Communication

Asymmetric Catalysis Using Aromatic Aldehydes as Chiral #-Alkoxyalkyl Anions

Kenya Yabushita, Akihiro Yuasa, Kazunori Nagao, and Hirohisa Ohmiya

J. Am. Chem. Soc., **Just Accepted Manuscript** • Publication Date (Web): 18 Dec 2018

Asymmetric Catalysis Using Aromatic Aldehydes as Chiral α-Alkoxyalkyl Anions

Kenya Yabushita, Akihiro Yuasa, Kazunori Nagao, and Hirohisa Ohmiya*

Division of Pharmaceutical Sciences, Graduate School of Medical Sciences, Kanazawa University, Kakuma-machi, Kanazawa 920-1192, Japan

Supporting Information Placeholder

ABSTRACT: We 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 co-workers prepared chiral α-alkoxyalkyllithium compounds by enantiotopic α-deprotonation of aliphatic alcohol derivatives with highly basic alkyllithium reagents and a stoichiometric amount of chiral amines (Figure 1b).[2] 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 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 the asymmetric version by use of a chiral ligand in the copper catalyst (Figure 1e). Here, we report an asymmetric catalysis using aromatic aldehydes as chiral α-alkoxyalkyl anions (Figure 1a, left). The reaction between 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]

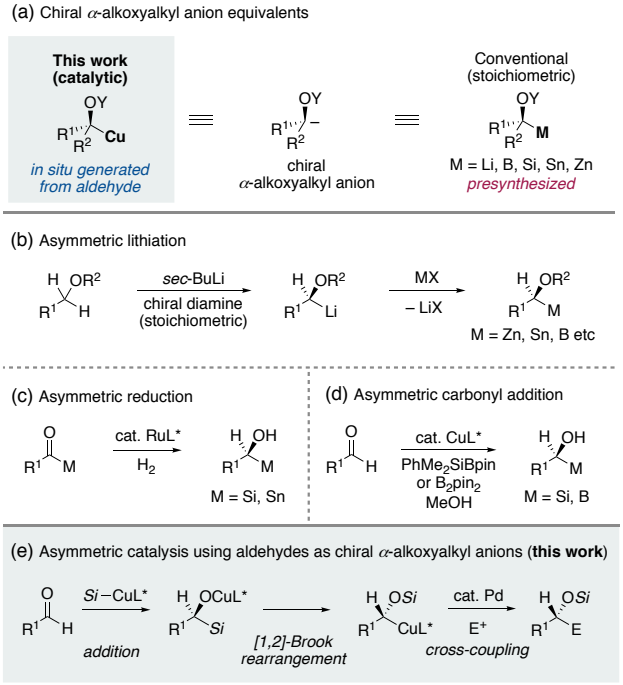
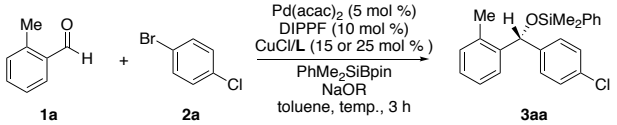


Figure 1. Generation of chiral α-alkoxyalkyl anions.

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 between *o*-tolualdehyde **1a** (0.3 mmol) and bromochlorobenzene **2a** (0.2 mmol) with (dimethylphenylsilyl)boronic acid pinacol ester [$PhMe_2SiB(pin)$] (0.3 mmol) in the presence of palladium(II) acetylacetonate [$Pd(acac)_2$] (5 mol %), 1,1'-bis(diisopropylphosphino)ferrocene (DIPPF) (10 mol %), 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*

