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Copper-Catalyzed Enantioselective Reductive Cross-Coupling of Aldehydes and Imines

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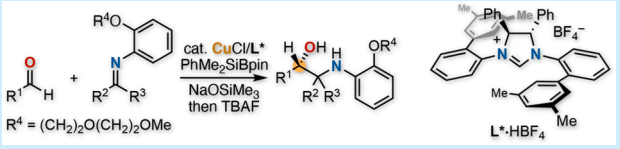
ABSTRACT: A copper-catalyzed enantioselective reductive cross-coupling using aromatic aldehydes and imines, producing chiral β-amino alcohols, is described. The catalytic formation of enantioenriched chiral α-alkoxyalkylcopper(I) species from aromatic aldehydes and the subsequent reaction with imine electrophiles are attractive features of this protocol.



Chiral β-amino alcohols are ubiquitous and valuable scaffolds in various pharmaceuticals, agrochemicals, and bioactive natural products. Many synthetic methods for chiral β-amino alcohols have been reported so far.[1,2] One of the most direct and facile methods is the enantioselective reductive cross-coupling using carbonyls and imines due to the high availability of these substrates in organic synthesis. However, this method is limited to only a few cases.[3] Specifically, Lin, Xu, and co-workers demonstrated the enantioselective cross-pinacol type coupling of aldehydes and Ellman's chiral sulfinyl imines (Figure 1A-a).[3a] Although this protocol showed high stereoselectivity and broad substrate scope, stoichiometric amounts of chiral auxiliary and SmI_2 reductant were required. Alternatively, Sato, Mita, and co-workers demonstrated the stereoselective addition of enantioenriched α-amidosilanes, which are prepared from chiral sulfinyl imines, to carbonyls such as aldehydes and ketones (Figure 1A-b).[3b] Therein, the imines acted as chiral α-aminoalkyl anion equivalents.

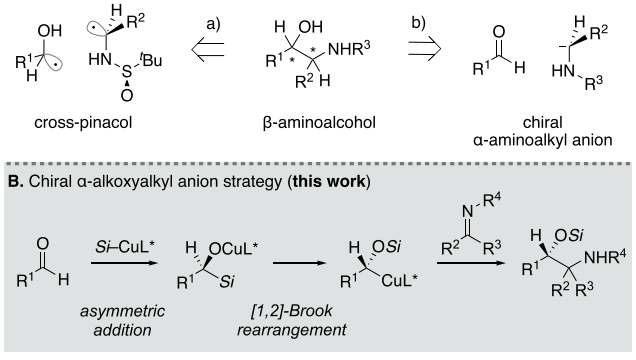


Figure 1. Enantioselective reductive cross-coupling between aldehydes and imines.

Previously, we reported that a chiral α-silyloxyalkylcopper(I) species can be formed catalytically from aromatic aldehydes via the enantioselective addition of a chiral *N*-heterocyclic carbene (NHC)-ligated silylcopper(I) complex followed by [1,2]-Brook rearrangement and subsequently coupled with carbon electrophiles in a stereospecific manner (Figure 1B).[4] This finding of an asymmetric umpolung system prompted us to consider whether the enantioenriched α-alkoxyalkylcopper(I) species could couple with imine electrophiles, thus producing a chiral β-amino alcohol product.

Herein, we report a copper-catalyzed enantioselective reductive cross-coupling between aromatic aldehydes and imines, producing chiral β-amino alcohols. This copper-catalyzed protocol provides new and efficient access to chiral β-amino alcohol derivatives.

Based on our preliminary research with achiral NHC–copper catalysts,[4c] we initially examined the cross-coupling between benzaldehyde **1a** (0.3 mmol) and aldimine **2a** (0.2 mmol) with (dimethylphenylsilyl)boronic acid pinacol ester [$PhMe_2SiB(pin)$] (0.3 mmol) under catalytic amounts of CuCl (10 mol %), a ring-saturated C_2-symmetric NHC ligand, (*S*, *S*)-**L1** (10 mol %), that exhibited high performance in our previous study of enantioselective copper-catalyzed cross-pinacol coupling,[4c] and $NaOtBu_3$ (0.22 mmol) in toluene at 80 °C, followed by desilylation, to afford the corresponding β-amino alcohol **3aa** (Table 1, entry 1). Slight enantioselectivity was induced. Next, we introduced diverse substituents (X) having different electronic and steric natures to the *N*-aromatic ring of aldimines **2** for improvement of enantiocontrol in the copper-catalyzed reductive cross-coupling. When a 2-methoxyphenyl group was used as the *N*-aryl substituent, a significant increase in the enantioselectivity was observed (entry 2). However, the 4-methoxyphenyl group did not improve the enantioselectivity (entry 3). Installation of the sterically

