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Reductive Coupling between Aromatic Aldehydes and Ketones or Imines by Copper Catalysis

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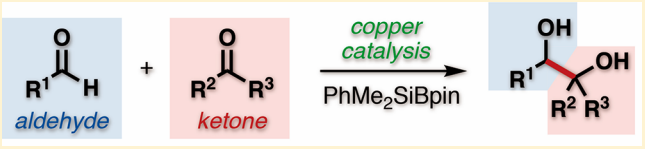
Supporting Information

ABSTRACT: The copper-catalyzed reductive coupling of two different carbonyl compounds has been achieved. The reaction of aromatic aldehydes and arylketones with a silylboronate in the presence of a catalytic amount of a CuCl−N-heterocyclic carbene (NHC) complex and a stoichiometric amount of alkoxide base yielded cross-coupled 1,2-diol derivatives. A reaction pathway is proposed that involves the catalytic formation of a nucleophilic α-silyloxybenzylcopper(I) species from the aromatic aldehyde and its subsequent coupling with the arylketone. This process was amenable to asymmetric catalysis. This copper catalyst system also enabled the reductive coupling between aromatic aldehydes and imines.



1. INTRODUCTION

1,2-Diols are common scaffolds in many pharmaceuticals, agrochemicals, and natural products. In addition, they are valuable building blocks in organic synthesis. The development of facile and efficient methods for the synthesis of 1,2-diols is thus important. One of the most promising methods is the pinacol-coupling reaction, which is a direct conversion of readily available carbonyl compounds to 1,2-diols.[1] Conventionally, the pinacol coupling reaction entails the single electron reduction of carbonyl moieties to generate the corresponding ketyl radical intermediates, which then undergo carbon−carbon bond formation between the two radical species (Figure 1A, right). The reaction has been extensively studied using low-valent metals in this single-electron transfer manifold. Although tremendous advances in the homopinacol coupling or intramolecular cross-pinacol coupling have been realized, the intermolecular cross-pinacol coupling that can produce a single cross-coupled 1,2-diol (**AB**) selectively from among the three possible 1,2-diols (**AB**, **AA**, and **BB**) that could be formed from two different carbonyl compounds (**A** and **B**) still remains a challenge (Figure 1B). The nature of the mechanism can render it difficult to discriminate between two different carbonyls in the reaction. Strategies to address the issue of chemoselective control (homo- versus cross-coupling) in the intermolecular cross-pinacol coupling include employing one coupling partner in large quantities or using highly functionalized carbonyl compounds.[2]

Recently, we demonstrated that a nucleophilic α-silyloxyalkylcopper(I) species can be generated catalytically from aldehydes through the addition of a silylcopper(I) species followed by [1,2]-Brook rearrangement[3] and then successfully intercepted with aryl electrophiles under palladium catalysis.[4] This finding of an umpolung strategy prompted us to consider whether the α-alkoxyalkylcopper(I) species could intercept another carbonyl compound, thus providing a 1,2-diol product (Figure 1C). Here, we report a copper-catalyzed reductive coupling of two simple carbonyls, namely, an aldehyde and a ketone, producing an unsymmetrical 1,2-diol derivative. This copper catalysis provides an unprecedented strategy for the organic synthesis of 1,2-diols (Figure 1A, left).[5]

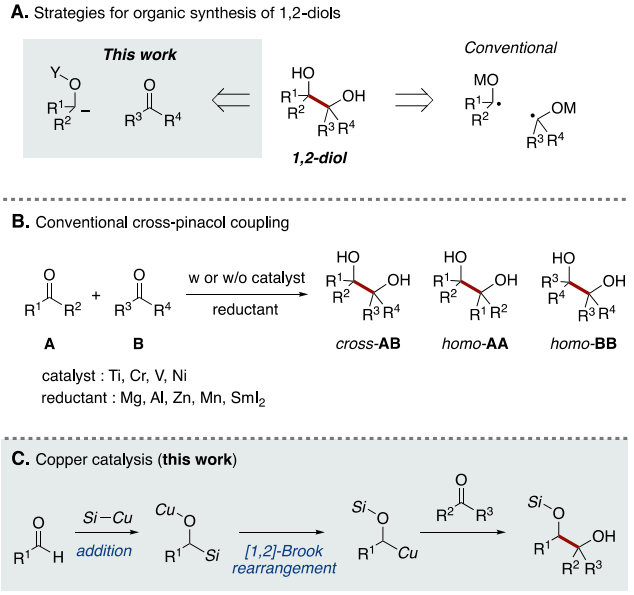


Figure 1. Cross-pinacol coupling.

