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Asymmetric Catalysis Using Aromatic Aldehydes as Chiral α-Alkoxyalkyl Anions

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Supporting Information

ABSTRACT: We have developed a new umpolung strategy for catalytically forming a chiral α-alkoxyalkyl anion from an aromatic aldehyde for use in asymmetric synthesis. The reaction between aromatic aldehydes and aryl or allyl electrophiles with a silylboronate utilizing a chiral copper−N-heterocyclic carbene catalyst and a palladium−bisphosphine catalyst in a synergistic manner occurred with high enantioselectivities to deliver the three-component coupling products, chiral silyl-protected secondary alcohol derivatives. Our method features the catalytic generation of enantioenriched chiral α-alkoxyalkylcopper(I) intermediates from aldehydes and their subsequent palladium-catalyzed stereospecific cross-coupling.

Chiral α-heteroatom-substituted carbanions are attractive C(sp^3) nucleophiles for the organic synthesis of chiral molecules. Specifically, α-alkoxyalkyl anions are highly valuable in constructing chiral alcohols found in a majority of pharmaceutical drugs and bioactive natural products.[1] Conventionally, chiral α-alkoxyalkyl anions are presynthesized as stoichiometric organometallic reagents (Figure 1a, right).[2−5] Hoppe and Hense[2a] prepared chiral α-alkoxyalkyllithium compounds by enantiotopic α-deprotonation of aliphatic alcohol derivatives with highly basic alkyllithium reagents and stoichiometric amounts of chiral amines (Figure 1b). The obtained α-alkoxyalkyllithiums could be converted into other organometallic reagents, such as organozinc, organostannane, and organoboron compounds. Alternatively, the asymmetric reduction of acylmetal compounds such as acylsilanes or acylstannanes, which are presynthesized in multistep operations, allows the preparation of chiral α-hydroxycarbanion equivalents (Figure 1c).[3] More recently, copper-catalyzed enantioselective nucleophilic silylation and borylation of carbonyl compounds have been introduced as new approaches for the preparation of α-alkoxyalkylmetal compounds, but their application to organic synthesis has been underdeveloped (Figure 1d).[4]

Earlier we showed that a nucleophilic α-alkoxyalkylcopper(I) species was formed catalytically from aldehydes through the addition of a silylcopper(I) species followed by a 1,2-Brook rearrangement in the palladium-catalyzed cross-coupling with aryl bromides.[6,7] This prompted us to investigate whether the process could be adapted to an asymmetric version by the use of a chiral ligand in the copper catalyst (Figure 1e). Here we

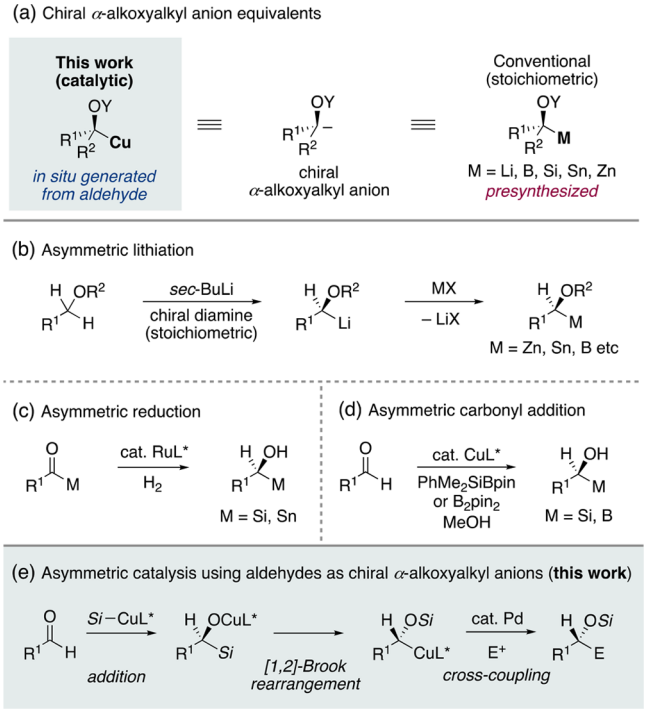

Figure 1. Generation of chiral α-alkoxyalkyl anions.

report an asymmetric catalysis using aromatic aldehydes as chiral α-alkoxyalkyl anions (Figure 1a, left). The reaction of aromatic aldehydes and aryl or allyl electrophiles with a silylboronate by the merger of a chiral copper−N-heterocyclic carbene (NHC) catalyst and a palladium−bisphosphine catalyst in a synergistic manner occurred with high enantioselectivities to deliver the three-component coupling products, chiral silyl-protected secondary alcohol derivatives.[8]

