JOC The Journal of Organic Chemistry

Featured Article

Copper-Catalyzed Regioselective Ring-Opening Hydroamination of Methylenecyclopropanes

Daiki Nishikawa, Ryosuke Sakae, Yuya Miki, Koji Hirano, and Masahiro Miura

J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.6b02483 • Publication Date (Web): 02 Dec 2016

Just Accepted

ACS Publications

The Journal of Organic Chemistry is published by the American Chemical Society.
1155 Sixteenth Street N.W., Washington, DC 20036

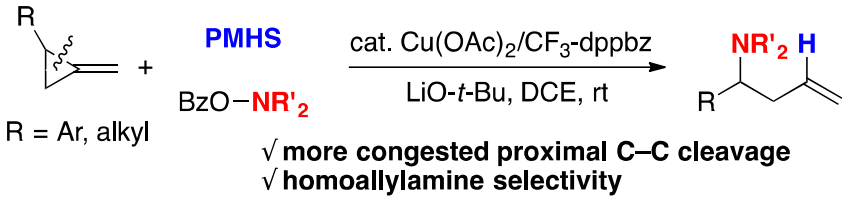
Copper-Catalyzed Regioselective Ring-Opening Hydroamination of Methylenecyclopropanes

Daiki Nishikawa, Ryosuke Sakae, Yuya Miki, Koji Hirano, and Masahiro Miura**

Department of Applied Chemistry, Graduate School of Engineering, Osaka University, Suita, Osaka 565-0871, Japan

RECEIVED DATE (to be automatically inserted after your manuscript is accepted if required according to the journal that you are submitting your paper to)

k_hirano@chem.eng.osaka-u.ac.jp; miura@chem.eng.osaka-u.ac.jp



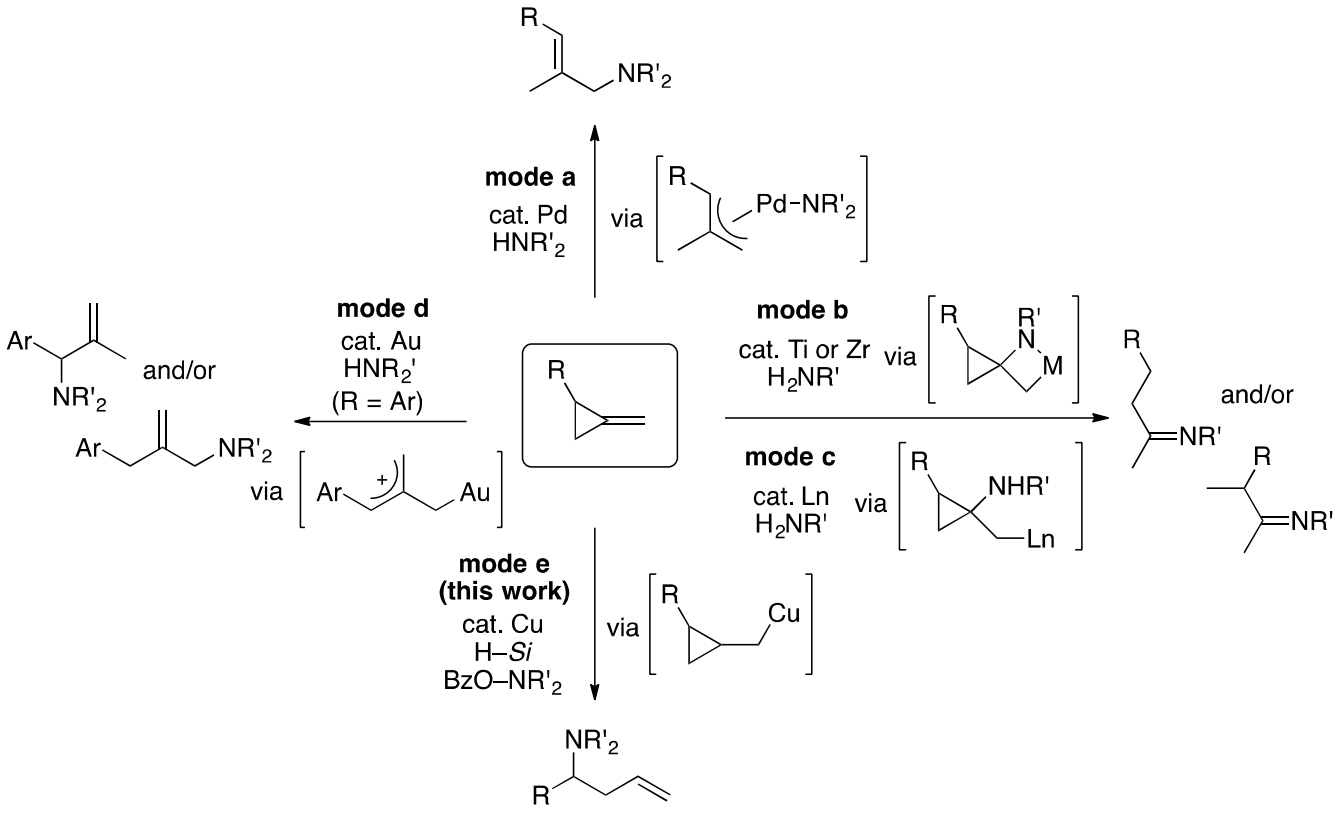
A copper-catalyzed ring-opening hydroamination of methylenecyclopropanes with polymethylhydrosiloxane (PMHS) and *O*-benzoylhydroxylamines has been developed. The cyclopropane C–C bond cleavage occurs selectively at the more congested proximal position, and the corresponding homoallylamines are obtained in good to excellent yields. The umpolung electrophilic amination strategy with the hydroxylamine derivatives can provide a new reaction mode of methylenecyclopropanes in the catalytic hydroamination reaction.

Introduction

Methylenecyclopropanes (MCPs) are useful C4 building blocks in synthetic organic chemistry because of their uniquely high reactivity associated with the large ring strain.[1] Therefore, there are many reports of synthetic applications with use of MCPs, particularly, transition-metal-catalyzed coupling reactions with various nucleophiles and π components.[2] Among them, the catalytic ring-opening hydroamination can provide a unique approach to alkylamines of high value in fine chemical industries. To date, three reaction modes of MCPs have been reported (Scheme 1). In 1998, Yamamoto developed a palladium-catalyzed ring-opening hydroamination of MCPs with secondary amines and imides (mode a).[3] The cyclopropane ring cleavage occurs at the distal position, and subsequent isomerization forms a π-allylpalladium intermediate, thus leading to the corresponding allylamine products. Afterward, Shi reported a similar palladium catalysis with sulfonamide nitrogen nucleophiles.[4] Titanium and zirconium amide complexes are also known to catalyze the ring-opening hydroamination of MCPs with primary amines, in which a unique azametallacyclobutane intermediate is generated and the corresponding imines are finally obtained (mode b).[5] The regioselectivity in the ring-opening step is highly dependent on the metal center: the titanium catalyst delivers the linear imines as the major products while the branched isomers are preferably formed under the zirconium catalysis. Organolanthanide catalysts also promoted the formation of the same imines from MCPs and primary amines but through the completely different intermediates (mode c).[6] Additionally, a gold-catalyzed ring-opening process has been recently reported by Widenhoefer (mode d).[7] In this case, the reactivity of MCPs is controlled by the substituent on the cyclopropane ring: only when R is an aryl group, the gold-promoted ring-opening reaction proceeds to form the allylamine derivative. On the other hand, a 2-alkyl-substituent on methylenecyclopropane leads to the ring-retaining cyclopropylmethylamine selectively. Subsequent computational studies have suggested an allyl cation intermediate in the ring-opening hydroamination.[8]

Meanwhile, our research group[9] and Buchwald group[10] recently focused on the unique electrophilic nature of hydroxylamine derivatives[11] and independently developed the copper-catalyzed formal hydroamination reaction of various alkenes with hydrosilanes and hydroxylamines. In these reactions, the silanes and the amines work as the nucleophilic hydride and electrophilic nitrogen functions, respectively, and the corresponding hydroaminated products are produced via a completely distinct mechanism from that of the conventional hydroamination reactions with simple NH compounds.[12] During our continuous interest in the umpolung electrophilic amination-enabled hydroamination of alkenes, we then paid our attention into MCPs.[13] Herein, we report a copper-catalyzed highly regioselective ring-opening hydroamination of 2-substituted 1-methylenecyclopropanes with a hydrosilane such as polymethylhydrosiloxane (PMHS) and *O*-benzoylhydroxylamines (mode e): the cyclopropanes undergo ring-opening reaction exclusively at the more congested proximal position, and the corresponding homoallylamines are produced in good to excellent yields. To the best of our knowledge, this is the first example of the homoallylamine product selectivity in the catalytic ring-opening hydroamination of MCPs.