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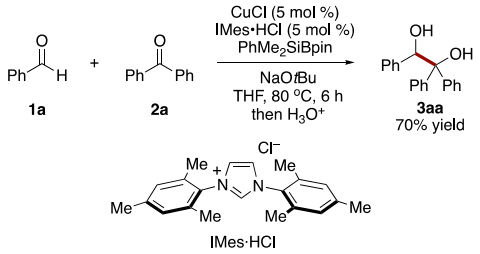
2. RESULTS AND DISCUSSIONS

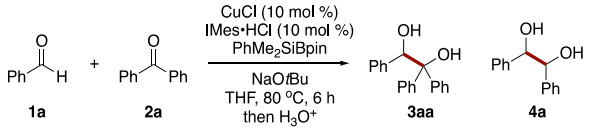
2.1. Discovery of the Reaction and Screening of Conditions. The reaction of benzaldehyde **1a** (0.3 mmol) and benzophenone **2a** (0.2 mmol) with (dimethylphenylsilyl)-boronic acid pinacol ester [$PhMe_2SiB(pin)$] (0.3 mmol) occurred in the presence of catalytic amounts of CuCl (5 mol %) and 1,3-bis(2,4,6-trimethylphenyl)imidazolium chloride IMes·HCl (5 mol %) and a stoichiometric amount of NaO*t*Bu (0.21 mmol) in THF (1 mL) at 80 °C, followed by a hydrolytic workup, to afford the corresponding 1,2-diol **3aa** (Scheme 1). The yield of the purified **3aa** was 70%.

Scheme 1. Copper-Catalyzed Reductive Coupling between 1a and 2a



The effects of different ligands are summarized in Table 1. In the earlier stage of the investigation, we used 10 mol % of the copper complex for the reaction between **1a** and **2a**. Our ligand screening identified IMes to be the best (entry 1). The NMR analysis of the crude product confirmed no occurrence of homocoupling.[6] Even without the ligand, the reductive coupling proceeded in 43% yield under essentially the same conditions (entry 2). A ring-saturated SIMes performed with a similar level of yield to that of IMes (entry 3). The use of sterically demanding SIPr or IPr gave a moderate yield (entries 4 and 5).[4a] Bisphosphine ligands such as DPPE, DPPB, or BINAP were less effective (entries 6−8). In the case of DPPE or BINAP, a small amount of homocoupling product **4a** from aldehyde **1a** was observed (entries 6 and 8). The monophosphine PPh_3 inhibited the reaction (entry 9). No reaction took place with a nitrogen-based ligand (entry 10).

Table 1. Screening of Reaction Conditions[a]



entry	change from standard conditions	yield (%) of **3aa**	yield (%) of **4a**
1	none	85	0
2	without IMes·HCl	43	0
3	SIMes·HCl instead of IMes·HCl	79	0
4	SIPr·HCl instead of IMes·HCl	41	0
5	IPr·HCl instead of IMes·HCl	22	0
6	DPPE instead of IMes·HCl	37	8
7	DPPB instead of IMes·HCl	69	0
8	*rac*-BINAP instead of IMes·HCl	33	3
9	PPh_3 instead of IMes·HCl	4	12
10	1,10-Phen instead of IMes·HCl	0	0
11	LiO^tBu instead of NaO^tBu	30	13
12	KO^tBu instead of NaO^tBu	69	12
13	NaOMe instead of NaO^tBu	0	0
14	NaO^tBu 20 mol % instead of 1.1 equiv (relative to **2a**)	0	0

[a]Reaction was carried out with **1a** (0.4 mmol), **2a** (0.2 mmol), $PhMe_2SiBpin$ (0.4 mmol), CuCl (10 mol %), ligand (10 mol %), and base (0.22 mmol) in THF (1.0 mL) at 80 °C for 6 h. SIMes·HCl, 1,3-bis(2,4,6-trimethylphenyl) imidazolinium chloride. SIPr·HCl, 1,3-bis(2,6-diisopropylphenyl)imidazolinium chloride. IPr·HCl, 1,3-bis-(2,6-diisopropylphenyl)imidazolium chloride. DPPE, 1,2-bis-(diphenylphosphino)ethane. DPPB, 1,4-bis(diphenylphosphino)-butane. BINAP, 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl. 1,10-Phen, 1,10-phenanthroline.