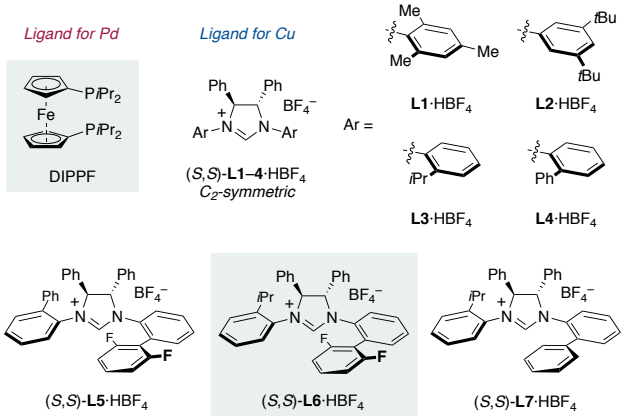
situ from CuCl, **L**·HBF_4, and $NaOSiMe_3$. The ring-saturated C_2-symmetric NHC ligand [(*S*,*S*)-**L1**],[10] which has two stereogenic carbon centers in the imidazolidine ring with two mesityl groups at both nitrogen atoms, possessed slight catalytic activity (20%) and enantioselectivity (21% ee) (entry 1). Similar chiral NHC ligands bearing 3,5-di-*t*-butyl-phenyl (**L2**), 2-isopropyl-phenyl (**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).

Table 1. Screening of chiral NHC ligands and bases for cross-coupling between **1a** and **2a**.[a] The HBF_4 salts of **L2**, **L5–L7** were newly synthesized in this study.



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

entry	Cu cat. (mol %)	NHC	base	temp.	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	–

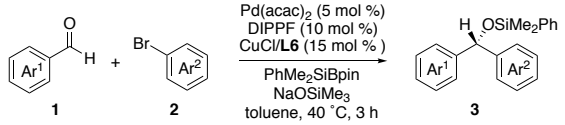


[a] Reaction was carried out with **1a** (0.3 mmol), **2a** (0.2 mmol), $PhMe_2SiBpin$ (0.3 mmol), $Pd(acac)_2$ (5 mol%), DIPPF (10 mol %), CuCl/**L**·HBF_4 (15 or 25 mol %), alkoxide base (0.25 mmol) in toluene (1.0 mL) at 40 or 60 °C for 3 h. DIPPF, 1,1'-bis(diisopropylphosphino)ferrocene. [b] Enantiomeric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

Next, we prepared a 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 (87% ee) slightly better than 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 (72%) and enantioselectivity (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.

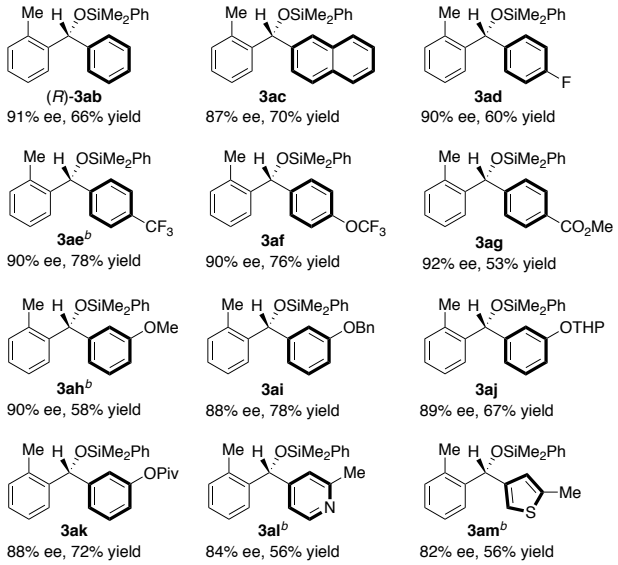
The steric and electronic nature of the alkoxide moiety of the base was important (Table 1). Thus, the use of more basic NaO*t*Bu instead of $NaOSiMe_3$ diminished the product yield and enantioselectivity (entry 10). This result might be due to the formation of achiral silyl(*tert*-butoxy)cuprate species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

Table 2. Substrate scope[a]