Scheme 1. Reaction Modes of Methylenecyclopropanes in Catalytic Ring-Opening Hydroamination

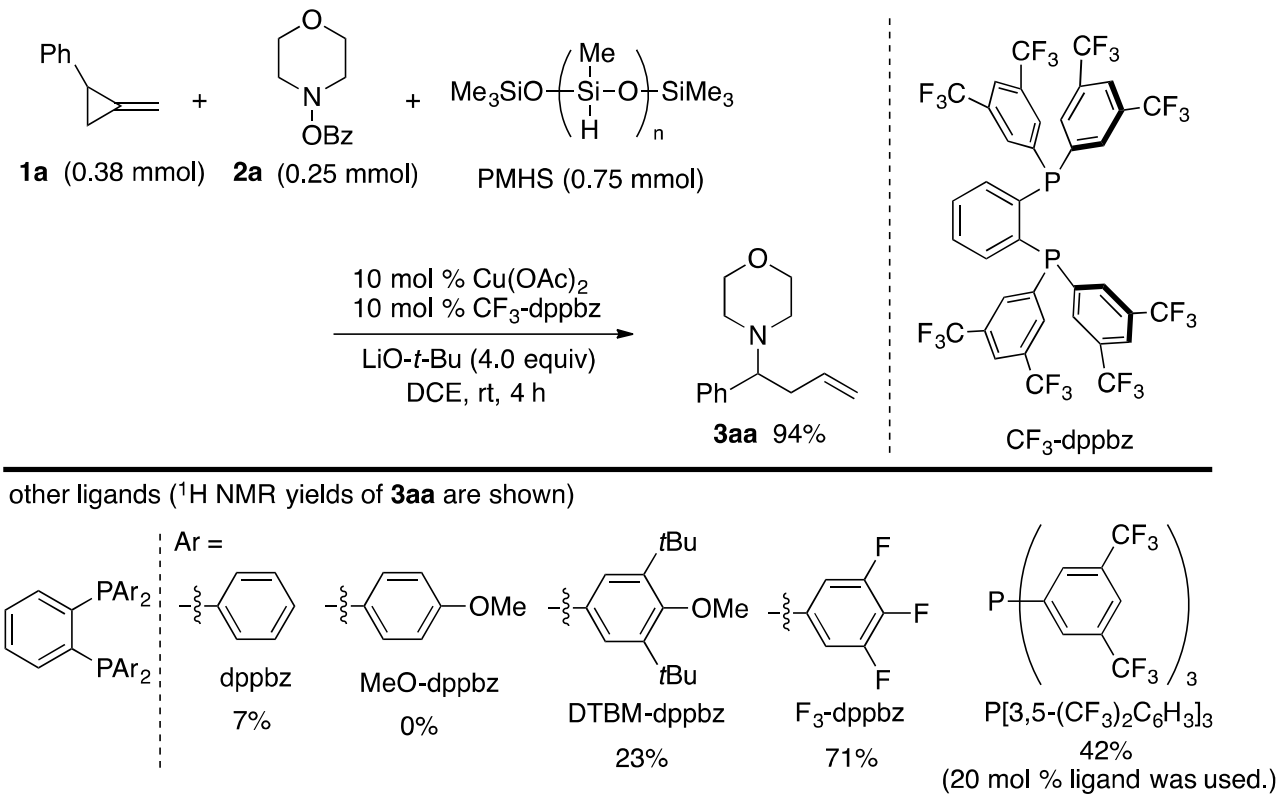


Results and Discussion

On the basis of our previous work on the formal alkene hydroamination,[8] we chose 2-phenyl-1-methylenecyclopropane (**1a**; 0.38 mmol), morpholino benzoate (**2a**; 0.25 mmol), and polymethylhydrosiloxane (PMHS; 0.75 mmol based on the Si-H moiety) as model substrates and started the optimization studies by screening a number of phosphorous ligands in the presence of a $Cu(OAc)_2$ catalyst (10 mol %) and a LiO-*t*-Bu base (4.0 equiv). Pleasingly, we found that a $Cu(OAc)_2/CF_3$-dppbz (dppbz = 1,2-bis(diphenylphosphino)benzene) catalyst system promoted the ring-opening hydroamination smoothly at room temperature in DCE, and the corresponding homoallylamine **3aa** was obtained in 94% yield (Scheme 2). Notably, the alkylamine **3aa** could be easily isolated by the simple acid/base extraction without chromatographic purification (see the Experimental Section for details). The remarkable ligand effects were observed: the parent dppbz and

electron-rich MeO-dppbz showed the sluggish reactivity. On the other hand, the bulky DTBM-dppbz and relatively electron-deficient F_3-dppbz gave the product in moderate yields. The use of 20 mol % (to Cu) of the monodentate variant of CF_3-dppbz, namely $P[3,5\text{-}(CF_3)_2C_6H_3]_3$, also promoted the reaction to some extent. On the basis of the above phenomena, the rigid chelating nature as well as steric bulkiness and electron deficiency of CF_3-dppbz could be all essential for the high reaction efficiency. Additionally, as far as we tested, no other regio- and constitutional isomers of **3aa** were detected.

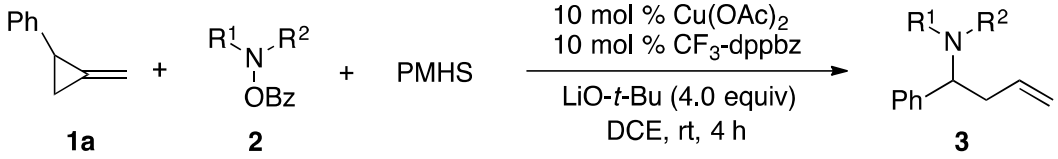
Scheme 2. Optimal Conditions for Copper-Catalyzed Regioselective Ring-Opening Hydroamination of Methylenecyclopropane 1a with Hydroxylamine 2a and Remarkable Ligand Effects



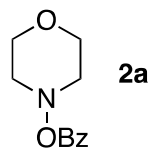
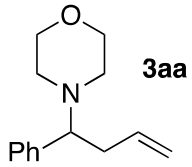
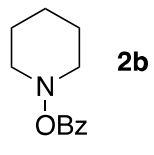
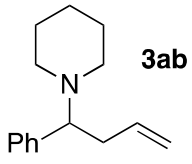
With the optimal conditions in hand, we initially investigated the scope of the hydroxylamine derivatives **2** (Table 1). In addition to the morpholine **2a**, the copper catalyst accommodated other