2.2. Substrate Scope. We next explored the scope of the aldehydes in the copper-catalyzed reductive coupling using benzophenone (**2a**) (Table 2). The reaction of *p*-tolualdehyde or *p*-*tert*-butylbenzaldehyde gave the corresponding 1,2-diol products (**3ba** and **3ca**). A sterically hindered aromatic aldehyde such as *o*-tolualdehyde underwent the coupling reaction (**3da**). 2-Naphthaldehyde served as a substrate (**3ea**). Functional groups such as methoxy, benzyloxy, trifluoromethoxy, methylthio, bromo, chloro, and fluoro substituents were tolerated at the *meta*- or *para*-positions of the aromatic ring of the aldehyde (**3fa**−**3ma**). Heteroaromatic aldehydes were compatible with the reaction. Specifically, heteroaromatic rings such as furan and thiophene were tolerated regardless of the substituent pattern (**3na**−**3pa**). Electron-deficient heteroaromatic quinoline underwent the reaction, although the yield was moderate (**3qa**). Aliphatic aldehydes did not participate in the reaction (data not shown). Thus, the reaction of aliphatic aldehydes gave significant amounts of the corresponding α-silyl-substituted alcohol and acylsilane. This result suggested the Brook rearrangement in aliphatic aldehydes was slower than that in aromatic aldehydes.

Various diarylketone derivatives were examined (Table 2). The benzophenone derivatives bearing *p*-tolyl or biphenyl groups served as substrates (**3ab** and **3ac**). A π-extended aromatic ketone such as 2-naphthylphenyl ketone participated in the reaction (**3ad**). Fluoro, methoxy, and trifluoromethoxy groups were tolerated at the *meta*- or *para*-positions of the benzene ring of the benzophenone (**3ae**−**3ag**). A heteroaromatic ring such as thiophene could be introduced to the substrate (**3ah**).

The copper catalyst system was not limited to the coupling reaction with diarylketones but could also be applied to alkyl aryl ketones (Table 2). SIMes was better than IMes as a ligand in terms of the product yield. For example, the simplest substrate acetophenone reacted with benzaldehyde **1a**, giving the corresponding 1,2-diol (**3ai**) in 70% yield. More sterically demanding alkyl substituents such as ethyl, isobutyl, or cyclohexyl groups were tolerated in the alkyl aryl ketone (**3aj**−**3al**). Alkene or ester at the terminus of the aliphatic chain was tolerated in this reaction (**3am** and **3an**). 2-Acetonaphthone underwent the reaction (**3ao**). Notably, 2,2,2-trifluoroacetophenone was utilized for this reductive coupling to furnish the corresponding 1,2-diol (**3ap**).

