavage product **7** and C–N bond cleavage product **8** were produced under our reaction conditions, suggesting the occurrence of allylic fragmentation of the substrate by the Cu–Bpin catalyst. The reaction significantly slowed over time, and the product ratio of **7** and **8** was 3:1 at 72% conversion. Both these products were isolated, and surprisingly their ee's were both determined to be >99%. The results indicate that the **L7**–copper catalyst perfectly differentiated one C=C face of the bicycle structure from the other.

Scheme 2. Ring Opening of Various Bicyclic Hydrazines



With these results in hand, we tried a kinetic resolution of **1e** to measure the relative speed of the C–O and C–N bond cleavages (Scheme 3). The reaction was stopped at 48% conversion and gave 43% ee of the recovered starting material, from which the *s* factor was calculated to be about 4.[12] This indicates that the C–O bond cleavage is approximately 4 times as fast as the C–N bond cleavage in the substrate **1e**.

Scheme 3. Kinetic Resolution of 1e



To demonstrate the synthetic utility of a ring-opened product, we carried out the addition of boronic ester **3a** to various aldehydes (Scheme 4).[13,14] **9a** was obtained by the reaction with benzaldehyde, in good yield and without much loss of enantioselectivity. Electron-rich or -deficient aryl aldehydes and alkyl aldehydes also afforded the corresponding addition products **9b**–**9e** in moderate and good yields. The formation of a mixture of diastereomers was only observed in the case of valeraldehyde, affording **9d**.

The Bpin moiety of **3b** was successfully converted to BF_3K salt **10** in moderate isolated yield.[15] In addition, conversion of **3b** into **11** was accomplished by a series of steps as reported in the literature (Scheme 5).[16] The absolute configuration and

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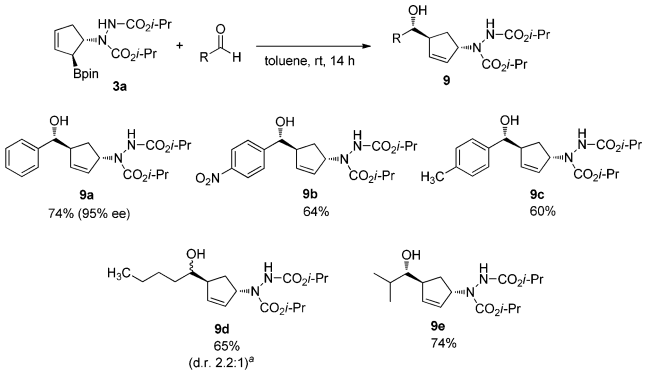
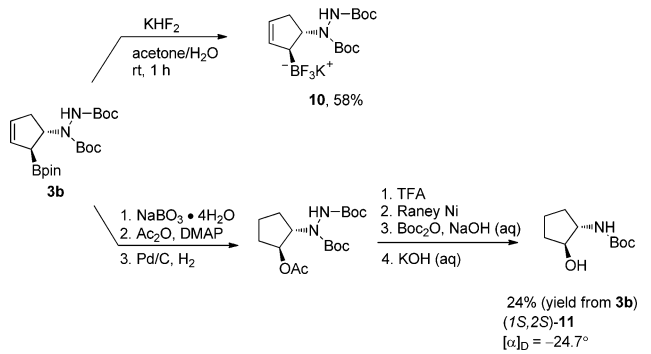
Scheme 4. Addition of 3a into Various Aldehydes[a]



[a]Diastereomeric ratio determined by ^{1}H NMR analysis of a crude reaction mixture.

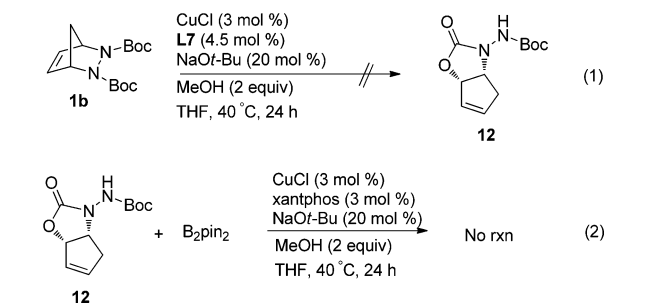
relative stereoselectivity of **3b** was confirmed by comparing the optical rotation value of **11** with a literature value.[17]

Scheme 5. Organic Reactions of 3-Bpin-4-Hydrazino Cyclopentene (3b)

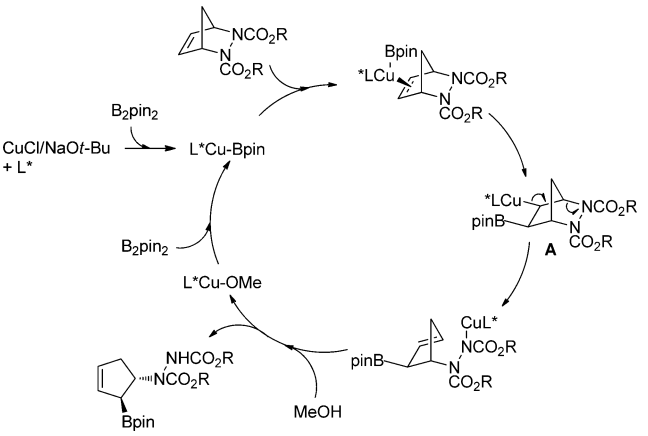


Lewis acid-catalyzed ring-rearrangement of bicyclic hydrazines such as **1b** has been previously reported by Pineschi[18a] and Lautens[18b] to form **12** using $Cu(OTf)_2$ as a Lewis acid. To verify whether a similar ring opening reaction takes place under our catalytic conditions, we examined the asymmetric ring opening of **1b** in the absence of B_2pin_2. The desired intermediate **12** was not produced (Scheme 6, (1)). Furthermore, additional ring opening reaction of **12**, which was prepared by following the previous reports,[18] did not occur under our catalytic conditions (Scheme 6, (2)), eliminating the possibility of prerearrangement of hydrazine and its further ring opening by Cu−B catalyst. Therefore, we propose a plausible catalytic cycle for the enantioselective ring opening of diazabicycles, as given in Scheme 7.

Scheme 6. Ring-Opening Study



Scheme 7. Possible Reaction Pathway



The active ligand-coordinated Cu−Bpin species[19] is generated in situ from copper precursors and B_2pin_2, insertion of a diazabicycle into the Cu−B bond generates intermediate **A**, and subsequent anti-β-elimination[11d,e] leads to the ring-opened 3-Bpin-4-hydrazino cyclopentene compound. Lastly, the active catalyst is regenerated by reaction with B_2pin_2.

In summary, we developed a copper(I)-catalyzed, highly enantioselective ring opening of bicyclic hydrazines with a mild boron nucleophile. We found that the (*R*,*R*)-taniaphos ligand is extremely enantioselective for the asymmetric ring opening, giving optimized ee greater than 99% with B_2pin_2 as the nucleophile. Moreover, kinetic resolution of a bicyclic oxazine gave information about the relative cleavage speeds of C−O versus C−N.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.6b02208.

Experimental procedures and characterization of products and copies of the ^{1}H and ^{13}C spectra (PDF)

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Notes

The authors declare no competing financial interest.

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