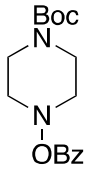
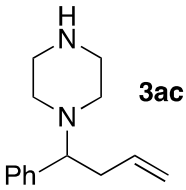
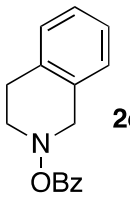
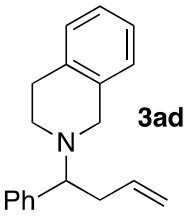
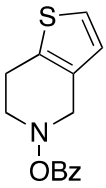
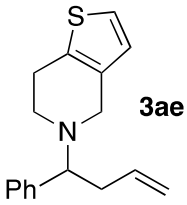
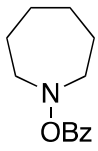
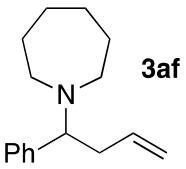
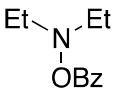
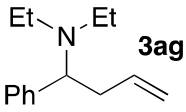
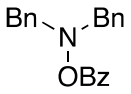
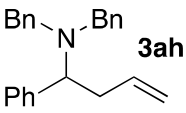
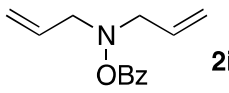
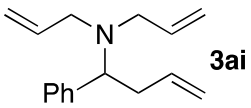
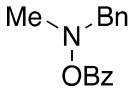
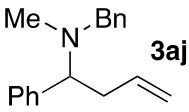
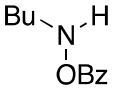
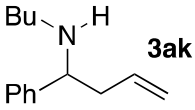
six-membered cyclic amines including piperidine **2b** and *N*-Boc piperazine **2c** (entries 2 and 3). In the latter case, the Boc protection was spontaneously removed in the acid/base extraction step to form the NH-free piperazine **3ac**. The bicyclic tetrahydroisoquinoline **2d**, thienopiperidine **2e**, and seven-membered azepane **2f** could also be employed, and the corresponding homoallylamines **3ad**–**3af** in good yields (entries 4–6). Additionally, the acyclic amines coupled with the methylenecyclopropane **1a** without any difficulties: *N,N*-diethyl-, *N,N*-dibenzyl-, *N,N*-diallyl-, and *N*-benzyl-*N*-methylamines **2g**–**2j** were well tolerated under the standard reaction conditions (entries 7–10). Particularly, the benzyl and allyl moieties in **3ah**–**3aj** can be easily deprotected under appropriate conditions[14] to furnish the NH_2 amines, which are useful synthetic handles for further manipulations. Particularly notable is the successful ring-opening hydroamination with the somewhat challenging secondary hydroxylamine **2k** (entry 11). Again, each of the products was readily obtained in high purity form by the simple acid/base extraction technique. Moreover, regardless of the steric and electronic nature of the hydroxylamines, the homoallylamines **3** were exclusively formed.

Table 1. Copper-Catalyzed Regioselective Ring-Opening Hydroamination of 2-Phenyl-1-methylenecyclopropane (1) with Various Hydroxylamines 2[a]



1a **2** **3**

entry	**2**	**3**	yield (%)
1	 **2a**	 **3aa**	94
2	 **2b**	 **3ab**	99

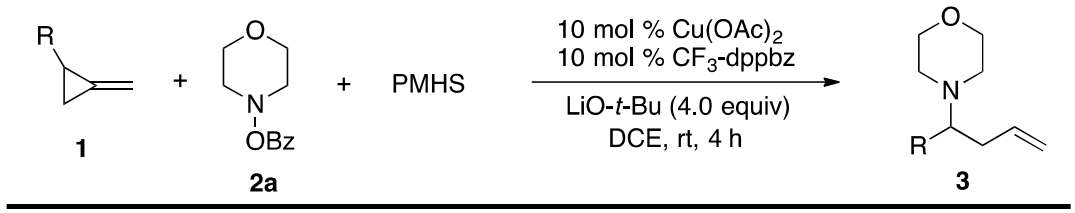
3[b]		**2c**		**3ac**	66
4		**2d**		**3ad**	81
5		**2e**		**3ae**	89
6		**2f**		**3af**	88
7		**2g**		**3ag**	53
8		**2h**		**3ah**	79
9		**2i**		**3ai**	95
10		**2j**		**3aj**	91
11		**2k**		**3ak**	63

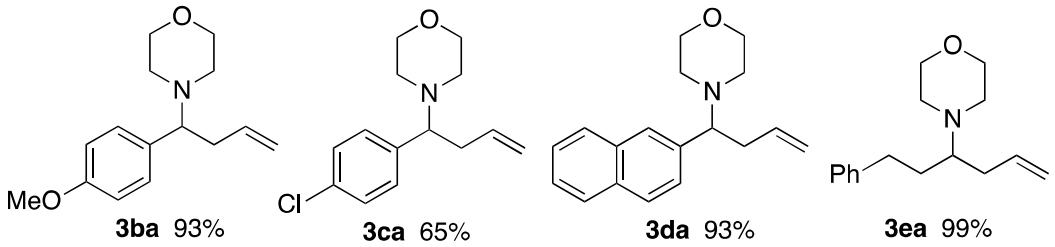
[a] Reaction conditions: **1a** (0.38 mmol), **2** (0.25 mmol), PMHS (0.75 mmol based on Si-H), $Cu(OAc)_2$ (0.025 mmol), CF_3-dppbz (0.025 mmol), LiO-*t*-Bu (1.0 mmol), DCE (1.5 mL), rt, N_2, 4 h. [b] Isolated as the NH-free piperazine.

The copper catalysis was compatible with several 2-substituted methylenecyclopropanes **1** (Scheme 3a). The substrates that bear the aromatic substituents underwent the ring-opening hydroamination with **2a** efficiently to deliver the homoallylamines **3ba**–**3da** in good yields. The reaction of the alkyl-substituted methylenecyclopropane also proceeded well, and the ring cleavage occurred at the same more congested proximal position (**3ea**). However, the 2,2-disubstituted system **1f** gave a 37:63 mixture of **3fa** and **3fa'** (Scheme 3b). Apparently, the C–C cleavage around the highly sterically demanding quaternary carbon center was unfavored, thus mainly leading to the less congested isomer **3fa'** (vide infra). Additionally notable is the reaction of 2,3-disubstituted 9-methylenebicyclo[6.1.0]nonane (**1g**): the ring-opening hydroamination did not occur at all, and the ring-retaining cyclopropylmethylamine **4ga** was instead formed[7] with 61:39 dr[15] (Scheme 3c). These outcomes indicate that the C–C bond cleavage process is highly sensitive to both steric and electronic factors around the breaking carbon-carbon bond.[16]

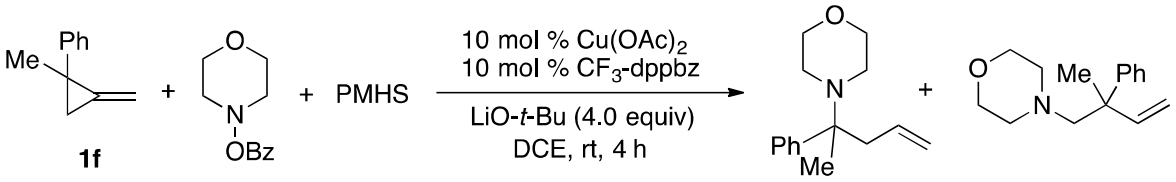
Scheme 3. Scope of Methylenecyclopropanes 1

a) Reaction of 2-monosubstituted methylenecyclopropanes



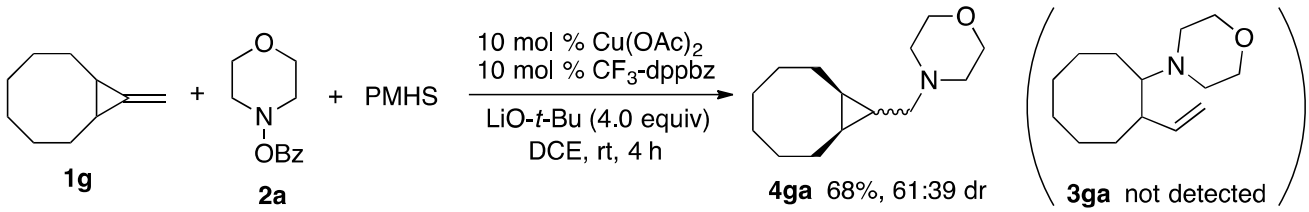


b) Reaction of 2,2-disubstituted methylenecyclopropane **1f**



99% (**3fa**/**3fa'** = 37:63)