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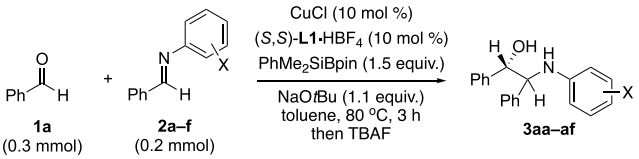
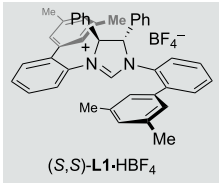
Table 1. Screening of Conditions for Coupling between 1a and 2a[a]





entry	X	change from standard conditions	yield[b,c] (%)	ee (% ee)[c]
1	H (**2a**)	none	99 (96)	24, 22
2	2-OMe (**2b**)	none	96 (93)	58, 51
3	4-OMe (**2c**)	none	96 (89)	26, 26
4	2-*t*Bu (**2d**)	none	59 (58)	12, 18
5	2-O$(CH_2)_2$OEt (**2e**)	none	82 (82)	71, 72
6	2-O$(CH_2)_2$O$(CH_2)_2$OMe (**2f**)	none	99	79, 76
7	**2f**	*c*-octane instead of tol	99	82, 78
8	**2f**	THF instead of tol	99	24, 24
9	**2f**	DME instead of tol	99	4, 4
10	**2f**	*c*-octane, $NaOSiMe_3$ instead of tol, NaO*t*Bu	99	83, 81
11	**2f**	*c*-octane, $NaOSiMe_3$, 40 °C instead of tol, NaO*t*Bu, 80 °C	99 (81)	89, 89
12	**2f**	entry 11 with 15-crown 5-ether	85	7, 5

[a]Reaction conditions: **1a** (0.3 mmol), **2a** (0.2 mmol), NaO*t*Bu (0.22 mmol), $PhMe_2SiBpin$ (0.3 mmol), CuCl (10 mol %), (*S*, *S*)-**L1**·HBF_4 (10 mol %), toluene (1 mL), 80 °C, 3 h. [b]^{1}H NMR yield based on **2**. Yield of the isolated product is in parentheses. [c]Diastereomeric ratio (1:1−1:2).

hindered *t*Bu substituent at the *ortho* position caused a decrease in both the product yield and enantioselectivity (entry 4). Thus, the positive effect of the *o*-methoxy group in entry 2 is caused by its coordination ability not its steric bulk. To increase this effect, longer ethylene glycol groups were introduced (entries 5 and 6). The improvement of enantioselectivity was found to be in good correlation with the ethylene glycol length. The reaction with imine **2f** resulted in 79% enantioselectivity of **3af**.

Changing the solvent to the less polar cyclooctane slightly improved the enantioselectivity (Table 1, entry 7). Ether solvents such as THF and DME greatly inhibited the asymmetric induction (entries 8 and 9). By changing the alkoxide base from NaO*t*Bu to $NaOSiMe_3$ and lowering the reaction temperature, the *β*-amino alcohol was obtained in 99% yield and high enantioselectivity (entries 10 and 11). Addition of 15-crown 5-ether resulted in low enantioselectivity (entry 12).

With the optimal conditions in hand, we investigated the scope of both aldehydes **1** and imines **2** in this enantioselective reductive cross-coupling. Scheme 1, left summarizes the reaction with aromatic aldehydes **1**. Various substituent patterns of alkyl moieties on the aromatic ring did not affect the enantioselectivity and product yield (**3bf**−**3ef**). Functionalities such as methoxy, fluoro and chloro, methylthio and trifluoromethoxy groups were tolerated at the *meta* and *para* positions of the benzene ring of the aromatic aldehydes (**3ff**−**3jf**). The chiral *β*-amino alcohol containing a heteroaromatic ring could be prepared with a useful level of enantioselectivity (**3kf**). Aliphatic aldehydes resulted in no cross-coupling and gave the corresponding *α*-silyl-substituted alcohol without the production of *β*-amino alcohol (data not shown). Thus, the Brook rearrangement in aliphatic aldehydes was slower than that in aryl aldehydes.