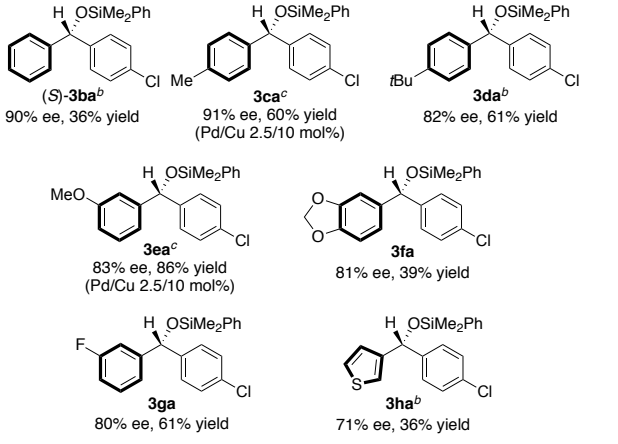


1 **2** **3**

Scope of Arylbromide** with **1a



Scope of Arylaldehyde** with **2a



[a] Reaction was 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 %), $NaOSiMe_3$ (0.23 mmol) in toluene (1.0 mL) at 40 °C for 3 h.

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.

Table 2 summarizes the results of the reactions of various aryl bromides under the Cu–**L6** catalyst system.[14] Bromobenzene or 2-bromonaphthalene reacted with **1a** with high enantioselectivities (**3ab** and **3ac**). Due to 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*-positions of the aromatic ring reacted to afford the corresponding chiral benzhydryl silyl ether products with high enantioselectivities (88–92% ees) (**3ad**–**3ak**). 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 or *p*-*tert*-butyl-benzaldehyde reacted with **2a** with high enantioselectivities (**3ba**–**3da**). Functionalized benzaldehydes such as *m*-anisaldehyde, piperonal or 3-fluorobenzaldehyde underwent the coupling, giving the corresponding chiral benzhydryl silyl ethers with a useful level of enantioselectivities (**3ea**–**3ga**). 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]

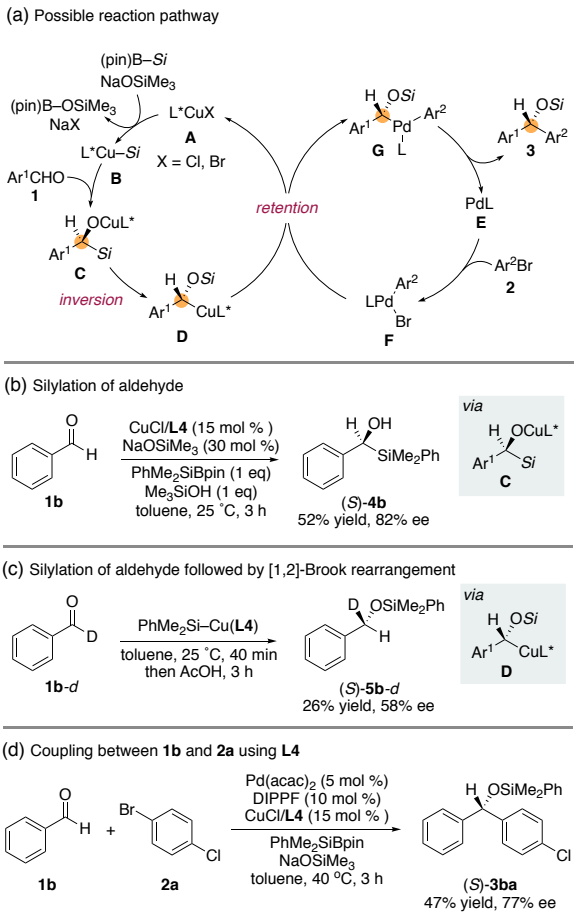


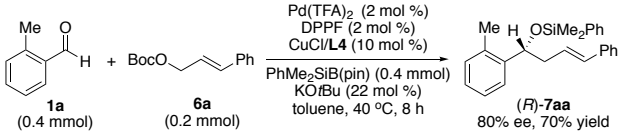
Figure 2. Mechanistic considerations.