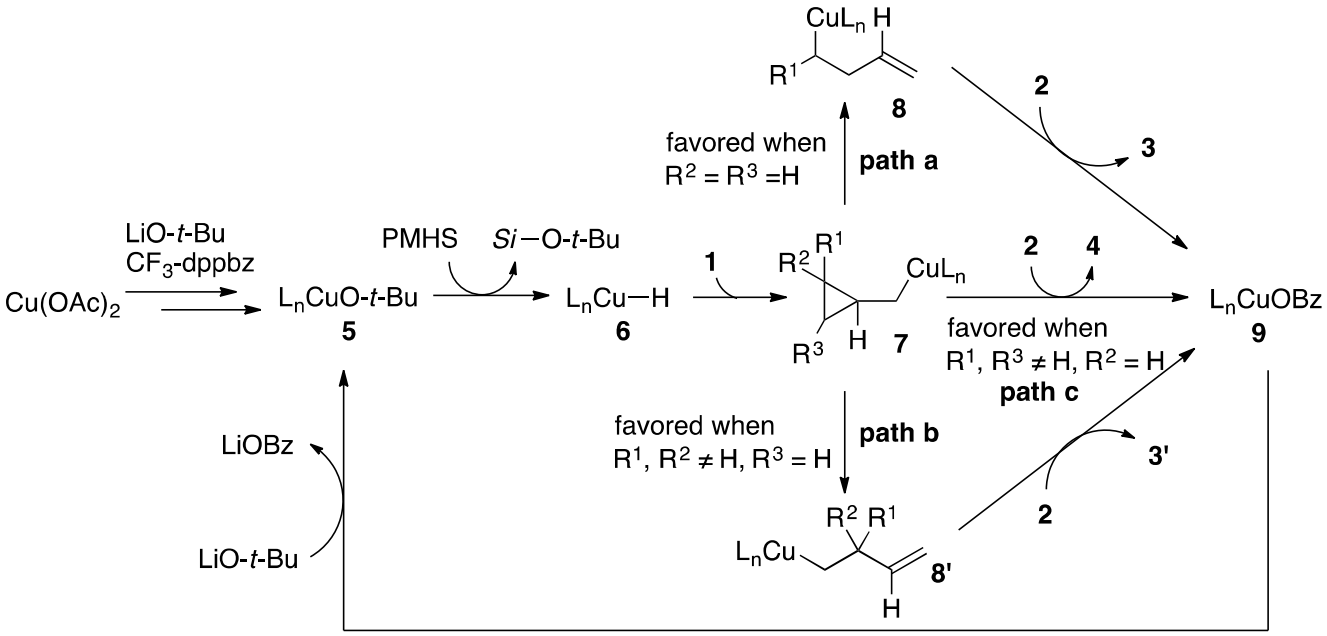
c) Reaction of 2,3-disubstituted methylenecyclopropane **1g**



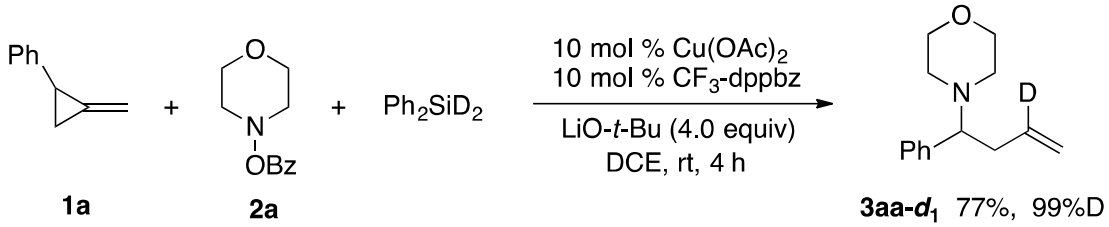
Based on our findings and literature information,[10f] we are tempted to assume the hydroamination mechanism as follows (Scheme 4). An initial reduction[17] and salt metathesis of $Cu(OAc)_2$ with LiO-*t*-Bu and ligand coordination forms the starting L_nCuO-*t*-Bu species **5**. Subsequent σ-bond metathesis with PMHS generates a copper hydride key intermediate **6**. In the insertion step of the methylenecyclopropane **1**, the bulkier copper center is located at the less congested terminal carbon to afford the cyclopropylmethylcopper **7**, from which the substrate-dependent three distinct pathways are available. In the case of the mono-substituted methylenecyclopropanes **1a**–**1e**, the *β*-carbon elimination occurs selectively at the more congested proximal position, probably because of electronic

factors, to produce the secondary alkylcopper **8** (path a). However, when the 2,2-disubstituted methylenecyclopropane **1f** is applied, the alkylcopper **8** derived from the *β*-carbon elimination at the more crowded position is the highly sterically demanding tertiary alkylmetal. Thus, the C–C bond cleavage at the less congested position competitively occurs, leading to a regiomixture of **8** and **8'** (path a and path b). After these ring-opening events, the alkylcoppers **8** and **8'** react with the hydroxylamine **2**[18] to furnish the ring-opening hydroaminated products **3** and **3'**, respectively. A similar ring-opening mechanism has been proposed in the palladium-catalyzed hydrostannylation[19] and rhodium-catalyzed hydrosilylation.[20] On the other hand, if the cyclopropane ring has substituents at both 2 and 3 positions, the *β*-carbon elimination of the alkylcopper **7** can be relatively slow, and direct coupling with the hydroxylamine **2** predominantly proceeds to deliver the ring-retaining hydroaminated product **4** (path c). Irrespective of the reaction course, the copper benzoate **9** is generated after the C–N bond formation and finally transformed to the starting copper alkoxide **5** by the ligand exchange with LiO-*t*-Bu.[21] The result of the following deuterium-labeling experiment with Ph_2SiD_2 is also consistent with the proposed mechanism (Scheme 5): the hydride was derived from the hydrosilane and selectively incorporated to the internal position of the methylene moiety of **1a**.

Scheme 4. Plausible Mechanism. L = CF_3-dppbz.



Scheme 5. Deuterium-Labeling Experiment with Ph_2SiD_2



Conclusion

We have developed a copper-catalyzed highly regioselective ring-opening hydroamination of 2-substituted 1-methylenecyclopropanes with hydrosilanes and hydroxylamines. The formal hydroamination strategy is based on the umpolung electrophilic amination and provides the first access to the homoallylamine products in the catalytic ring-opening hydroamination of the methylenecyclopropanes, to the best of our knowledge. The present electrophilic amination catalysis can open the door to a new reaction mode of MCPs in the ring-opening hydroamination reaction. Further studies on clarification of the detailed mechanism and catalytic asymmetric induction are ongoing in our laboratory.

Experimental Section

Instrumentation and Chemicals ^{1}H, ^{13}C, and ^{2}H NMR spectra were recorded at 400, 100, 60 MHz, respectively, for $CDCl_3$ solutions. HRMS data were obtained by CI or APCI using a double-focusing mass spectrometer or TOF, respectively. TLC analyses were performed on commercial glass plates bearing a 0.25 mm layer of Wako NH_2 Silica gel $60F_{254}$. DCE was freshly distilled from CaH_2 prior to use. Methylenecyclopropanes **1**[22], *O*-benzoylhydroxylamines **2**[11b,c], and CF_3-dppbz[23] are prepared according to the literature.