On the basis of our preliminary research with the achiral catalyst system,[6] various chiral NHC ligands on copper were examined for catalytic activity and enantiocontrol in the cross-coupling of *o*-tolualdehyde (**1a**) (0.3 mmol) and *p*-bromochlorobenzene (**2a**) (0.2 mmol) with (dimethylphenylsilyl)boronic acid pinacol ester [PhMe$_2$SiB(pin)] (0.3 mmol) in the presence of palladium(II) acetylacetonate [Pd(acac)$_2$] (5 mol %), 1,1′-bis(diisopropylphosphino)ferrocene (DIPPF) (10 mol %),

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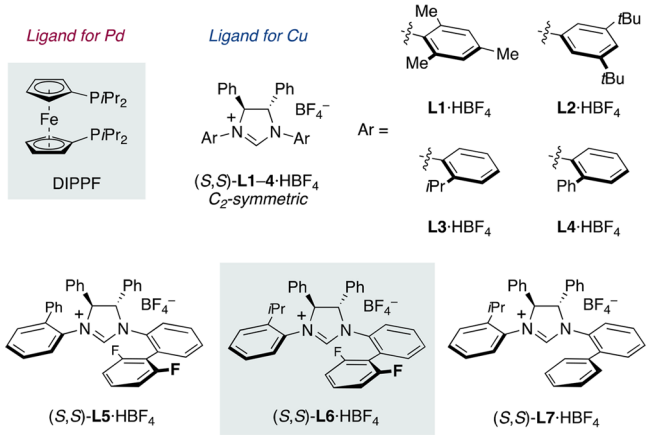
CuCl (25 mol %), a chiral imidazolinium salt (25 mol %), and $NaOSiMe_3$ (0.25 mmol) as a base in toluene at 60 °C (Table 1).[9] Copper–NHC complexes were prepared in situ from

Table 1. Screening of Chiral NHC Ligands and Bases for Cross-Coupling between 1a and 2a;[a] The HBF_4 Salts of L2 and L5–L7 Were Newly Synthesized in This Study

1a 2a 3aa

entry	Cu cat. mol %	NHC[d]	base	T (°C)	yield (%)	ee (%)[b]
1	25	**L1**	$NaOSiMe_3$	60	20	21
2	25	**L2**	$NaOSiMe_3$	60	20	44
3	25	**L3**	$NaOSiMe_3$	60	51	74
4	25	**L4**	$NaOSiMe_3$	60	60	86
5	25	**L5**	$NaOSiMe_3$	60	54	87
6	25	**L6**	$NaOSiMe_3$	60	72	89
7	25	**L7**	$NaOSiMe_3$	60	73	74
8[c]	15	**L6**	$NaOSiMe_3$	60	78	89
9[c]	15	**L6**	$NaOSiMe_3$	40	52	90
10	25	**L6**	NaO*t*Bu	60	13	57
11	25	**L6**	NaOMe	60	0	–

[a]The reactions were carried out with **1a** (0.3 mmol), **2a** (0.2 mmol), $PhMe_2SiBpin$ (0.3 mmol), $Pd(acac)_2$ (5 mol %), DIPPF (10 mol %), CuCl/**L**·HBF_4 (15 or 25 mol %), and alkoxide base (0.25 mmol) in toluene (1.0 mL) at 40 or 60 °C for 3 h. DIPPF is 1,1′-bis(diisopropylphosphino)ferrocene. [b]Enantiomeric excess determined by HPLC analysis. [c]$NaOSiMe_3$ (0.23 mmol) was used. [d]The ligands are shown below:



CuCl, L·HBF_4, and $NaOSiMe_3$. The ring-saturated C_2-symmetric NHC ligand [(*S*,*S*)-**L1**],[10] which has two stereogenic carbon centers in the imidazolidine ring with two mesityl groups at both nitrogen atoms, possessed slight catalytic activity (20%) and enantioselectivity (21% ee) (entry 1). Similar chiral NHC ligands bearing 3,5-di-*tert*-butylphenyl (**L2**), 2-isopropylphenyl (**L3**)[11] or 2-biphenyl (**L4**)[12] groups instead of the mesityl groups in **L1** were examined (entries 2–4). Among them, **L4** was the most effective for the product yield (60%) and enantioselectivity (86% ee) (entry 4).