A reaction mechanism consisting of two distinct catalytic cycles, namely copper and palladium catalysis, is illustrated in Figure 2a.[6a] Initially, the reaction of a chiral NHC-ligated copper complex (**A**), a silylboronate and $NaOSiMe_3$ forms a silylcopper(I) species (**B**) and trimethylsilyloxyboronate. The enantioselective addition of silylcopper(I) (**B**) across the C=O bond of aldehyde **1** produces a stereodefined α-silyl-substituted copper(I) alkoxide (**C**),[4a] which subsequently undergoes 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**, regenerating 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** due to the 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 occurred to give (*S*)-α-silyl-substituted benzyl alcohol **4b** in 52% isolated yield with 82% enantioselectivity (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^tBu (1/1/1/2), with deuterated benzaldehyde-α-d1 (**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 (*S*) configuration.[20,21] The stereochemical outcomes observed in the three-component reactions indicated 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 the benzhydryl silyl ether (**3ba**) obtained by the coupling reaction with aryl bromide (Scheme 1d) indicated that the Cu/Pd transmetalation between a 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** occurred to produce 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.

Scheme 1. Allylic cross-coupling.



In conclusion, asymmetric reactions between 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 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. Experimental details and characterization data for all new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

ohmiya@p.kanazawa-u.ac.jp

ORCID

Hirohisa Ohmiya: 0000-0002-1374-1137
Kazunori Nagao: 0000-0003-3141-5279

ACKNOWLEDGMENT

This work was supported by JSPS KAKENHI Grant Number JP18H01971 to Scientific Research (B), JSPS KAKENHI Grant Number JP17H06449 (Hybrid Catalysis), Kanazawa University SAKIGAKE project 2018 and the Uehara Memorial Foundation.

REFERENCES

(1) For selected papers on reactions with chiral α-alkoxyalkylmetal reagents, see: (a) Ye, J.; Bhatt, R. K.; Falck, J. R. Stereospecific Palladium/Copper Cocatalyzed Cross-Coupling of α-Alkoxy- and α-Aminostannanes with Acyl Chlorides. *J. Am. Chem. Soc.* **1994**, *116*, 1. (b) Goli, M.; He, A.; Falck, J. R. Pd-catalyzed Cross-Coupling of α-(Acyloxy)-tri-*n*-butylstannanes with Alkenyl, Aryl, and Heteroaryl Electrophiles. *Org. Lett.* **2011**, *13*, 344. (c) Molander, G. A.; Wisniewski, S. R. Stereospecific Cross-Coupling of Secondary Organotrifluoroborates: Potassium 1-(Benzyloxy)alkyltrifluoroborates. *J. Am. Chem. Soc.* **2012**, *134*, 16856. (d) Dakarapu, R.; Falck, J. R. Stereospecific Stille Cross-Couplings Using Mn(II)Cl_2. *J. Org. Chem.* **2018**, *83*, 1241.

(2) (a) Hoppe, D.; Hense, T. Enantioselective Synthesis with Lithium/(−)-Sparteine Carbanion Pairs. *Angew. Chem. Int. Ed.* **1997**, *36*, 2282. (b) Papillon, J. P. N.; Taylor, R. J. K. The Preparation of Nonracemic Secondary α-(Carbamoyloxy)alkylzinc and Copper Reagents. A Versatile Approach to Enantioenriched Alcohols. *Org. Lett.* **2002**, *4*, 119.

(3) (a) Soderquist, J. A.; Anderson, C. L.; Miranda, E. I.; Rivera, I.; Kabalka, G. W. Essentially homochiral 1-silyl alcohols from the reduction of aliphatic acylsilanes with chlorodiisopinocampheylborane. *Tetrahedron Lett.* **1990**, *31*, 4677. (b) Takeda, K.; Ohnishi, Y.; Koizumi, T. Enantioselective Reduction of α,β-Unsaturated Acylsilanes by Chiral Lithium Amides. *Org. Lett.* **1999**, *1*, 237. (c) Huckins, J. R.; Rychnovsky, S. D. Synthesis of Optically Pure Arylsilylcarbinols and Their Use as Chiral Auxiliaries in Oxacarbenium Ion Reactions. *J. Org. Chem.* **2003**, *68*, 10135. (d) Arai, N.; Suzuki, K.; Sugizaki, S.; Sorimachi, H.; Ohkuma, T. Asymmetric Hydrogenation of Aromatic, Aliphatic, and α,β-Unsaturated Acyl Silanes Catalyzed by Tol-binap/Pica Ruthenium(II) Complexes: Practical Synthesis of Optically Active α-Hydroxysilanes. *Angew. Chem. Int. Ed.* **2008**, *47*, 1770.