Typical Procedure for Copper-Catalyzed Ring-Opening Hydroamination of Methylenecyclopropanes 1 with PMHS and Hydroxylamines 2. The synthesis of **3aa** is representative (Scheme 1). $Cu(OAc)_2$ (4.5 mg, 0.025 mmol), 1,2-bis[bis{3,5-di(trifluromethyl)phynyl}phosphino]benzene (CF_3-dppbz; 25 mg, 0.025 mmol), and LiO-*t*-Bu (80 mg, 1.0 mmol) were placed in a 20 mL two-necked reaction flask, which was filled with nitrogen by using the Schlenk technique. 1,2-Dichloroethane (DCE; 0.50 mL) was then added to the flask, and the suspension was stirred for 15 min at ambient temperature. Polymethylhydrosiloxane (PMHS; 50 μL, 0.75 mmol based on Si-H) and a solution of 2-phenyl-1-methylenecyclopropane (**1a**; 49 mg, 0.38 mmol) and morpholino benzoate (**2a**; 52 mg, 0.25 mmol) in DCE (1.0 mL) were sequentially added dropwise. After stirring was continued at ambient temperature for additional 4 h, the resulting mixture was quenched with water. An aqueous solution of 6 M HCl (30 mL) was added to the mixture. The aqueous layer was washed three times with Et_2O, neutralizes with 6 M NaOH aq. (30 mL), and then extracted three times with Et_2O. The combined organic layer was dried over magnesium sulfate and filtered through a pad of Celite. Concentration in vacuo gave 4-(1-phenylbut-3-en-1-yl)morpholine (**3aa**; 51 mg, 0.24 mmol) in 94% yield in high purity.

4-(1-Phenylbut-3-en-1-yl)morpholine (3aa). yellow oil, 51 mg (94%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.36-2.41 (m, 2H), 2.44-2.53 (m, 3H), 2.62-2.69 (m, 1H), 3.30 (dd, *J* = 5.2, 8.8 Hz, 1H), 3.67 (t, *J* = 4.8 Hz, 4H), 4.91 (dddd, *J* = 1.2, 1.2, 2.0, 10.2 Hz, 1H), 4.95 (dddd, *J* = 1.6, 1.6, 2.0, 17.2 Hz, 1H), 5.59 (dddd, *J* = 6.8, 6.8, 10.2, 17.2 Hz, 1H), 7.22-7.26 (m, 3H), 7.29-7.33 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 37.3, 51.2, 67.4, 70.3, 116.6, 127.3, 128.2, 128.8, 135.5, 140.3; HRMS (CI) m/z ($[M+H]^+$) calcd for $C_{14}H_{20}NO$: 218.1539, found: 218.1544.

1-(1-Phenylbut-3-en-1-yl)piperidine (3ab). yellow oil, 53 mg (99%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.31-1.37 (m, 2H), 1.47-1.60 (m, 4H), 2.36 (t, *J* = 4.8 Hz, 4H), 2.53-2.61 (m, 1H), 2.62-2.70 (m, 1H), 3.39 (dd, *J* = 5.2, 9.2 Hz, 1H), 4.89 (dddd, *J* = 1.2, 1.2, 2.0, 10.2 Hz, 1H), 4.96 (dddd, *J* = 1.6, 1.6, 2.0, 17.2 Hz, 1H), 5.63 (dddd, *J* = 6.8, 6.8, 10.2, 17.2 Hz, 1H), 7.19-7.25 (m, 3H), 7.28-7.32 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.7, 26.4, 37.2, 51.3, 70.3, 116.1, 126.9, 127.8, 128.8, 136.2, 139.9; HRMS (CI) m/z ($[M+H]^+$) calcd for $C_{15}H_{22}N$: 216.1747, found: 216.1750.

1-(1-Phenylbut-3-en-1-yl)piperazine (3ac). yellow oil, 36 mg (66%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.53 (bs, 1H), 2.35-2.44 (m, 4H), 2.49-2.57 (m, 1H), 2.63-2.70 (m, 1H), 2.83-2.86 (m, 4H), 3.34 (dd, *J* = 5.2, 8.8 Hz, 1H), 4.90 (dddd, *J* = 1.2, 1.2, 2.0, 10.2 Hz, 1H), 4.96 (dddd, *J* = 1.6, 1.6, 2.0, 17.2 Hz, 1H), 5.61 (dddd, *J* = 6.8, 6.8, 10.2, 17.2 Hz, 1H), 7.20-7.26 (m, 3H), 7.28-7.33 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 37.2, 46.6, 51.8, 70.4, 116.4, 127.2, 128.1, 128.9, 135.9, 140.1; HRMS (APCI) m/z ($[M+H]^+$) calcd for $C_{14}H_{21}N_2$: 217.1699, found: 217.1690.

2-(1-Phenylbut-3-en-1-yl)-1,2,3,4-tetrahydroisoquinoline (3ad). yellow oil, 53 mg (81%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.56-2.67 (m, 2H), 2.74-2.91 (m, 4H), 3.56 (dd, *J* = 5.2, 8.8 Hz, 1H), 3.59 (d, *J* = 14.4 Hz, 1H), 3.76 (d, *J* = 14.4 Hz, 1H), 4.90-4.94 (m, 1H), 4.96-5.02 (m, 1H), 5.65 (dddd, *J* = 7.2, 7.2, 10.2, 17.2 Hz, 1H), 6.96-6.99 (m, 1H), 7.04-7.11 (m, 3H), 7.23-7.27 (m, 1H), 7.29-7.34 (m, 4H); ^{13}C

NMR (100 MHz, $CDCl_3$) δ 29.5, 37.8, 47.8, 53.5, 69.5, 116.6, 125.6, 126.1, 126.8, 127.3, 128.2, 128.7, 128.8, 134.7, 135.3, 135.8, 140.5; HRMS (APCI) m/z ($[M+H]^+$) calcd for $C_{19}H_{22}N$: 264.1747, found: 264.1744.

5-(1-Phenylbut-3-en-1-yl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine (3ae). yellow oil, 60 mg (89%); ^1H NMR (400 MHz, $CDCl_3$) δ 2.60-2.67 (m, 2H), 2.73-2.83 (m, 3H), 2.87-2.93 (m, 1H), 3.51 (d, *J* = 14.4 Hz, 1H), 3.60 (dd, *J* = 5.2, 8.8 Hz, 1H), 3.71 (d, *J* = 14.4 Hz, 1H), 4.90-4.94 (m, 1H), 4.96-5.02 (m, 1H), 5.64 (dddd, *J* = 6.8, 6.8, 10.2, 17.2 Hz, 1H), 6.68 (d, *J* = 5.2 Hz, 1H), 7.03 (d, *J* = 5.2 Hz, 1H), 7.24-7.34 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.9, 37.8, 47.9, 50.5, 69.2, 116.7, 122.7, 125.5, 127.3, 128.2, 128.7, 133.6, 134.2, 135.7, 140.5; HRMS (APCI) m/z ($[M+H]^+$) calcd for $C_{17}H_{20}NS$: 270.1311, found: 270.1306.

1-(1-Phenylbut-3-en-1-yl)azepane (3af). yellow oil, 50 mg (88%); ^1H NMR (400 MHz, $CDCl_3$) δ 1.52-1.61 (m, 8H), 2.48-2.58 (m, 3H), 2.62-2.70 (m, 3H), 3.66 (dd, *J* = 6.0, 8.4 Hz, 1H), 4.92 (dddd, *J* = 1.2, 1.2, 2.0, 10.2 Hz, 1H), 5.01 (dddd, *J* = 1.6, 1.6, 2.0, 17.2 Hz, 1H), 5.72 (dddd, *J* = 6.8, 6.8, 10.2, 17.2 Hz, 1H), 7.20-7.32 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.1, 29.3, 37.5, 52.0, 69.0, 116.0, 126.8, 127.9, 128.6, 136.8, 141.5; HRMS (CI) m/z ($[M+H]^+$) calcd for $C_{16}H_{24}N$: 230.1903, found: 230.1910.

