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Copper-Catalyzed Enantioselective Formal Hydroamination of Oxa- and Azabicyclic Alkenes with Hydrosilanes and Hydroxylamines

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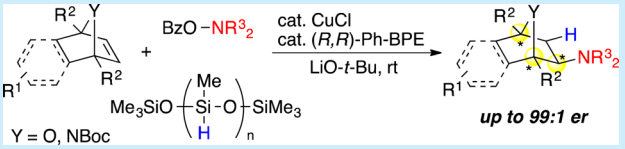
Supporting Information

ABSTRACT: A CuCl/(*R*,*R*)-Ph-BPE-catalyzed enantioselective formal hydroamination of oxa- and azabicyclic alkenes with polymethylhydrosiloxane (PMHS) and *O*-benzoylhydroxylamines has been developed. The efficient and stereoselective net addition of hydrogen and nitrogen atoms provides the corresponding optically active oxa- and azanorbornenyl- and -norbornanylamines in good yields and good enantiomeric ratios.

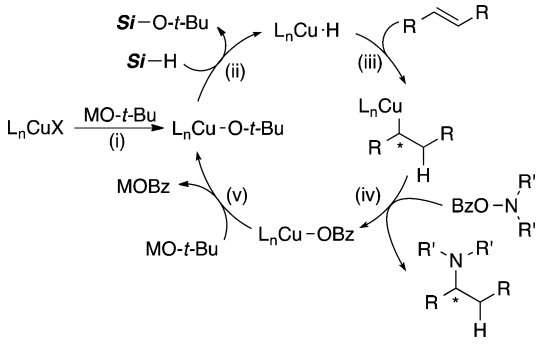


The catalytic net addition of hydrogen and nitrogen atoms, that is, the hydroamination reaction of C−C unsaturated molecules, is now one of the most active research areas in the field of transition-metal catalysis since it can readily transform relatively simple starting materials into nitrogen-containing organic molecules of high value in medicinal and material chemistry.[1] Although a variety of transition-metal catalysts have been developed for the intermolecular hydroamination,[2,3] there are still some limitations. In particular, the asymmetric catalysis is largely restricted in scope and selectivity. In this context, our group[4a] and Buchwald[4b] independently have introduced an umpolung, electrophilic amination strategy[5,6] and succeeded in the development of copper-catalyzed enantioselective formal hydroamination of the challenging β-substituted styrenes with hydrosilanes and hydroxylamines. The postulated catalytic cycle consists of (i) initial generation of L_nCuO-*t*-Bu complex by the off-cycle salt metathesis of L_nCuX with MO-*t*-Bu, (ii) formation of L_nCu−H species by the action of the hydrosilanes,[7] (iii) insertion of alkenes into the Cu−H bond,[8] (iv) electrophilic amination with the hydroxylamines,[5,6] and (v) catalyst regeneration via ligand exchange between L_nCuOBz and MO-*t*-Bu.

The enantioselectivity-determining step is believed to be the insertion step (iii), and subsequent stereoretentive[5i,6f] C−N bond formation delivers the desired chiral amines (Scheme 1). In the course of extension studies, we focused on the oxa- and azabenzonorbornadienes as the next unsaturated components because they are an inaccessible substrate class under the precedented asymmetric hydroamination catalysis, to the best of our knowledge.[9] Additional motivation is that the expected products, oxa- and azabenzonorbornenylamines, are potential dopaminergic and adrenergic ligands as well as inhibitors for the neutral nicotinic acetylcholine receptor and that they have been synthesized only in a racemic form via Hg(II)-mediated azamercurations of benzonorbornadienes.[10]

Here, we report a CuCl/1,2-bis[(2*R*,5*R*)-2,5-diphenylphospholano]ethane ((*R*,*R*)-Ph-BPE) catalyst system for the formal hydroamination of oxa- and azabicyclic alkenes with polymethylhydrosiloxane (PMHS) and *O*-benzoylhydroxylamines.

Scheme 1. Proposed Catalytic Cycle for Formal Hydroamination of Alkenes Based on Umpolung, Electrophilic Amination Strategy



The asymmetric copper catalysis can provide a catalytic and enantioselective approach to the above amines of interest in medicinal chemistry.