(4) (a) Oestreich, M.; Hartmann, E.; Mewald, M. Activation of the Si–B Interelement Bond: Mechanism, Catalysis, and Synthesis. *Chem. Rev.* **2013**, *113*, 402. (b) Hensel, A.; Oestreich, M. Asymmetric Addition of Boron and Silicon Nucleophiles, *Top. Organomet. Chem.* **2016**, *58*, 135. (c) 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. (d) Delvos, L, B.; Hensel, A.; Oestreich, M. McQuade's Six-Membered NHC–Copper(I) Complexes for Catalytic Asymmetric Silyl Transfer. *Synthesis* **2014**, *46*, 2957. (e) Kubota, K.; Yamamoto, E.; Ito, H. Copper(I)-Catalyzed Enantioselective Nucleophilic Borylation of Aldehydes: An Efficient Route to Enantiomerically Enriched α-Alkoxyorganoboronate Esters. *J. Am. Chem. Soc.* **2015**, *137*, 420. (f) Kubota, K.; Osaki, S.; Jin, M.; Ito, H. Copper(I)-Catalyzed Enantioselective Nucleophilic Borylation of Aliphatic Ketones: Synthesis of Enantioenriched Chiral Tertiary α-Hydroxyboronates. *Angew. Chem. Int. Ed.* **2017**, *56*, 6646.

(5) (a) Smirnov, P.; Mathew, J.; Nijs, A.; Katan, E.; Karni, M.; Bolm, C.; Apeloig, Y.; Marek, I. One-Pot Zinc-Promoted Asymmetric Alkynylation/Brook-Type Rearrangement/Ene–Allene Cyclization: Highly Selective Formation of Three New Bonds and Two Stereocenters in Acyclic Systems. *Angew. Chem. Int. Ed.* **2013**, *52*, 13717. (b) Rong, J.; Oost, R.; Desmarchelier, A.; Minnaard, A. J.; Harutyunyan, S. R. Catalytic Asymmetric Alkylation of Acylsilanes. *Angew. Chem. Int. Ed.* **2015**, *54*, 3038. (c) Han, M.-Y.; Xie, X.; Zhou, D.; Li, P.; Wang, L. Organocatalyzed Direct Aldol Reaction of Silyl Glyoxylates for the Synthesis of α-Hydroxysilanes. *Org. Lett.* **2017**, *19*, 2282. (d) An, P.; Huo, Y.; Chen, Z.; Song, C.; Ma, Y. Metal-free enantioselective addition of nucleophilic silicon to aromatic aldehydes catalyzed by a [2.2]paracyclophane-based N-heterocyclic carbene catalyst. *Org. Biomol. Chem.* **2017**, *15*, 3202. (e) Han, M.-Y.; Luan, W.-Y.; Mai, P.-L.; Li, P.; Wang, L. Organocatalytic Asymmetric Vinylogous Aldol Reaction of Allyl Aryl Ketones to Silyl Glyoxylates. *J. Org. Chem.* **2018**, *83*, 1518.

(6) (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. Commum.* **2018**, *54*, 6776. See also: (b) Takeda, M.; Nagao, K.; Ohmiya, H. Reductive Coupling between Aldehydes and Ketones by Copper Catalysis. *Submitted.*

(7) For non-enantioselective reaction involving catalytic generation of α-oxygenated enolates from α-ketoesters through [1,2]-phospha-Brook rearrangement, followed by an S_NAr reaction, see: Kondoh, A.; Aoki, T.; Terada, M. Efficient Synthesis of Polysubstituted Pyrroles Based on [3+2] Cycloaddition Strategy Utilizing [1,2]-Phospha-Brook Rearrangement under Brønsted Base Catalysis. *Chem. Eur. J.* **2018**, *24*, 15246.