N,N-Diethyl-1-phenylbut-3-en-1-amine (3ag). yellow oil, 27 mg (53%); ^1H NMR (400 MHz, $CDCl_3$) δ 1.00 (t, *J* = 7.2 Hz, 6H), 2.38 (dq, *J* = 7.2, 14.4 Hz, 2H), 2.47-2.55 (m, 1H), 2.60-2.68 (m, 1H), 2.64 (dq, *J* = 7.2, 14.4 Hz, 2H), 3.71 (dd, *J* = 5.6, 9.2 Hz, 1H), 4.90 (dddd, *J* = 1.2, 1.2, 2.0, 10.2 Hz, 1H), 4.97 (dddd, *J* = 1.6, 1.6, 2.0, 17.2 Hz, 1H), 5.65 (dddd, *J* = 6.8, 6.8, 10.2, 17.2 Hz, 1H), 7.20-7.32 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.8, 37.2, 43.2, 64.6, 116.1, 126.9, 128.0, 128.8, 136.7, 141.5; HRMS (CI) m/z ($[M+H]^+$) calcd for $C_{14}H_{22}N$: 204.1747, found: 204.1751.

N,N-Dibenzyl-1-phenylbut-3-en-1-amine (3ah). yellow oil, 65 mg (79%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.53-2.60 (m, 1H), 2.81-2.89 (m, 1H), 3.19 (d, *J* = 13.6 Hz, 2H), 3.77-3.83 (m, 1H), 3.80 (d, *J* = 13.6 Hz, 2H), 5.00 (dddd, *J* = 1.2, 1.2, 2.0, 10.2 Hz, 1H), 5.04 (dddd, *J* = 1.6, 1.6, 2.0, 17.2 Hz, 1H), 5.79 (dddd, *J* = 6.4, 7.2, 10.2, 17.2 Hz, 1H), 7.19-7.24 (m, 4H), 7.26-7.33 (m, 5H), 7.34-7.40 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 35.4, 53.6, 61.6, 116.1, 126.8, 127.1, 128.0, 128.2, 128.8, 129.0, 136.7, 138.6, 140.3; HRMS (CI) m/z ($[M+H]^+$) calcd for $C_{24}H_{26}N$: 328.2060, found: 328.2064.

N,N-Diallyl-1-phenylbut-3-en-1-amine (3ai). yellow oil, 54 mg (95%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.48-2.56 (m, 1H), 2.64-2.72 (m, 1H), 2.83 (dd, *J* = 7.2, 14.4 Hz, 2H), 3.26 (dddd, *J* = 1.6, 1.6, 5.2, 14.4 Hz, 2H), 3.82 (dd, *J* = 6.4, 8.4 Hz, 1H), 4.93 (dddd, *J* = 1.2, 1.2, 2.0, 10.2 Hz, 1H), 4.99 (dddd, *J* = 1.6, 1.6, 2.0, 17.2 Hz, 1H), 5.09-5.12 (m, 2H), 5.13-5.18 (m, 2H), 5.70 (dddd, *J* = 6.8, 6.8, 10.2, 17.2 Hz, 1H), 5.82 (dddd, *J* = 5.2, 7.2, 10.2, 17.2 Hz, 2H), 7.21-7.26 (m, 3H), 7.29-7.33 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 36.5, 52.7, 63.4, 116.0, 116.8, 126.9, 127.9, 128.7, 136.4, 136.9, 139.9; HRMS (CI) m/z ($[M+H]^+$) calcd for $C_{16}H_{22}N$: 228.1747, found: 228.1753.

N-Benzyl-N-methyl-1-phenylbut-3-en-1-amine (3aj). yellow oil, 57 mg (91%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.12 (s, 3H), 2.54-2.62 (m, 1H), 2.72-2.80 (m, 1H), 3.26 (d, *J* = 13.6 Hz, 1H), 3.59-3.63 (m, 1H), 3.60 (d, *J* = 13.6 Hz, 1H), 4.96 (dddd, *J* = 1.2, 1.2, 2.0, 10.2 Hz, 1H), 5.02 (dddd, *J* = 1.6, 1.6, 2.0, 17.2 Hz, 1H), 5.74 (dddd, *J* = 6.8, 6.8, 10.2, 17.2 Hz, 1H), 7.19-7.36 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 37.1, 38.3, 58.6, 68.2, 116.3, 126.9, 127.2, 128.1, 128.3, 128.9 (2C), 136.4, 140.0, 140.1; HRMS (CI) m/z ($[M+H]^+$) calcd for $C_{18}H_{22}N$: 252.1747, found: 252.1753.

N-Butyl-1-phenylbut-3-en-1-amine (3ak). colorless oil, 32 mg (63%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.86 (t, *J* = 7.2 Hz, 3H), 1.12-1.33 (m, 2H), 1.38-1.46 (m, 3H), 2.37-2.44 (m, 4H), 3.64 (dd, *J* = 6.0, 7.6

Hz, 1H), 5.05 (dddd, *J* = 1.2, 1.2, 2.0, 10.0 Hz, 1H), 5.09 (dddd, *J* = 1.6, 1.6, 2.0, 17.2 Hz, 1H), 5.67 (dddd, *J* = 6.4, 6.4, 10.0, 17.2 Hz, 1H), 7.21-7.27 (m, 1H), 7.30-7.35 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 20.6, 32.5, 43.2, 47.6, 62.8, 117.6, 127.0, 127.3, 128.4, 135.8, 144.4; HRMS (APCI) m/z ($[M+H]^+$) calcd for $C_{14}H_{22}N$: 204.1747, found: 204.1751.

4-(1-(4-Methoxyphenyl)but-3-en-1-yl)morpholine (3ba). colorless oil, 60 mg (97%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.35-2.51 (m, 5H), 2.60-2.67 (m, 1H), 3.26 (dd, *J* = 5.2, 9.2 Hz, 1H), 3.67 (t, *J* = 4.8 Hz, 4H), 3.79 (s, 3H), 4.91 (dddd, *J* = 1.2, 1.2, 2.0, 10.2 Hz, 1H), 4.92-4.98 (m, 1H), 5.59 (dddd, *J* = 6.8, 6.8, 10.2, 17.2 Hz, 1H), 6.85 (d, *J* = 8.8 Hz, 2H), 7.14 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 37.3, 51.1, 55.3, 67.3, 69.7, 113.5, 116.5, 129.7, 132.2, 135.7, 158.8; HRMS (APCI) m/z ($[M+H]^+$) calcd for $C_{15}H_{22}NO_2$: 248.1645, found: 248.1646.

4-(1-(4-Chlorophenyl)but-3-en-1-yl)morpholine (3ca). colorless oil, 41 mg (65%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.34-2.40 (m, 2H), 2.43-2.49 (m, 3H), 2.59-2.66 (m, 1H), 3.27 (dd, *J* = 4.8, 8.8 Hz, 1H), 3.67 (t, *J* = 4.8 Hz, 4H), 4.91-4.96 (m, 2H), 5.55 (dddd, *J* = 6.8, 6.8, 10.2, 17.2 Hz, 1H), 7.18 (d, *J* = 8.4 Hz, 2H), 7.28 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 37.3, 51.2, 67.3, 69.7, 117.1, 128.4, 130.0, 132.9, 135.0, 139.1; HRMS (APCI) m/z ($[M+H]^+$) calcd for $C_{14}H_{19}ClNO$: 252.1150, found: 252.1151.