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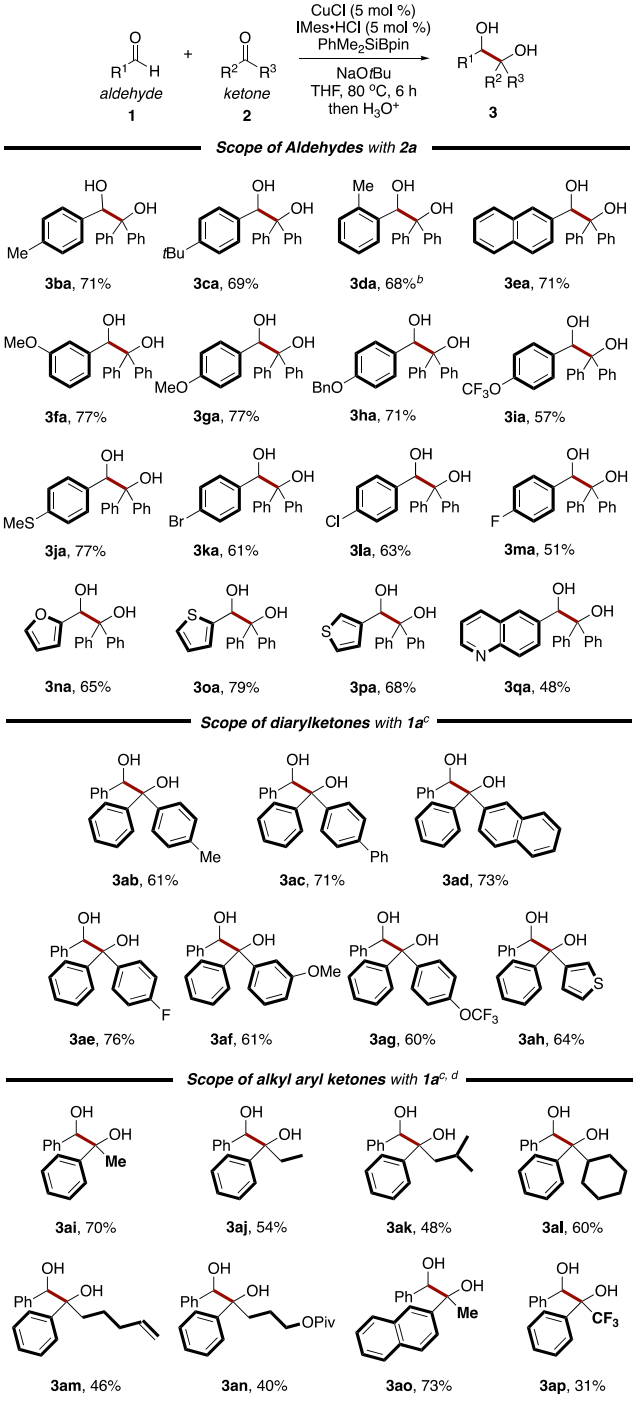
Table 2. Substrate Scope[a]



[a]Reactions were carried out with **1** (0.3 mmol), **2** (0.2 mmol), $PhMe_2SiBpin$ (0.3 mmol), CuCl (5 mol %), IMes·HCl (5 mol %), and NaO*t*Bu (0.21 mmol) in THF (1.0 mL) at 80 °C for 6 h. [b]**1** (0.4 mmol), $PhMe_2SiBpin$ (0.4 mmol), CuCl (10 mol %), IMes·HCl (10 mol %), and NaO*t*Bu (0.22 mmol) were used. [c]Diastereomeric ratio (1:1−1.8:1). [d]SIMes·HCl (5 mol %) was used as a ligand.

2.3. Mechanistic Considerations for the Reaction Pathway. Competition experiment on the copper-catalyzed carbonyl silylation using *tert*-butyl alcohol as a proton source was conducted. The reaction with benzaldehyde **1a** and benzophenone **2a** gave benzyl silyl ether **1a′** along with full recovery of **2a** (Figure 2A). The result suggested the copper catalysis is initiated by chemoselective silylation to aldehyde.