(8) For reviews on enantioselective preparation of chiral diarylmethanols, see: (a) Ameen, D.; Snape, T. J. Chiral 1,1-diaryl compounds as important pharmacophores. *Med. Chem. Commun.* **2013**, *4*, 893. (b) Schmidt, F.; Stemmler, R. T.; Rudolph, J.; Bolm, C. Catalytic asymmetric approaches towards enantiomerically enriched diarylmethanols and diarylmethylamines. *Chem. Soc. Rev.* **2006**, *35*, 454. For selected recent papers, see: (c) Touge, T.; Nara, H.; Fujiwhara, M.; Kayaki, Y.; Ikariya, T. Efficient Access to Chiral Benzhydrols via Asymmetric Transfer Hydrogenation of Unsymmetrical Benzophenones with Bifunctional Oxo-Tethered Ruthenium Catalysts. *J. Am. Chem. Soc.* **2016**, *138*, 10084−10087. (d) Lee, T.; Wilson, T. W.; Berg, R.; Ryberg, P.; Hartwig, J. F. Rhodium-Catalyzed Enantioselective Silylation of Arene C–H Bonds: Desymmetrization of Diarylmethanols. *J. Am. Chem. Soc.* **2015**, *137*, 6742. (e) Salvi, L.; Kim, J. G.; Walsh, P. J. Practical Catalytic Asymmetric Synthesis of Diaryl-, Aryl Heteroaryl-, and Diheteroarylmethanols. *J. Am. Chem. Soc.* **2009**, *131*, 12483.

(9) Chiral bisphosphine ligand such as DTBM-SEGPHOS resulted in no reaction. See ref 4c.

(10) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. Synthesis and Activity of a New Generation of Ruthenium-Based Olefin Metathesis Catalysts Coordinated with 1,3-Dimesityl-4,5-dihydroimidazol-2-ylidene Ligands. *Org. Lett.* **1999**, *1*, 953.

(11) Faller, J. W.; Fontaine, P. P. Stereodynamics and Asymmetric Hydrosilylation with Chiral Rhodium Complexes Containing a Monodentate N-Heterocyclic Carbene. *Organometallics* **2006**, 25, 5887.

(12) Lillo, V.; Prieto, A.; Bonet, A.; Díaz-Requejo, M. M.; Ramírez, J.; Peŕez, P. J.; Fernańdez, E. Asymmetric β-Boration of α,β-Unsaturated Esters with Chiral (NHC)Cu Catalysts. *Organometallics* **2009**, *28*, 659.

(13) To test the assumption, we investigated the reaction without NHC ligand for a copper under 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 Supporting Information for details.

(15) The reason for the slight drop in enantiomeric excess of **3al** and **3am** is unclear. The reaction of electron-rich aryl halides resulted in low product yield 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 the Brook rearrangement in aliphatic aldehydes was slower than that in aromatic aldehydes.

(17) 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.