4-(1-(Naphthalen-2-yl)but-3-en-1-yl)morpholine (3da). colorless oil, 62 mg (93%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.39-2.45 (m, 2H), 2.52-2.62 (m, 3H), 2.70-2.77 (m, 1H), 3.43 (dd, *J* = 4.8, 9.2 Hz, 1H), 3.65-3.71 (m, 4H), 4.88 (dddd, *J* = 1.2, 1.2, 2.0, 10.2 Hz, 1H), 4.93-4.98 (m, 1H), 5.58 (dddd, *J* = 6.8, 6.8, 10.2, 17.2 Hz, 1H), 7.40-7.48 (m, 3H), 7.64-7.65 (m, 1H), 7.79-7.82 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 37.3, 51.5, 67.3, 70.6, 116.8, 125.8, 126.1, 126.6, 127.7 (2C), 127.9, 128.0, 133.0, 133.3, 135.4, 138.3; HRMS (APCI) m/z ($[M+H]^+$) calcd for $C_{18}H_{22}NO$: 268.1696, found: 268.1693.

4-(1-Phenylhex-5-en-3-yl)morpholine (3ea). colorless oil, 61 mg (99%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.46-1.55 (m, 1H), 1.82-1.91 (m, 1H), 2.25-2.29 (m, 3H), 2.36 (t, *J* = 4.4 Hz, 4H), 2.51 (ddd, *J* = 7.2, 10.0, 14.0 Hz, 1H), 2.70 (ddd, *J* = 5.2, 10.0, 14.0 Hz, 1H), 3.66 (t, *J* = 4.8 Hz, 2H), 3.67 (t, *J* = 4.8 Hz, 2H), 5.05 (dd, *J* = 2.0, 17.2 Hz, 1H), 5.10 (dd, *J* = 2.0, 10.4 Hz, 1H), 5.61-5.70 (m, 1H), 7.14-7.18 (m, 3H), 7.24-7.28 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 33.2, 34.3, 40.7, 54.0, 63.9, 67.0, 115.5, 125.8, 128.4, 128.5, 141.5, 142.7; HRMS (APCI) m/z ($[M+H]^+$) calcd for $C_{16}H_{24}NO$: 246.1852, found: 246.1840.

A 37:63 mixture of 4-(2-phenylpent-4-en-2-yl)morpholine (3fa) and 4-(2-phenylbut-3-en-1-yl)morpholine (3fa'). colorless oil, 58 mg (99%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.33 (s, 0.37×3H for **3fa**), 1.44 (s, 0.63×3H for **3fa'**), 2.18-2.23 (m, 0.63×2H for **3fa'**), 2.30-2.35 (m, 0.63×2H for **3fa'**), 2.38-2.44 (m, 0.37×3H for **3fa**), 2.50-2.58 (m, 0.37×3H for **3fa**), 2.62 (d, *J* = 2.8 Hz, 0.63×2H for **3fa'**), 3.54 (t, *J* = 4.8 Hz, 0.63×4H for **3fa'**), 3.65-3.68 (m, 0.37×4H for **3fa**), 4.86-4.90 (m, 0.37×2H for **3fa**), 5.03 (dd, *J* = 1.2, 17.6 Hz, 0.63×1H for **3fa'**), 5.11 (dd, *J* = 1.2, 10.8 Hz, 0.63×1H for **3fa'**), 5.33-5.43 (m, 0.37×1H for **3fa**), 6.20 (dd, *J* = 10.8, 17.6 Hz, 0.63×1H for **3fa'**), 7.15-7.22 (m, 1H), 7.24-7.31 (m, 2H), 7.37 (d, *J* = 8.4 Hz, 0.63×2H for **3fa'**),7.46 (d, *J* = 8.4 Hz, 0.37×2H for **3fa**); ^{13}C NMR (100 MHz, $CDCl_3$) for mixture: δ 16.2, 23.6, 45.7, 45.8, 46.9, 55.7, 62.5, 67.4, 68.0, 69.3, 112.5, 117.2, 126.0, 126.5, 127.1, 127.3, 127.9, 128.0, 135.0, 145.8, 146.2, 146.6; HRMS (APCI) m/z ($[M+H]^+$) calcd for $C_{15}H_{22}NO$: 232.1696, found: 232.1695.

A 61:39 diastereomixture of 4-(bicyclo[6.1.0]nonan-9-ylmethyl)morpholine (4ga). colorless oil, 38 mg (68%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.24-0.29 (m, 0.61×1H), 0.41-0.44 (m, 0.61×2H), 0.69 (m, 0.39×2H), 0.81-0.89 (m, 0.39×1H), 0.91-1.01 (m, 0.61×2H), 1.04-1.10 (m, 0.39×2H), 1.26-1.43 (m, 0.39×5H and 0.61×4H), 1.52-1.67 (m, 0.39×3H and 0.61×4H), 1.72-1.76 (m, 0.39×2H), 1.98-2.02 (m,

0.61×2H), 2.30 (d, *J* = 6.4 Hz, 0.61×2H), 2.39 (d, *J* = 6.0 Hz, 0.39×2H), 2.46-2.52 (m, 4H), 3.72-3.75 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) for major diastereomer δ 21.2, 22.4, 26.6, 26.7, 29.8, 53.7, 63.6, 67.2; HRMS (APCI) m/z ($[M+H]^+$) calcd for $C_{14}H_{26}NO$: 224.2009, found: 224.2010.

4-(1-Phenyl-3-deuteriobut-3-en-1-yl)morpholine (3aa-d$_1$). pale yellow oil, 42 mg (77%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.36-2.42 (m, 2H), 2.44-2.52 (m, 3H), 2.65 (dd, *J* = 5.2, 14.0 Hz, 1H), 3.29 (dd, *J* = 5.2, 8.8 Hz, 1H), 3.67 (t, *J* = 4.8 Hz, 4H), 4.90 (bs, 1H), 4.94 (d, *J* = 2.0 Hz, 1H), 7.22-7.25 (m, 3H), 7.29-7.33 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 37.2, 51.2, 67.3, 70.4, 116.5, 127.3, 128.2, 128.8, 135.2 (t, *J* = 23.4 Hz), 140.3; ^{2}H NMR (60 MHz, $CDCl_3$) δ 5.62 (s); HRMS (APCI) m/z ($[M+H]^+$) calcd for $C_{14}H_{19}DNO$: 219.1608, found: 219.1599.

Associated Content

Author Information

Corresponding Authors

*E-mail: k_hirano@chem.eng.osaka-u.ac.jp.

*E-mail: miura@chem.eng.osaka-u.ac.jp.

Notes

The authors declare no competing financial interest.

Acknowledgment. This work was supported by JSPS KAKENHI Grant Nos. JP 15K13696 (Grant-in-Aid for Exploratory Research), and JP 15H05485 (Grant-in-Aid for Young Scientists (A)) to K.H. and JP 24225002 (Grant-in-Aid for Scientific Research (S)) to M.M.

Supporting Information: ^{1}H, $^{13}C\{^{1}H\}$, and ^{2}H NMR spectra for products. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) *Carbocyclic Three-Membered Ring Compounds*; de Meijere, A., Ed.; Houben-Weyl: Thieme, Stuttgart, Germany, 1996; vol. E17. (b) Brandi, A.; Goti, A. *Chem. Rev.* **1998**, *98*, 598. (c) Bach, R. D.; Dmitrenko, O. *J. Am. Chem. Soc.* **2004**, *126*, 4444.

(2) (a) Matsuda, T. Reactions of Three Membered Ring Compounds. In *Cleavage of Carbon-Carbon Single Bonds by Transition Metals;* Murakami, M., Chatani, N., Eds.; Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim: Germany, 2015; pp 35–88. (b) Nakamura, I.; Yamamoto, Y. *Adv. Synth. Catal.* **2002**, *344*, 111. (c) Pellissier, H. *Tetrahedron* **2010**, *66*, 8341. (d) Masarwa, A.; Marek, I. *Chem.–Eur. J.* **2010**, *16*, 9712. (e) Yu, L.; Liu, M.; Chen, F.; Xu, Q. *Org. Biomol. Chem.* **2015**, *13*, 8379.