The scope of imine **2** as a coupling partner was also examined (Scheme 1, right). The enantiocontrol of the *α*-stereogenic center in the obtained chiral *β*-amino alcohol was secured regardless of the steric or electronic natures of the imines. For example, alkyl substituents at the *para*-position or *ortho*-position of the aromatic ring of **2** were tolerated (**3cg**−**3ci**). A halogen substituent remained untouched (**3cj**). Aldimines having aromatic systems such as naphthalene and thiophene served as suitable substrates (**3ck** and **3cl**). The aliphatic imines resulted in no cross-coupling (data not shown). This protocol was also applicable to ketimine **2m**, allowing the construction of chiral *β*-amino alcohols **3am**−**3cm** and **3gm** bearing a highly congested carbon scaffold. These *β*-amino alcohols are difficult to prepare with the reductive cross-coupling system reported by Lin and Sato.[3]

Next, the deprotection of the aromatic substituent on the nitrogen atom in the *β*-amino alcohol obtained by the enantioselective copper catalysis was examined (Scheme 2). The chiral *β*-amino alcohol **3af** was derivatized to *N*-aryl oxazolidinone **4af** utilizing carbodiimidazole under basic conditions. On the other hand, several representative deprotection conditions using oxidants and acids were not effective due to the occurrence of carbon−carbon bond cleavage (retro-pinacol type reaction) producing the aldehyde and imine.[5] The *N*-aryl group was smoothly removed by trichloroisocyanuric acid to provide the oxazolidinone **5af**.[6,7] The diastereomers of **5af** could be easily separated by silica gel column chromatography.

On the basis of our previous study on copper catalysis using aldehydes as *α*-alkoxyalkyl anions,[4] a possible reaction pathway for this reductive cross-coupling is outlined in Figure 2. The transmetalation of chiral NHC-ligated copper(I) alkoxide complex (**A**) with a silylboronate produced the silylcopper(I) species (**B**) and $Me_3SiOBpin$. The enantioselective addition of **B** across the carbonyl moiety of aromatic aldehyde (**1**)[8] followed by [1,2]-Brook rearrangement with inversion of configuration generates the chiral *α*-silyloxybenzylcopper(I) intermediate (**D**).[9] After the conversion of **D** to the cuprate intermediate (**E**) with an additional alkoxide base, **E** reacts with the imine (**2**) in a stereospecific manner to give the corresponding sodium amide **F** and regenerates the copper catalyst **A**. The intramolecular coordination between the *ortho* ethylene glycol group and a sodium center in **F** might suppress the dissociation of the chiral NHC ligand caused by the coordination of **F** to a copper center.

In conclusion, we have presented a copper-catalyzed enantioselective reductive cross-coupling using aromatic