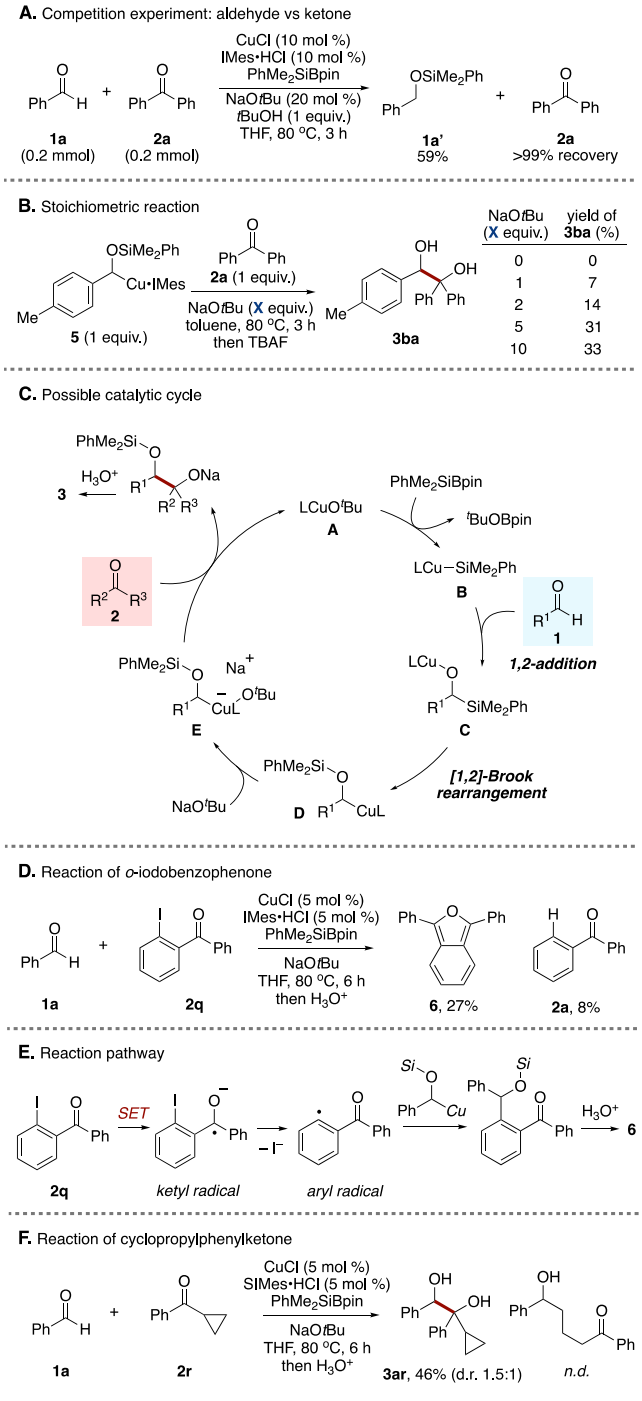


Figure 2. Mechanistic considerations.

The reaction in the presence of only 20 mol % of NaO*t*Bu (relative to **2a**), which should be consumed to form the alkoxycopper(I)−NHC complex (10 mol %), under otherwise identical conditions resulted in no reaction (see Table 1, entry 14). The active organocopper intermediate of the reductive coupling reaction is likely in the form of a monoorganoalkoxycuprate rather than a neutral organocopper(I) species. To test this assumption, we investigated the NaO*t*Bu loading on the product yields of the reaction of IMes-ligated α-silyloxybenzylcopper(I) complex **5**, which was prepared *in situ* from *p*-tolualdehyde (**1b**), (IMes)CuCl, $PhMe_2SiBpin$, and NaO*t*Bu, with benzophenone **2a** (Figure 2B).[7] The reaction without an additional alkoxide base resulted in no product

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formation. The product yield was markedly improved as the NaO*t*Bu/**5** ratio was increased in the range from 1 to 10. These results are in accord with the above assumption.[8]

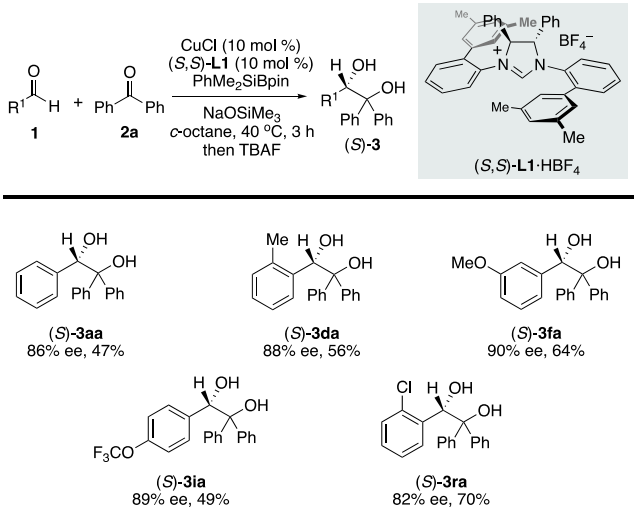
On the basis of the information obtained by the reactions in Figures 2A and 2B and our scenario (Figure 1C), a reaction mechanism for the copper-catalyzed reductive coupling, in which a copper catalyst discriminates between these two carbonyls, namely, aromatic aldehyde **1** and arylketone **2**, is outlined in Figure 2C. Initially, the reaction of CuCl, IMes·HCl, and NaO*t*Bu forms a *t*-butoxycopper−NHC complex (**A**). B/Cu transmetalation between **A** and a silylboronate occurs to form the silylcopper(I) complex (**B**) and *t*-BuOBpin. Next, the selective addition of silylcopper(I) (**B**) across the C═O bond of aldehyde **1**[9] followed by [1,2]-Brook rearrangement from the resulting α-silyl-substituted copper(I) alkoxide (**C**) occurs to form an α-silyloxybenzylcopper(I) species (**D**).[7] Next, the sodium alkoxide base reacts with the copper complex (**D**) to form the sodium alkoxo(α-silyloxybenzyl)cuprate(I) species (**E**). Finally, the heterocuprate (**E**) reacts with arylketone **2** to furnish the cross-coupled product and regenerate the *t*-butoxycopper(I) complex (**A**) for the next catalytic cycle.