We initially tested the hydroamination of oxabenzonorbornadiene **1a** with morpholino benzoate (**2a**) under our previous racemic conditions ($Cu(OAc)_2$/1,2-bis[bis[3,5-di(trifluoromethyl)phenyl]phosphino]benzene (CF_3-dppbz), LiO-*t*-Bu, and PMHS in $ClCH_2CH_2Cl$)[4a] to check whether our postulated formal hydroamination pathway could be operative toward the benzonorbornadiene unsaturated systems. To our delight, the desired *exo*-hydroaminated product **3aa** was obtained in 89% yield (Table 1, entry 1). Conceivable ring-opening byproducts[11] were not detected at all. With this promising result in hand, we next investigated asymmetric catalysts based on optically active bisphosphines in conjunction with a CuCl salt. 1,2-Bisphosphinoarene systems including DuPhos-type ligands and (*R*,*R*)-QuinoxP* were not promising (entries 2−5). While the ethane-tethered (*S*,*S*)-Chiraphos and (*S*,*S*,*R*,*R*)-Tangphos also gave unsatisfactory outcomes (entries

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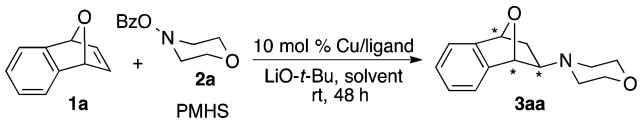
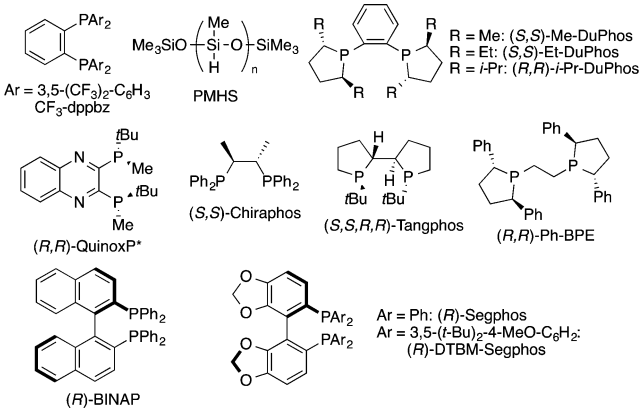
Table 1. Optimization Studies for Copper-Catalyzed Enantioselective Formal Hydroamination of Oxabenzonorbornadiene 1a with PMHS and Morpholino Benzoate (2a)[a]



entry	Cu/ligand	solvent	3aa, % yield, er[b]
1[c]	$Cu(OAc)_2/CF_3$-dppbz	$ClCH_2CH_2Cl$	89, –
2	CuCl/(*S,S*)-Me-DuPhos	THF	90, 70:30
3	CuCl/(*S,S*)-Et-DuPhos	THF	99, 71:29
4	CuCl/(*R,R*)-*i*-Pr-DuPhos	THF	95, 79:21
5	CuCl/(*R,R*)-QuinoxP*	THF	86, 30:70
6	CuCl/(*S,S*)-Chiraphos	THF	99, 57:43
7	CuCl/(*S,S,R,R*)-Tangphos	THF	91, 39:61
8	CuCl/(*R,R*)-Ph-BPE	THF	96, 97:3
9	CuCl/(*R*)-BINAP	THF	82, 60:40
10	CuCl/(*R*)-Segphos	THF	87, 43:57
11	CuCl/(*R*)-DTBM-Segphos	THF	61, 26:74
12[d]	$Cu(OAc)_2$/(*R,R*)-Ph-BPE	THF	12, n.d.[e]
13[d]	CuCl/(*R,R*)-Ph-BPE	THF	trace, n.d.[e]
14	CuCl/(*R,R*)-Ph-BPE	CPME	99, 89:11
15	CuCl/(*R,R*)-Ph-BPE	DME	81, 99:1
16	CuCl/(*R,R*)-Ph-BPE	1,4-dioxane	97, 81:19

[a]Reaction conditions: Cu (0.025 mmol), ligand (0.025 mmol), LiO-*t*-Bu (1.0 mmol), **1a** (0.50 mmol), **2a** (0.25 mmol), PMHS (0.75 mmol based on Si–H), solvent (1.5 mL), rt, 48 h, N_2. [b]Determined by chiral HPLC analysis on a chiral stationary phase. [c]With 0.38 mmol of **1a**. [d]Without LiO-*t*-Bu. [e]n.d. = not determined.