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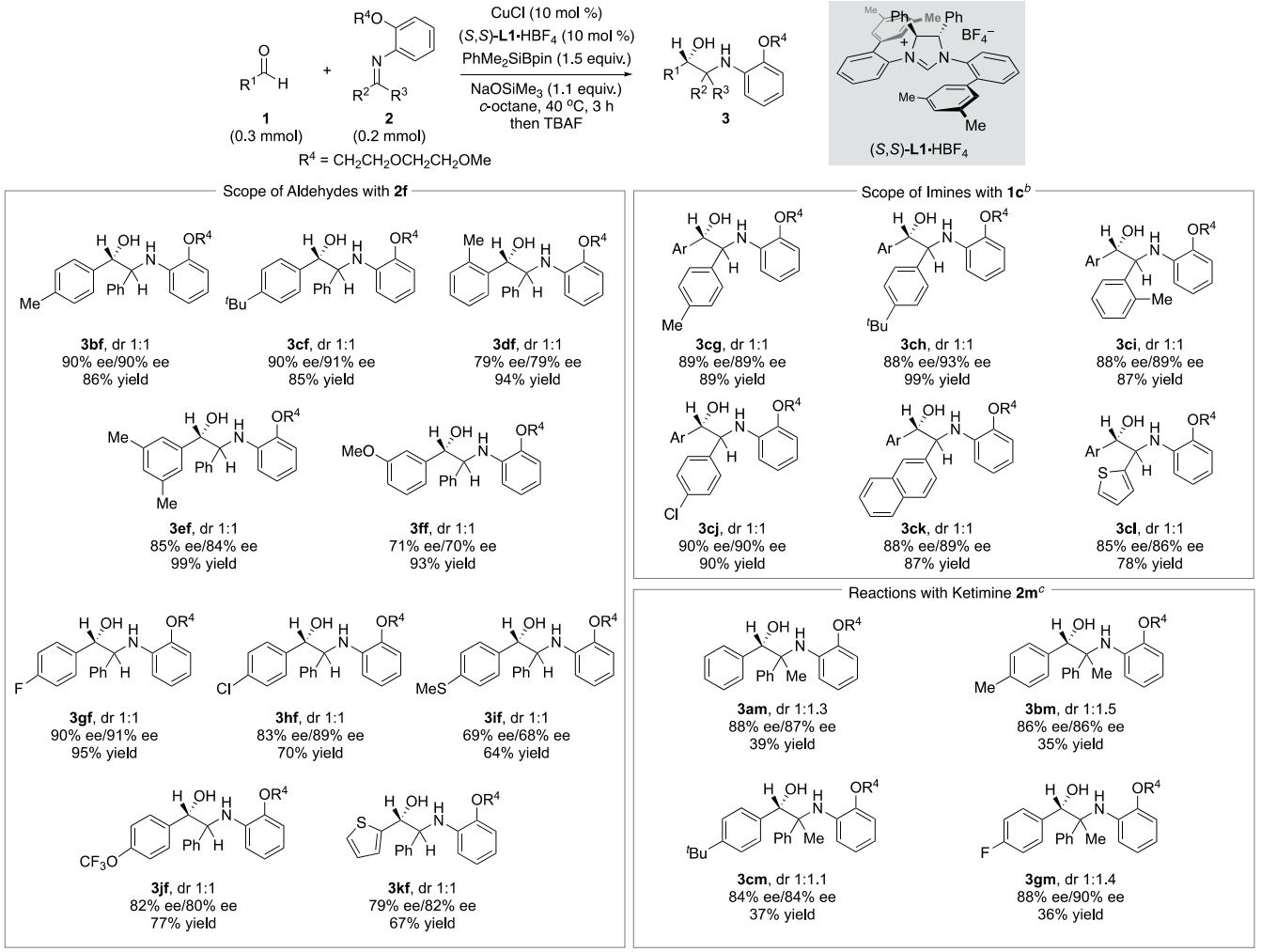
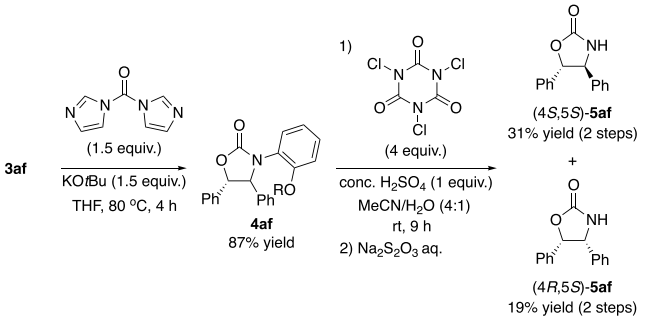
Scheme 1. Substrate Scope[a]



[a]Reaction conditions: **1** (0.3 mmol), **2** (0.2 mmol), $NaOSiMe_3$ (0.22 mmol), $PhMe_2SiBpin$ (0.3 mmol), CuCl (10 mol %), (*S, S*)-**L1**·HBF_4 (10 mol %), *c*-octane (1 mL), 40 °C, 3 h. [b]Ar = 4-*t*Bu-C_6H_4-. [c]*E*/*Z* mixture of **2m** was used.