Next, we prepared the new chiral NHC ligand **L5** bearing a 2-(2,6-difluorophenyl)phenyl group instead of one of the 2-biphenyl groups in **L4** to modify the steric hindrance in close proximity to the copper center. The Cu–**L5** catalyst system imparted an enantioselectivity of 87% ee, which was slightly better than that of the system with the non-fluorinated NHC ligand **L4** (entry 5). Changing the 2-biphenyl group of **L5** to a 2-isopropylphenyl group (**L6**) increased the product yield to 72% and the enantioselectivity to 89% ee (entry 6). The Cu loading could be reduced to 15 mol % with a slightly increased yield, and the high enantioselectivity remained unchanged (entry 8). The enantioselectivity was further increased to 90% ee by lowering the reaction temperature to 40 °C (entry 9). The use of the corresponding non-fluorinated NHC ligand **L7** resulted in a significant reduction in enantioselectivity (entry 7). Thus, the fluoro groups in **L6** were important.

The steric and electronic nature of the alkoxide moiety of the base was important (Table 1). Thus, the use of more basic NaO*t*Bu instead of $NaOSiMe_3$ diminished the product yield and enantioselectivity (entry 10). This result might be due to the formation of achiral silyl(*tert*-butoxy)cuprate species upon partial dissociation of the NHC ligand.[13] The smaller and weaker alkoxide base NaOMe induced no reaction (entry 11).

Table 2 summarizes the results of the reactions of various aryl bromides under the Cu–**L6** catalyst system.[14] Bromobenzene and 2-bromonaphthalene reacted with **1a** with high enantioselectivities (**3ab** and **3ac**). Because of the mildness of the reaction conditions, various functional groups were tolerated. For example, aryl bromides bearing fluoro, trifluoromethyl, trifluoromethoxy, methoxycarbonyl, methoxy, benzyl ether, THP ether, and pivaloyl substituents at the meta or para position of the aromatic ring reacted to afford the corresponding chiral benzhydryl silyl ether products with high enantioselectivities (88–92% ee) (**3ad**–**ak**). Heteroaryl bromides such as bromopyridine or bromothiophene were compatible with the enantioselective reaction (**3al** and **3am**).[15]

The range of aldehydes is also shown in Table 2.[14] Benzaldehyde, *p*-tolualdehyde, and *p*-*tert*-butylbenzaldehyde reacted with **2a** with high enantioselectivities (**3ba**–**da**). Functionalized benzaldehydes such as *m*-anisaldehyde, piperonal, and 3-fluorobenzaldehyde underwent the coupling, giving the corresponding chiral benzhydryl silyl ethers with useful levels of enantioselectivity (**3ea**–**ga**). The reaction with 3-thiophenecarboxaldehyde afforded the coupling product with moderate enantiocontrol (**3ha**). Aliphatic aldehydes and aromatic or aliphatic ketones did not participate in the reaction (data not shown).[16]

A reaction mechanism consisting of two distinct catalytic cycles, namely, copper and palladium catalysis, is illustrated in Figure 2a.[6] Initially, the reaction of chiral NHC-ligated copper complex **A**, a silylboronate, and $NaOSiMe_3$ forms silylcopper(I) species **B** and trimethylsilyloxyboronate. The enantioselective addition of **B** across the C=O bond of aldehyde **1** produces stereodefined α-silyl-substituted copper(I) alkoxide **C**,[4a] which subsequently undergoes a stereospecific [1,2]-Brook rearrangement to give chiral α-silyloxybenzylcopper(I) species **D**.[17] Next, the stereospecific Cu/Pd transmetalation between **D** and arylpalladium(II) bromide **F**, which is generated from oxidative addition of aryl bromide **2** to palladium(0)–bisphosphine complex **E**, produces the corresponding chiral organopalladium(II) complex **G**.[18] Finally, reductive elimination from **G** releases the enantioenriched product **3** and regenerates the palladium(0) complex **E** for the next catalytic cycle.

To obtain stereochemical information on the present palladium/copper-catalyzed pathway, two-component reactions between aldehydes and a silylboronate were examined. For this study, we used **L4** instead of **L6** because of the