For the reaction pathway of the heterocuprate (**E**) with arylketone **2**, two types of mechanisms are conceivable. One involves a nucleophilic addition mechanism, and the other is an SET (single electron transfer) mechanism.[10,11] We conducted ketyl radical probe experiments. The reaction using *o*-iodobenzophenone (**2q**) gave 1,3-diphenylisobenzofuran **6** in 27% yield along with a dehalogenated compound **2a** in 8% yield (Figure 2D and see the Supporting Information).[12] The corresponding 1,2-diol was not observed. Additionally, the reaction of **1a** using iodobenzene instead of **2q** under otherwise identical conditions was examined, and the coupling product, diphenylmethanol, was not detected (data not shown). Thus, the carbon−carbon bond formation step in the copper-catalyzed reaction between **1a** and **2q** was initiated by the generation of a ketyl radical not an aryl radical (Figure 2E). On the other hand, the reaction with cyclopropylphenylketone (**2r**) gave the corresponding 1,2-diol **3ar**, and the ring opening of cyclopropyl group was not observed (Figure 2F).[13,14] These results indicated an interesting mechanistic difference between the two ketone substrates, diarylketone and alkyl aryl ketone. The reaction mechanism (nucleophilic addition or SET) would rely on the nature of ketone substrates.

2.4. Enantioselective Reductive Coupling. We examined the catalytic enantioselective reductive coupling (Table 3). When a new ring-saturated C_2-symmetric carbene (*S*,*S*)-**L1** was used as a ligand on copper, the reductive coupling of various aromatic aldehydes using benzophenone (**2a**) proceeded with high enantioselectivities (**3aa**, **3da**, **3fa**, **3ia**, and **3ra**). Notably, the asymmetric intermolecular cross-pinacol coupling of two simple carbonyls still remains a challenge.[2,5a]

To obtain the stereochemical information of enantioselective reductive coupling, two reactions were examined (Figure 3). The copper-catalyzed carbonyl addition of a silylboronate to benzaldehyde **1a** using trimethylsilanol as a proton source occurred to give (*S*)-α-silyl-substituted benzyl alcohol **1a′** in 79% yield with 89% enantioselectivity (Figure 3A). Next, the reaction of a stoichiometric amount of a chiral silylcopper(I) complex, which was prepared *in situ* from CuCl, (*S*,*S*)-**L1**·HBF_4, $PhMe_2SiB(pin)$, and NaO*t*Bu (1/1/2), with deuterated benzaldehyde-α-*d*1 (**1a**-*d*) was performed without any proton sources (Figure 3B). The reaction gave, after addition of acetic acid, chiral-deuterated benzyl silyl ether **1aC**-*d* with (*S*) configuration. The observed stereochemical outcomes suggested that a stereodefined α-silyloxybenzylcopper(I) intermediate (**E**), which is generated from the enantioselective addition of a silylcopper(I) complex to aldehyde (**B** → **C**) followed by [1,2]-Brook rearrangement with inversion of configuration (**C** → **D**), reacts with arylketone **2** in a stereospecific manner (see Figure 2C).

Table 3. Enantioselective Reductive Coupling[a]



[a]Reactions were carried out with **1** (0.3 mmol), **2a** (0.2 mmol), $PhMe_2SiBpin$ (0.3 mmol), CuCl (10 mol %), (*S*,*S*)-**L1**·HBF_4 (10 mol %), and $NaOSiMe_3$ (0.22 mmol) in cyclooctane (1 mL) at 40 °C for 3 h. Enantiomeric excess was determined by HPLC analysis.