(3) (a) Nakamura, I.; Itagaki, H.; Yamamoto, Y. *J. Org. Chem.* **1998**, *63*, 6458. (b) Siriwardana, A. I.; Kamada, M.; Nakamura, I.; Yamamoto, Y. *J. Org. Chem.* **2005**, *70*, 5932.

(4) Shi, M.; Chen, Y.; Xu, B. *Org. Lett.* **2003**, *5*, 1225.

(5) (a) Smolensky, E.; Kapon, M.; Eisen, M. S. *Organometallics* **2005**, *24*, 5495. (b) Smolensky, E.; Kapon, M.; Eisen, M. S. *Organometallics* **2007**, *26*, 4510.

(6) Ryu, J.-S.; Li, G. Y.; Marks, T. J. *J. Am. Chem. Soc.* **2003**, *125*, 12584.

(7) Timmerman, J. C.; Robertson, B. D.; Widenhoefer, R. A. *Angew. Chem., Int. Ed.* **2015**, *54*, 2251.

(8) Wang, C.; Ren, X.-R.; Qi, C.-Z.; Yu, H.-Z. *J. Org. Chem.* **2016**, *81*, 7326.

(9) (a) Miki, Y.; Hirano, K.; Satoh, T.; Miura, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 10830. (b) Miki, Y.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2014**, *16*, 1498. (c) Nishikawa, D.; Hirano, K.; Miura, M. *J. Am. Chem. Soc.* **2015**, *137*, 15620.

(10) (a) Zhu, S.; Niljianskul, N.; Buchwald, S. L. *J. Am. Chem. Soc.* **2013**, *135*, 15746. (b) Zhu, S.; Buchwald, S. L. *J. Am. Chem. Soc.* **2014**, *136*, 15913. (c) Niljianskul, N.; Zhu, S.; Buchwald, S. L.

Angew. Chem., Int. Ed. **2015**, *54*, 1638. (d) Shi, S.-L.; Buchwald, S. L. *Nat. Chem.* **2015**, *7*, 38. (e) Yang, Y.; Shi, S.-L.; Niu, D.; Liu, P.; Buchwald, S. L. *Science* **2015**, *349*, 62. (f) Bandar, J. S.; Pirnot, M. T.; Buchwald, S. L. *J. Am. Chem. Soc.* **2015**, *137*, 14812.

(11) For seminal works on the electrophilic amination with the hydroxylamines: (a)Tsutsui, H.; Hayashi, Y.; Narasaka, K. *Chem. Lett.* **1997**, *26*, 317. (b) Berman, A. M.; Johnson, J. S. *J. Am. Chem. Soc.* **2004**, *126*, 5680. (c) Berman, A. M.; Johnson, *J. Org. Chem.* **2006**, *71*, 219. (d) Liu, S.; Liebeskind, L. S. *J. Am. Chem. Soc.* **2008**, *130*, 6918. Selected reviews: (e) Erdik, E.; Ay, M. *Chem. Rev.* **1989**, *89*, 1947. (f) Narasaka, K.; Kitamura, M. *Eur. J. Org. Chem.* **2005**, *2005*, 4505. (g) Ciganek, E. *Org. React.* **2009**, *72*, 1. (h) Barker, T. J.; Jarvo, E. R. *Synthesis* **2011**, *2011*, 3954. (i) Dong, X.; Liu, Q.; Dong, Y.; Liu, H. *Chem.–Eur. J.* **2016**, DOI: 10.1002/chem.201601607.

(12) Reviews on the metal-catalyzed hydroamination: (a) Müller, T. E.; Hultzsch, K. C.; Yus, M.; Foubelo, F.; Tada, M. *Chem. Rev.* **2008**, *108*, 3795. (b) Fukumoto, Y. *Yuki Gosei Kagaku Kyokaishi* **2009**, *67*, 735. (c) Hesp, K. D.; Stradiotto, M. *ChemCatChem* **2010**, *2*, 1192. (d) Huang, L.; Arndt, M.; Gooβen, K.; Heydt, H.; Gooβen, L. J. *Chem. Rev.* **2015**, *115*, 2596. (e) Coman, S. M.; Parvulescu, V. I. *Org. Process Res. Dev.* **2015**, *19*, 1327. (f) Bernoud, E.; Lepori, C.; Mellah, M.; Schulz, E.; Hannedouche, J. *Catal. Sci. Technol.* **2015**, *5*, 2017. (g) Nishina, N.; Yamamoto, Y. Late Transition Metal-Catalyzed Hydroamination. In *Hydrofunctionalization;* Ananikov, V. P., Tanaka, M., Eds.; Springer-Verlag: Berlin, Heidelberg, 2013; pp 115–143. Also see the organocatalytic approach: (h) MacDonald, M. J.; Hesp, C. R.; Schipper, D. J.; Pesant, M.; Beauchemin, A. M. *Chem.–Eur. J.* **2013**, *19*, 2597.

(13) We previously reported the related aminoboration reaction of the methylenecyclopropane, in which the cyclopropane ring is completely retained: Sakae, R.; Matsuda, N.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2014**, *16*, 1228.

(14) (a) Jaime-Figueroa, S.; Liu, Y.; Muchowski, J. M.; Putman, D. G. *Tetrahedron Lett.* **1998**, *39*, 1313. (b) Cadierno, V.; García-Garrido, S. E.; Gimeno, J.; Nebra, N. *Chem. Commun.* **2005**, 4086. (c) Wang, J.-Y.; Wang, D.-X.; Zheng, Q.-Y.; Huang, Z.-T.; Wang, M.-X. *J. Org. Chem.* **2007**, *72*, 2040.

(15) The relative stereochemistry was not determined.

(16) O'Reilly, M. E.; Dutta, S.; Veige, A. S. *Chem. Rev.* **2016**, *116*, 8105.

(17) Liu, Q.; Wu, P.; Yang, Y.; Zeng, Z.; Liu, J.; Yi, H.; Lei, A. *Angew. Chem., Int. Ed.* **2012**, *51*, 4666.

(18) For recent computational mechanistic studies on the C–N bond formation step: Tobisch, S. *Chem.–Eur. J.* **2016**, *22*, 8290.

(19) Lautens, M.; Meyer, C.; Lorenz, A. *J. Am. Chem. Soc.* **1996**, *118*, 10676.

(20) Bessmertnykh, A. G.; Blinov, K. A.; Grishin, Yu. K.; Donskaya, N. A.; Tveritinova, E. V.; Yur'eva, N. M.; Beletskaya, I. P. *J. Org. Chem.* **1997**, *62*, 6069.

(21) A plausible alternative includes the direct regeneration of the copper hydride **6** through the σ-bond metathesis between the copper benzoate **9** and PMHS. See refs 10 and 18. Additionally, we cannot completely exclude the possibility of the organoheteroatomcuprate intermediacy because of the presence of excess LiO-*t*-Bu in the reaction medium.

(22) (a) Arota, S.; Binger, P. *Synthesis* **1974**, 801. (b) Kitatani, K.; Hiyama, T.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 3288. (c) Taniguchi, H.; Ohmura, T.; Suginome, M. *J. Am. Chem. Soc.* **2009**, *131*, 11298.

(23) (a) Ito, S.; Itoh, T.; Nakamura, M. *Angew. Chem., Int. Ed.* **2011**, *50*, 454. (b) Igawa, S.; Hashimoto, M.; Kawata, I.; Yashima, M.; Hoshino, M.; Osawa, M. *J. Mater. Chem. C* **2013**, *1*, 542.