Scheme 2. Deprotection



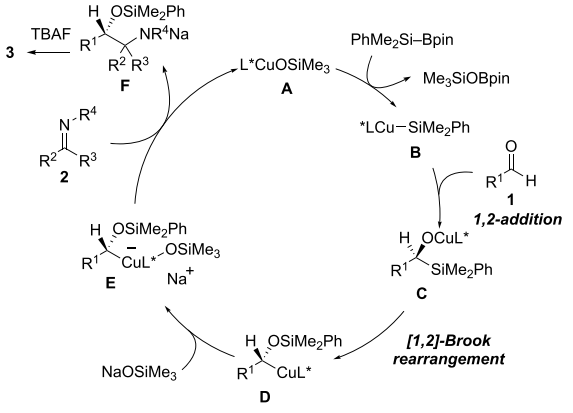


Figure 2. Possible catalytic cycle for reductive cross-coupling.

aldehydes and imines to synthesize chiral β-amino alcohol derivatives. The catalytic formation of enantioenriched chiral α-alkoxyalkylcopper(I) intermediates from aldehydes and their subsequent reaction with imine electrophiles are attractive features of this protocol. This copper-catalyzed umpolung provides an unprecedented strategy for the organic synthesis of chiral β-amino alcohols.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.9b04144.

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Experimental details and characterization data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) For selected reviews on the synthesis of β-amino alcohol, see: (a) Bergmeier, S. C. The Synthesis of Vicinal Amino Alcohols. *Tetrahedron* **2000**, *56*, 2561−2576. (b) Burchak, O. N.; Py, S. Reductive cross-coupling reactions (RCCR) between C = N and C = O for β-amino alcohol synthesis. *Tetrahedron* **2009**, *65*, 7333−7356. (c) Karjalainen, O. K.; Koskinen, A. M. P. Diastereoselective synthesis of vicinal amino alcohols. *Org. Biomol. Chem.* **2012**, *10*, 4311−4326. (d) Palomo, C.; Oiarbide, M.; Laso, A. Recent Advances in the Catalytic Asymmetric Nitroaldol (Henry) Reaction. *Eur. J. Org. Chem.* **2007**, *2007*, 2561−2574. (e) Blay, G.; Hernández-Olmos, V.; Pedro, J. R. Development of New *N,N*-Ligands for the Enantioselective Copper(II)-Catalyzed Henry Reaction. *Synlett* **2011**, *2011*, 1195−1211. (f) Matsunaga, S.; Shibasaki, M. Recent advances in cooperative bimetallic asymmetric catalysis: dinuclear Schiff base complexes. *Chem. Commun.* **2014**, *50*, 1044−1057. (g) Donohoe, T. J.; Callens, C. K. A.; Flores, A.; Lacy, A. R.; Rathi, A. H. Recent Developments in Methodology for the Direct Oxyamination of Olefins. *Chem. - Eur. J.* **2011**, *17*, 58−76.

(2) For selected recent papers on asymmetric synthesis of β-amino alcohols, see: (a) Li, K.; Shao, X.; Tseng, L.; Malcolmson, S. J. 2-Azadienes as Reagents for Preparing Chiral Amines: Synthesis of 1,2-Amino Tertiary Alcohols by Cu-Catalyzed Enantioselective Reductive Couplings with Ketones. *J. Am. Chem. Soc.* **2018**, *140*, 598−601. (b) Matsuda, N.; Hirano, K.; Satoh, T.; Miura, M. Regioselective and stereospecific copper-catalyzed aminoboration of styrenes with bis(pinacolato)diboron and O-benzoyl-N, N-dialkylhydroxylamines. *J. Am. Chem. Soc.* **2013**, *135*, 4934−4937. (c) Ye, C.-X.; Melcamu, Y. Y.; Li, H.-H.; Cheng, J.-T.; Zhang, T.- T.; Ruan, Y.-P.; Zheng, X.; Lu, X.; Huang, P.-Q. Dual Catalysis for Enantioselective Convergent Synthesis of Enantiopure Vicinal Amino Alcohols. *Nat. Commun.* **2018**, *9*, 410−418. (d) Rono, L. J.; Yayla, H. G.; Wang, D. Y.; Armstrong, M. F.; Knowles, R. R. Enantioselective Photoredox Catalysis Enabled by Proton-Coupled Electron Transfer: Development of an Asymmetric Aza-Pinacol Cyclization. *J. Am. Chem. Soc.* **2013**, *135*, 17735−17738.