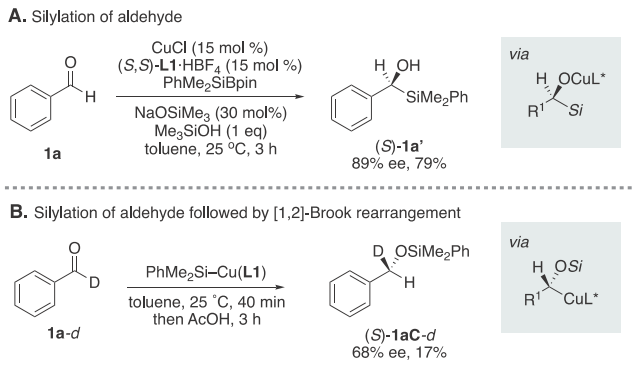


Figure 3. Stereochemical pathway.

2.5. Reductive Coupling between Aldehydes and Imines. To demonstrate the generality of our protocol, other carbonyls were examined. Imines were found to be suitable coupling partners in this reductive coupling (Table 4).[15] In this case, SIMes was a better ligand than IMes in terms of the product yield. For example, the reaction of benzaldehyde (**1a**) (0.3 mmol) and *N*,1-diphenylmethanimine (**7a**) (0.2 mmol) with $PhMe_2SiB(pin)$ (0.3 mmol) occurred in the presence of catalytic amounts of CuCl (10 mol %) and SIMes·HCl (10 mol %) and NaO*t*Bu (0.22 mmol) in toluene (1 mL) at 80 °C, followed by a desilylation, to produce the corresponding β-amino alcohol **8aa** in 74% yield.[16] The NMR analysis of the crude product confirmed no occurrence of homocoupling. Various aldimines bearing different substituents on nitrogen or

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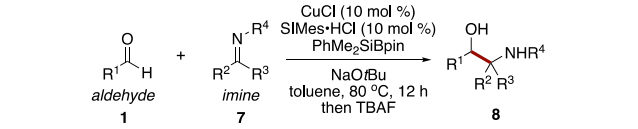
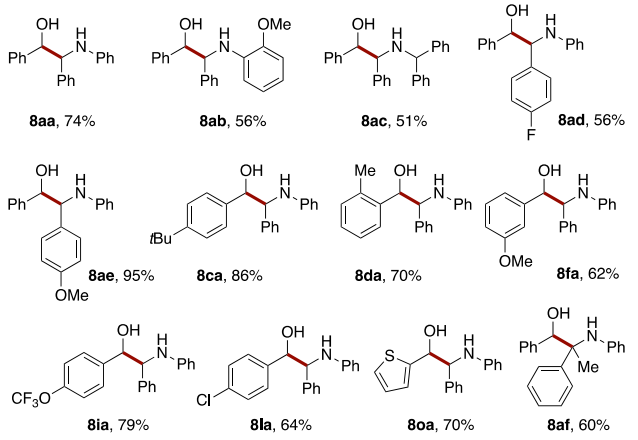
Table 4. Reductive Coupling of Aldehydes and Imines[a]





[a]Reactions were carried out with **1** (0.3 mmol), **7** (0.2 mmol), $PhMe_2SiBpin$ (0.3 mmol), CuCl (10 mol %), SIMes·HCl (10 mol %), and NaO*t*Bu (0.22 mmol) in toluene (1.0 mL) at 80 °C for 12 h. Diastereomeric ratio (1.2:1−3.5:1).

carbon atoms were evaluated. Also the steric hindrance of *o*-anisyl and benzhydryl groups on imine nitrogen did not affect the reaction efficiency (**8ab** and **8ac**). Electron-donating and -withdrawing groups on the aromatic ring at both aldehyde and imine were tolerated (**8ad**, **8ae**, **8ca**, **8da**, **8fa**, **8ia**, **8la**, and **8oa**). Notably, this protocol enabled the reductive coupling of aldehyde and ketimine to construct a complex *β*-amino alcohol scaffold (**8af**).

3. CONCLUSION

We have developed the copper-catalyzed reductive coupling of two different carbonyls. The reaction between aromatic aldehydes and arylketones with a silylboronate proceeded under mild conditions to produce cross-coupled 1,2-diol derivatives. A reaction pathway is proposed that involves the catalytic generation of *α*-silyloxybenzylcopper(I) from an aromatic aldehyde and its subsequent coupling with an arylketone. Asymmetric reductive coupling was also achieved with a new chiral NHC ligand on copper. This copper-catalyzed method provides a new and efficient umpolung strategy for the organic synthesis of 1,2-diol compounds. Efforts to expand the utility of this reaction are ongoing in our laboratory

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.8b13309.

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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