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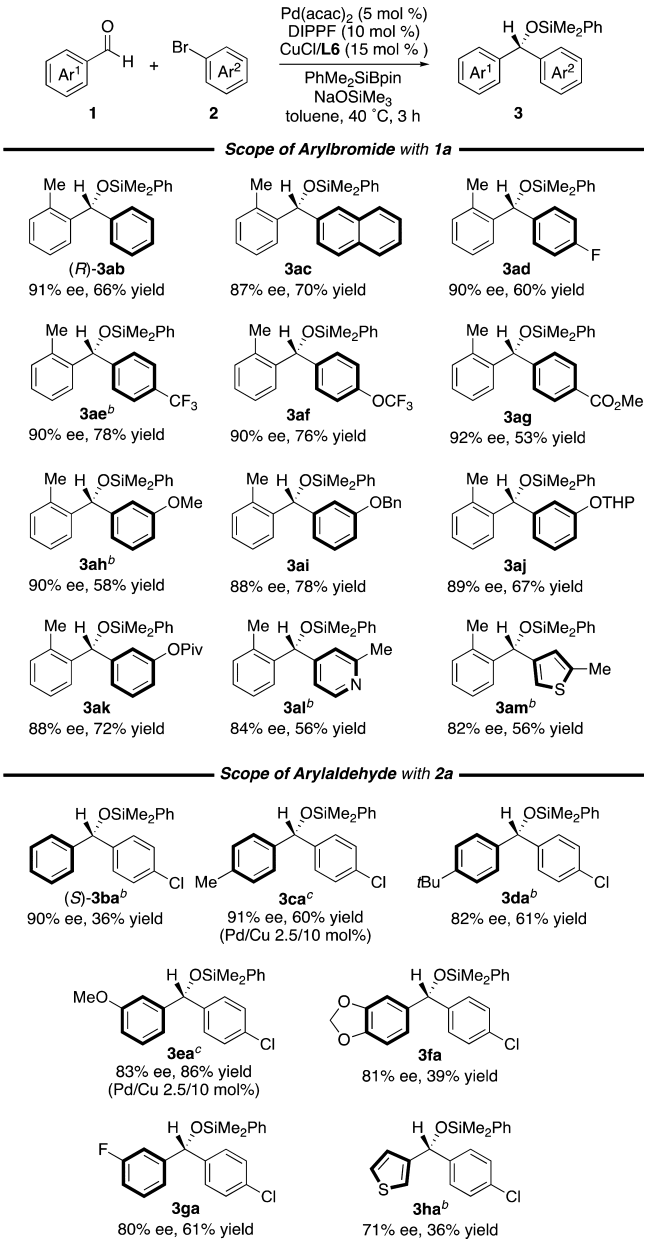
Table 2. Substrate Scope[a]



[a]The reactions were carried out with **1** (0.3 mmol), **2** (0.2 mmol), $PhMe_2SiBpin$ (0.3 mmol), $Pd(acac)_2$ (5 mol %), DIPPF (10 mol %), CuCl/**L6**·HBF_4 (15 mol %), and $NaOSiMe_3$ (0.23 mmol) in toluene (1.0 mL) at 40 °C for 3 h. The enantiomeric excess was determined by HPLC analysis. [b]The reaction temperature was increased to 60 °C. [c]$Pd(acac)_2$ (2.5 mol %), DIPPF (5 mol %), CuCl/**L6**·HBF_4 (10 mol %), and $NaOSiMe_3$ (0.22 mmol) were used, and the reaction temperature was increased to 80 °C.

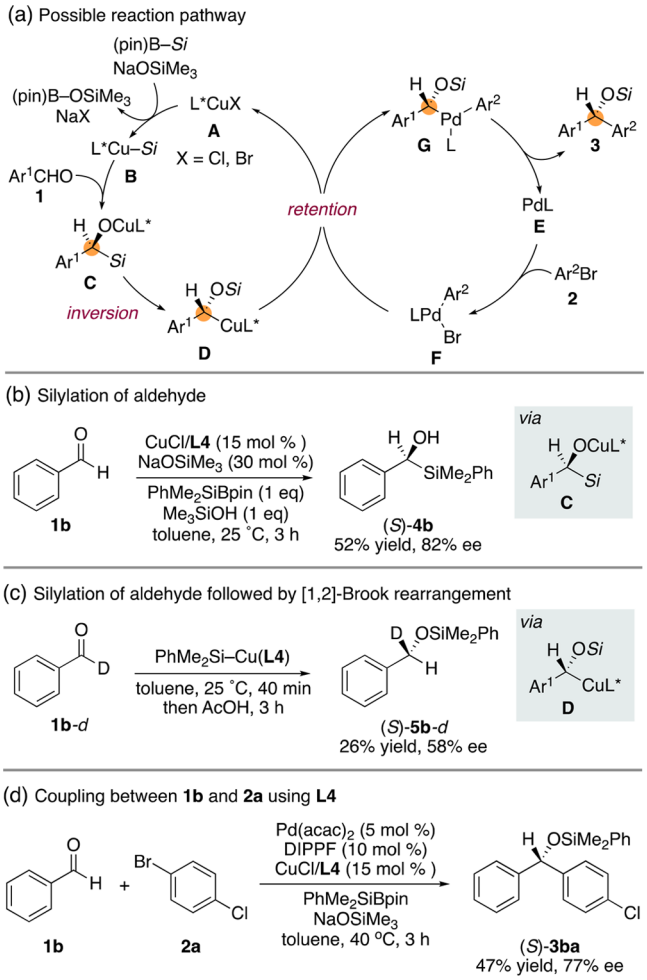


Figure 2. Mechanistic considerations.