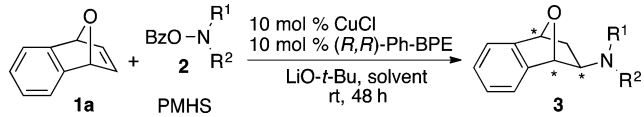


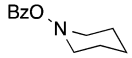
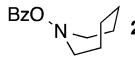
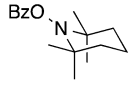
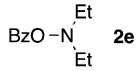
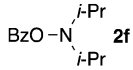
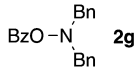
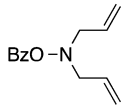
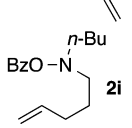
6 and 7), we obtained a high yield (96%) and good enantioselectivity (97:3 er) with (*R,R*)-Ph-BPE, which has more bulky Ph substituents around the phosphorus atoms to create suitable chiral environments (entry 8). On the other hand, common (*R*)-BINAP and (*R*)-Segphos derivatives did not induce the enantioselectivity more than (*R,R*)-Ph-BPE (entries 9–11). During optimization studies, Buchwald and co-workers reported a relevant catalytic asymmetric formal hydroamination of styrenes on the basis of a similar concept.[4b] In their system, the reaction proceeded well even in the absence of LiO-*t*-Bu by using $Cu(OAc)_2$ as the catalyst precursor. However, the present formal hydroamination of **1a** required LiO-*t*-Bu for good conversion (entry 12). Also under the CuCl/(*R,R*)-Ph-BPE-promoted conditions, LiO-*t*-Bu was necessary (entry 13). Among other solvents tested, CPME, DME, and 1,4-dioxane also worked well (entries 14–16), but the highest er (99:1) was obtained in DME (entry 15).

With the optimized conditions in hand, we conducted the enantioselective formal hydroamination of **1a** with an array of *O*-benzoylhydroxylamines **2** (Table 2). Six-membered piperidine and seven-membered azepane coupled with **1a** effectively to form the corresponding aminated oxabenzonorbornenes **3ab** and **3ac** in good yields and good enantiomeric ratios (entries 1 and 2). Also, much more bulky 2,2,6,6-tetramethylpiperidine **2d** was a suitable aminating reagent (entry 3). On the other hand, the asymmetric copper catalysis accommodated acyclic amines **2e–h** that bear *N,N*-diethyl, *N,N*-diisopropyl, *N,N*-dibenzyl, and *N,N*-diallyl substituents (entries 4–7). In the latter two cases, the selective deprotection of benzyl and allyl groups can provide an opportunity for further manipulations.[12] The reaction with **2i** containing a pendant olefin moiety afforded the usual hydroaminated product **3ai** exclusively, and no pyrrolidine derivative arising from a 5-*exo* cyclization was detected, indicating that an aminyl radical pathway was less likely (entry 8).[13] Notably, DME was uniquely effective for the reaction with **2a** (Table 1, entry 15). In general, CPME showed better performances in terms of yields and enantiomeric ratios (Table 2, entries 1–6), while we observed a trend that THF was beneficial for the hydroxylamines with coordinating olefin moieties (Table 2, entries 7 and 8).[14] However, the exact reason was not clear at this stage.