(18) For examples of synergistic palladium/copper catalysis, see: (a) Sonogashira, K.; Tohda, Y.; Hagihara, N. A convenient synthesis of acetylenes: catalytic substitutions of acetylenic hydrogen with bromoalkenes, iodoarenes and bromopyridines. *Tetrahedron Lett.* **1975**, *16*, 4467. (b) Liebeskind, L. S.; Fengl, R. W. 3-Stannylcyclobutenediones as nucleophilic cyclobutenedione equivalents. Synthesis of substituted cyclobutenediones and cyclobutenedione monoacetals and the beneficial effect of catalytic copper iodide on the Stille reaction. *J. Org. Chem*. **1990**, *55*, 5359. (c) Huang, J.; Chan, J.; Chen, Y.; Borths, C. J.; Baucom, K. D.; Larsen, R. D.; Faul, M. M. A Highly Efficient Palladium/Copper Cocatalytic System for Direct Arylation of Heteroarenes: An Unexpected Effect of Cu(Xantphos)I. *J. Am. Chem. Soc*. **2010**, *132*, 3674. (d) Nahra, F.; Macé, Y.; Lambin, D.; Riant, O. Copper/Palladium-Catalyzed 1,4 Reduction and Asymmetric Allylic Alkylation of α,β-Unsaturated Ketones: Enantioselective Dual Catalysis. *Angew. Chem. Int. Ed.* **2013**, *52*, 3208. (e) Vercruysse, S.; Cornelissen, L.; Nahra, F.; Collard, L.; Riant, O. Cu^{I}/Pd^{0} Cooperative Dual Catalysis: Tunable Stereoselective Construction of Tetra-Substituted Alkenes. *Chem. Eur. J*. **2014**, *20*, 1834. (f) Semba, K.; Nakao, Y. Arylboration of Alkenes by Cooperative Palladium/Copper Catalysis. *J. Am. Chem. Soc*. **2014**, *136*, 7567. (g) Smith, K. B.; Logan, K. M.; You, W.; Brown, M. K. *Chem. Eur. J*. **2014**, *20*, 12032. (h) Jia, T.; Cao, P.; Wang, B.; Lou, Y.; Yin, X.; Wang, M.; Liao, J. A Cu/Pd Cooperative Catalysis for Enantioselective Allylboration of Alkenes. *J. Am. Chem. Soc.* **2015**, *137*, 13760. (i) Logan, K. M.; Smith, K. B.; Brown, M. K. Copper/Palladium Synergistic Catalysis for the *syn*- and *anti*-Selective Carboboration of Alkenes. *Angew. Chem. Int. Ed.* **2015**, *54*, 5228. (j) Shintani, R.; Kurata, H.; Nozaki, K. Intermolecular Three-Component Arylsilylation of Alkynes under Palladium/Copper Cooperative Catalysis. *J. Org. Chem*. **2016**, *81*, 3065. (k) Logan, K. M.; Brown, M. K. Catalytic Enantioselective Arylboration of Alkenylarenes. *Angew. Chem. Int. Ed*. **2017**, *56*, 851. (l) Smith, K. B.; Brown, M. K. Regioselective Arylboration of Isoprene and Its Derivatives by Pd/Cu Cooperative Catalysis. *J. Am. Chem. Soc*. **2017**, *139*, 7721. (m) Sardini, S. R.; Brown, M. K. Catalyst Controlled Regiodivergent Arylboration of Dienes. *J. Am. Chem. Soc.* **2017**, *139*, 9823. (n) Huo, X.; He, R.; Fu, J.; Zhang, J.; Yang, G.; Zhang, W. Stereoselective and Site-Specific Allylic Alkylation of Amino Acids and Small Peptides via a Pd/Cu Dual Catalysis. *J. Am. Chem. Soc*. **2017**, *139*, 9819. (o) Chen, B.; Cao, P.; Yin, X.; Liao, Y.; Jiang, L.; Ye, J.; Wang, M.; Liao, J. Modular Synthesis of Enantioenriched 1,1,2-Triarylethanes by an Enantioselective Arylboration and Cross-Coupling Sequence. *ACS Catal*. **2017**, *7*, 2425. (p) Mateos, J.; Rivera-Chao, E.; Fañanás-Mastral, M. Synergistic Copper/Palladium Catalysis for the Regio- and Stereoselective Synthesis of Borylated Skipped Dienes. *ACS Catal*. **2017**, *7*, 5340. (q) Saito, A.; Kumagai, N.; Shibasaki, M. Cu/Pd Synergistic Dual Catalysis: Asymmetric α-Allylation of an α-CF_3 Amide. *Angew. Chem. Int. Ed.* **2017**, *56*, 5551. (r) Wei, L.; Xu, S.-M.; Zhu, Q.; Che, C.; Wang, C.-J. Synergistic Cu/Pd Catalysis for Enantioselective Allylic Alkylation of Aldimine Esters: Access to α, α-Disubstituted α-Amino Acids. *Angew. Chem. Int. Ed.* **2017**, *56*, 12312. (s) Pye, D. R.; Mankad, N. P. Bimetallic catalysis for C–C and C–X coupling reactions. *Chem. Sci*. **2017**, *8*, 1705. (t) Semba, K.; Ariyama, K.; Zheng, H.; Kameyama, R.; Sakaki, S.; Nakao, Y. Reductive Cross-Coupling of Conjugated Arylalkenes and Aryl Bromides with Hydrosilanes by Cooperative Palladium/Copper Catalysis. *Angew. Chem. Int. Ed.* **2016**, *55*, 6275. (u) Friis, S. D.; Pirnot, M. T.; Buchwald, S. L. Asymmetric Hydroarylation of Vinylarenes Using a Synergistic Combination of CuH and Pd Catalysis. *J. Am. Chem. Soc.* **2016**, *138*, 8372. (v) Friis, S. D.; Pirnot, M. T.; Dupuis, L. N.; Buchwald, S. L. A Dual Palladium and Copper Hydride Catalyzed Approach for Alkyl–Aryl Cross-Coupling of Aryl Halides and Olefins. *Angew. Chem. Int. Ed.* **2017**, *56*, 7242.