(3) (a) Zhong, Y.-W.; Dong, Y.-Z.; Fang, K.; Izumi, K.; Xu, M.-H.; Lin, G.-Q. A Highly Efficient and Direct Approach for Synthesis of Enantiopure β-Amino Alcohols by Reductive Cross-Coupling of Chiral N-*tert*-Butanesulfinyl Imines with Aldehydes. *J. Am. Chem. Soc.* **2005**, *127*, 11956−11957. (b) Mita, T.; Saito, K.; Sugawara, M.; Sato, Y. Stereoretentive Addition of N-tert-Butylsulfonyl-α-Amido Silanes to Aldehydes, Ketones, α,β-Unsaturated Esters, and Imines. *Chem. - Asian J.* **2016**, *11*, 1528−1531.

(4) (a) Takeda, M.; Yabushita, K.; Yasuda, S.; Ohmiya, H. Synergistic Palladium/Copper-Catalyzed Csp^3−Csp^2 Cross-Couplings Using Aldehydes as Latent α-Alkoxyalkyl Anion Equivalents. *Chem. Commun.* **2018**, *54*, 6776−6779. (b) Yabushita, K.; Yuasa, A.; Nagao, K.; Ohmiya, H. Asymmetric Catalysis Using Aromatic Aldehydes as Chiral α-Alkoxyalkyl Anions. *J. Am. Chem. Soc.* **2019**, *141*, 113−117. (c) Takeda, M.; Mitsui, A.; Nagao, K.; Ohmiya, H. Reductive Coupling between Aromatic Aldehydes and Ketones or Imines by Copper Catalysis. *J. Am. Chem. Soc.* **2019**, *141*, 3664−3669.

(5) Shimizu, M.; Makino, H. Oxidative carbon−carbon bond cleavage reaction of 1,2-diamines and 1,2-amino alcohols under an oxygen atmosphere. *Tetrahedron Lett.* **2001**, *42*, 8865−8868.

(6) (a) Verkade, J. M. M.; Van Hemert, L. J. C.; Quaedflieg, P. J. L. M.; Alsters, P. L.; Van Delft, F. L.; Rutjes, F. P. J. T. Mild and efficient deprotection of the amine protecting *p*-methoxyphenyl (PMP) group. *Tetrahedron Lett.* **2006**, *47*, 8109−8113. (b) Bartoli, G.; Bosco, M.; Carlone, A.; Locatelli, M.; Massaccesi, M.; Melchiorre, P.; Sambri, L. Asymmetric Aminolysis of Aromatic Epoxides: A Facile Catalytic Enantioselective Synthesis of anti-β-Amino Alcohols. *Org. Lett.* **2004**, *6*, 2173−2176.

(7) The absolute configurations of **3af** were determined to be (*S*,*R*) and (*S*,*S*) by the optical rotations of **5af**. Absolute configurations of the other products listed in Scheme 1 were assigned by consideration of the stereochemical pathway. See the Supporting Information for details.

(8) (a) Cirriez, V.; Rasson, C.; Hermant, T.; Petrignet, J.; Díaz Álvarez, J.; Robeyns, K.; Riant, O. Copper-Catalyzed Addition of Nucleophilic Silicon to Aldehydes. *Angew. Chem., Int. Ed.* **2013**, *52*, 1785−1788. (b) Oestreich, M.; Hartmann, E.; Mewald, M. Activation of the Si−B Interelement Bond: Mechanism, Catalysis, and Synthesis. *Chem. Rev.* **2013**, *113*, 402−441. (c) Delvos, L. B.; Hensel, A.; Oestreich, M. McQuade's Six-Membered NHC−Copper(I) Complexes for Catalytic Asymmetric Silyl Transfer. *Synthesis* **2014**, *46*, 2957−2964. (d) Hensel, A.; Oestreich, M. Asymmetric Addition of Boron and Silicon Nucleophiles. In *Progress in Enantioselective Cu(I)-catalyzed Formation of Stereogenic Centers*; Harutyunyan, S. R., Ed.; Top. Organomet. Chem.; Springer International Publishing, 2016; Vol. *58*, pp 135−167.

(9) For the synthesis of an α-silyloxybenzylcopper(I) complex through the stoichiometric reaction of an aromatic aldehyde and a silylcopper(I) complex, see: Kleeberg, C.; Feldmann, E.; Hartmann, E.; Vyas, D. J.; Oestreich, M. Copper-Catalyzed 1,2-Addition of Nucleophilic Silicon to Aldehydes: Mechanistic Insight and Catalytic Systems. *Chem. - Eur. J.* **2011**, *17*, 13538−13543.

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