The catalytic enantioselective formal hydroamination could be applied to various oxabenzonorbornadienes. Representative examples were shown in Scheme 2. Also in these cases, the best

Table 2. Copper-Catalyzed Enantioselective Formal Hydroamination of Oxabenzonorbornadiene 1a with Various *O*-Benzoylhydroxylamines 2[a]



entry	2	solvent	3, %yield, er[b]
1	 **2b**	CPME	**3ab**, 99, 88:12
2	 **2c**	CPME	**3ac**, 99, 84:16
3	 **2d**	CPME	**3ad**, 97, 88:12
4	 **2e**	CPME	**3ae**, 99, 94:6
5	 **2f**	CPME	**3af**, 98, 85:15
6	 **2g**	CPME	**3ag**, 88, 93:7
7	 **2h**	THF	**3ah**, 85, 78:22
8	 **2i**	THF	**3ai**, 96, 89:11

[a]Reaction conditions: CuCl (0.025 mmol), (*R,R*)-Ph-BPE (0.025 mmol), LiO-*t*-Bu (1.0 mmol), **1a** (0.50 mmol), **2** (0.25 mmol), PMHS (0.75 mmol based on Si–H), solvent (1.5 mL), rt, 48 h, N_2. [b]Determined by chiral HPLC analysis on a chiral stationary phase.

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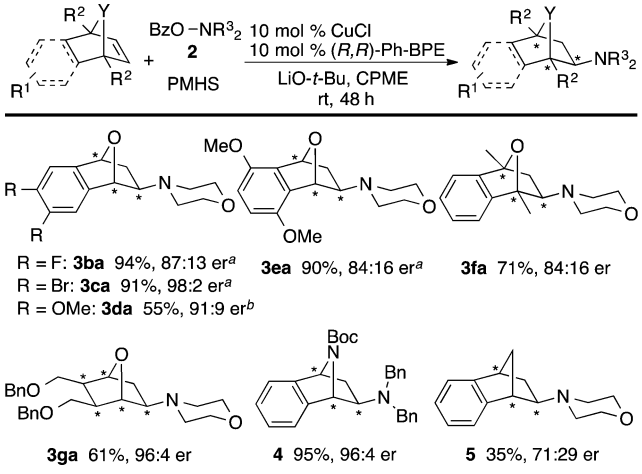
Scheme 2. Copper-Catalyzed Enantioselective Formal Hydroamination of Various Bicyclic Alkenes with *O*-Benzoylhydroxylamines 2



[a]InDME. [b]In CPME/DCE (2:1, v/v).

solvent was somewhat dependent on the structural and electronic natures of the norbornadiene substrates employed. Electronically diverse functions including fluoro, bromo, and methoxy groups at the 6 and 7 positions were tolerated, and **3ba**−**da** were formed in 87:13−98:2 enantiomeric ratios. In the case of **3ca**, the resultant aryl-Br moieties can be useful synthetic handles for further transformations by using palladium catalysts. Notably, a CPME/$ClCH_2CH_2Cl$ mixed solvent was essential for obtaining **3da** with acceptable yield and enantiomeric ratio, due to its poor solubility in CPME. The substituents at the 5 and 8 positions as well as at the 1 and 4 positions did not interfere with the reaction, providing **3ea** and **3fa** in the same 84:16 er. Moreover, nonbenzene-fused oxabicyclic alkene also could be employed, and the optically active **3ga** was formed in 61% yield and 96:4 er. We then tested nitrogen- and methylene-bridged analogues. Gratifyingly, the azabenzonorbornadiene underwent the stereoselective formal hydroamination smoothly to furnish the chiral diamine **4** in 95% yield and 96:4 er. However, the simple benzonorbornadiene resulted in lower yield and enantioselectivity (**5**). Thus, heteroatoms in the bridged position were found to play important roles in view of both reactivity and stereoselectivity.[15] The absolute configuration of **3ca** was determined to be 1*S*,2*R*,4*S* by X-ray analysis, and those of others were tentatively assigned by analogy (see the Supporting Information for details).

In conclusion, we have developed asymmetric copper catalysis for the enantioselective formal hydroamination of oxa- and azabicyclic alkenes with PMHS and *O*-benzoylhydroxylamines. The umpolung, electrophilic amination strategy allows common and less expensive copper salts[16] to be promising catalysts for unprecedented enantioselective hydroamination at room temperature. The optically active amines obtained here are of potential interest in pharmaceutical and medicinal chemistry. Further studies will seek to uncover the detailed stereochemical course and develop related enantioselective amination catalysis based on the electrophilic amination.

■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures and characterization data of compounds. 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.

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