(19) Huckins, J, R.; Rychnovsky, S, D. Synthesis of Optically Pure Arylsilylcarbinols and Their Use as Chiral Auxiliaries in Oxacarbenium Ion Reactions. *J. Org. Chem.* **2003**, *68*, 10135.

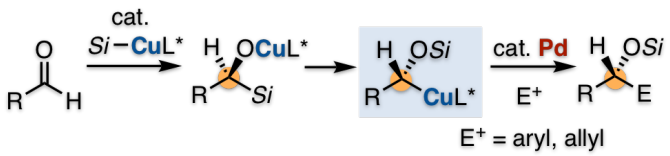
(20) (a) Wightman, R. H.; Staunton, J.; Battersby, A. R.; Hanson, K. R. Studies of enzyme-mediated reactions. Part I. Syntheses of deuterium- or tritium-labelled (3*S*)- and (3*R*)-phenylalanines: stereochemical course of the elimination catalysed by L-phenylalanine ammonia-lyase. *J. Chem. Soc., Perkin Trans. 1* **1972**, 2355. (b) Malova Krizkova, P.; Hammerschmidt, F. On the Configurational Stability of Chiral Heteroatom-Substituted [D_1]Methylpalladium Complexes as Intermediates of Stille and Suzuki–Miyaura Cross-Coupling Reactions. *Eur. J. Org. Chem.* **2013**, 5143.

(21) The erosion of enantiomeric excess of **5b** shown in Figure 2c might be due to the use of NaO*t*Bu. See the discussion for Table 1, entry 10. Unfortunately, the use of $NaOSiMe_3$ instead of NaO*t*Bu did not give **5b**, but gave **4b**.

(22) Inversion of stereochemistry in the copper-mediated bora-Brook rearrangement was suggested by DFT studies. See: Zhao, H.; Dang, L.; Marder, T. B.; Lin, Z. DFT Studies on the Mechanism of the Diboration of Aldehydes Catalyzed by Copper(I) Boryl Complexes. *J. Am. Chem. Soc.* **2008**, *130*, 5586.

(23) For the stereochemistry of the conventional [1,2]-Brook rearrangement, see: (a) Brook, A. G. Molecular rearrangements of organosilicon compounds. *Acc. Chem. Res*. **1974**, *7*, 77. (b) Fleming, I.; Barbero, A.; Walter, D. Stereochemical Control in Organic Synthesis Using Silicon-Containing Compounds. *Chem. Rev.* **1997**, *97*, 2063.

(24) Zheng, H.; Semba, K.; Nakao, Y.; Sakai, S. How to Control Inversion vs Retention Transmetalation between Pd^{II}–Phenyl and Cu^{I}–Alkyl Complexes: Theoretical Insight. *J. Am. Chem. Soc.* **2017**, *139*, 14065.


cat.
Si–CuL*
O
R
H
H
OCuL*
R
Si
H
OSi
R
CuL*
cat. Pd
E+
H
OSi
R
E
E+ = aryl, allyl