instability of the in situ-generated stoichiometric copper complex with **L6**. The copper-catalyzed carbonyl addition of a silylboronate to benzaldehyde (**1b**) using trimethylsilanol as a proton source afforded (*S*)-α-silyl-substituted benzyl alcohol **4b** in 52% isolated yield with 82% ee (Figure 2b).[19] Next, the reaction of a stoichiometric amount of a chiral silylcopper(I) complex, which was prepared in situ from CuCl, **L4**·HBF_4, $PhMe_2SiB(pin)$, and NaO*t*Bu (1:1:1:2), with deuterated benzaldehyde-α-d_1 (**1b**-*d*) was also performed without any proton sources (Figure 2c). The reaction gave, after addition of acetic acid, chiral deuterated benzyl silyl ether **5b**-*d* with the *S* configuration.[20,21] The stereochemical outcomes observed in the three-component reactions indicated that the copper-mediated [1,2]-Brook rearrangement proceeded with inversion of configuration (**C** → **D**; Figure 2a).[22,23] Additionally, comparison of the absolute configuration of **5b**-*d* with that of benzhydryl silyl ether **3ba** obtained by the coupling reaction with aryl bromide (Figure 2d) indicated that the Cu/Pd transmetalation between stereodefined α-silyloxybenzylcopper(I) species **D** and arylpalladium(II) intermediate **F** could occur with retention of configuration (**D** → **G**; Figure 2a).[24]

Finally, the present reaction was not limited to aryl electrophiles as coupling partners but was also applicable to different coupling partners. For example, the synergistic palladium/copper-catalyzed cross-coupling reaction using allylic carbonate **6a** produced enantioenriched chiral homoallylic alcohol derivative **7aa** with 80% ee in 70% yield (Scheme 1).[14] Without significant modification of the reaction conditions, especially with respect to the chiral NHC ligand, a high enantiomeric purity of the product is guaranteed.

In conclusion, asymmetric reactions of aromatic aldehydes and aryl bromides with a silylboronate occurred with high enantioselectivities to yield the three-component coupling products, chiral silyl-protected secondary alcohol derivatives. The reaction was enabled by the merging of a new chiral copper−N-heterocyclic carbene catalyst and a palladium−bisphosphine catalyst in a synergistic manner. Preliminary

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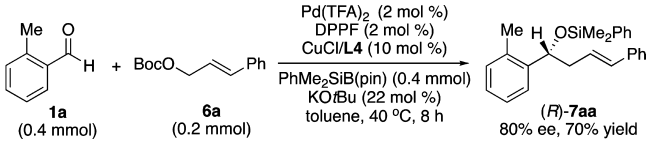
Scheme 1. Allylic Cross-Coupling



results showed that this palladium/copper catalysis is also amenable to the reaction of an allylic carbonate as the coupling partner. Our method features the catalytic generation of enantioenriched chiral α-alkoxyalkylcopper(I) intermediates from aldehydes and their subsequent palladium-catalyzed stereospecific cross-coupling with aryl or allyl electrophiles. This protocol provides a new umpolung strategy for catalytically forming a chiral α-alkoxyalkyl anion from an aromatic aldehyde for use in asymmetric synthesis. Mechanistic investigations aided by theoretical calculations are currently 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.8b11495.

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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(13) To test the assumption, we investigated the reaction without the NHC ligand for copper under the conditions shown in Table 1, entry 10. The coupling product was obtained in a low yield.

(14) The absolute configurations of **3ab** and **3ba** were determined by transforming them to the known diarylmethanols. The absolute configuration of **7aa** was determined by Mosher's NMR spectroscopic method. Absolute configurations of the other products listed in Table 2 were assigned by consideration of the stereochemical pathway. See the Supporting Information for details.

(15) The reason for the slight drop in the enantiomeric excess of **3al** and **3am** is unclear. The reaction of electron-rich aryl halides resulted in low product yields due to the slow oxidative addition step.

(16) When an aliphatic aldehyde was used as a substrate, significant amounts of the corresponding α-silyl-substituted alcohol and acylsilane were obtained. This result suggested that the Brook rearrangement in aliphatic aldehydes was slower than that in aromatic aldehydes.

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