Enantioselective Silylation

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Copper-Catalyzed Addition of Nucleophilic Silicon to Aldehydes**

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The transition metal-catalyzed transfer of silicon nucleophiles[1] onto various electrophiles, has recently gained considerable attention,[2] owing to the development of readily available silicon pro-nucleophiles. In particular, the reagent developed by the Suginome group, which possesses a Si–B linkage has become one of the major sources of nucleophilic silicon.[1a] This new method is particularly attractive, as it provides a facile access to metal–silicon reagents that render the use of any activating agents unnecessary.

These metal–silicon intermediates allow the catalytic transfer of a silicon nucleophile onto various electrophiles; our interest lies in the addition of such species to aldehydes, thus generating α-hydroxysilanes. This type of C–Si bond formation as well as the hydroxy group is of crucial importance in organic synthesis. Moreover, a stereogenic center is formed in this process, thus generating possible opportunities for asymmetric catalysis.

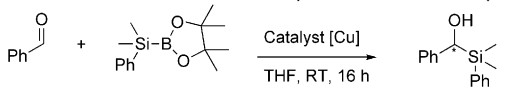
Optically active α-hydroxysilanes are a class of chiral organometallic compounds that contain a functional group. These molecules and their derivatives have been used for stereocontrolled C–C bond formation and rearrangements, which resulted in a wide variety of chiral organic compounds.[3–7] The majority of literature-known methods for the preparation of α-hydroxysilanes are based on the asymmetric reduction of acylsilanes[8] or the hydrogenation of enolsilanes.[9] However, the synthesis of acylsilanes usually requires several steps.[10] An alternative, but less used, approach is the one previously described, which includes the addition of a silicon nucleophile to a carbonyl compound.[11–14] Hiyama et al. introduced a fluoride-catalyzed Si–Si bond cleavage followed by the addition of released silicon nucleophiles to aldehydes.[11] However, yields were partially diminished by [1,2]-Brook rearrangement. Barrett and Hill[13] elaborated a practical procedure based on the addition of easy-to-form $Me_2PhSiLi$ to aliphatic and aromatic aldehydes, but the use of such strongly basic nucleophiles is not without problems for functionalized aldehydes.

Recently, Oestreich described the racemic 1,2-addition of a silicon nucleophile to imines and aldehydes, and proposed a mechanism involving a Cu–Si intermediate as the silyl transfer species.[2d,15] The mild copper-mediated generation of nucleophilic silicon from Si–B compounds might therefore be useful for catalytic one-step access to enantiomerically pure α-hydroxysilanes from readily available aldehydes.

Herein, we report the first enantiomeric version of the 1,2-addition of a silicon nucleophile to aromatic and aliphatic aldehydes catalyzed by copper(I) complexes.

Our investigation started with benzaldehyde, which was selected as a model substrate for initial screening. The reaction of **1a** with $Me_2PhSiBpin$ (**2**; =Si–B, pin = pinacolato)[16] in the presence of $CuF(PPh_3)_3{\cdot}2\,MeOH$ (**3**)[17] as the copper catalyst was completed in 2 h at room temperature, and resulted in the isolation of racemic α-hydroxysilane in 39% yield. To establish suitable reaction conditions, we first optimized the reaction temperature and solvent. We obtained the best results by running the reaction in THF at room temperature. We then screened different catalysts and additives, as shown in Table 1.

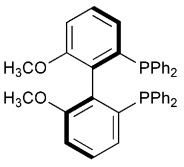
Table 1: Selected experiments from the optimization of the copper-catalyzed 1,2-addition reaction of nucleophilic silicon to aldehyde **1a**.



1a **2** (1.5 equiv) **4a**

Entry	[Cu] (5 mol%)	L (10 mol%)	Yield [%][a]	*ee* [%][b]
1	**3**	–	39[c]	–
2	**3**	(*rac*)-binap	37	–
3	**3**	**5**	49	5
4	CuCl/NaO*t*Bu	**5**	0	–
5	CuCl/NaO*t*Bu	**6**	12	20
6	CuCl/NaO*t*Bu	**7**	23	84
7[d]	CuCl/NaO*t*Bu	**7**	46	97

[a] Yield of isolated product after hydrolysis and flash chromatography on silica gel. [b] Determined by HPLC analysis on a chiral stationary phase. [c] Conversion was complete in 2 h. [d] MeOH (4 equiv) was used as an additive.



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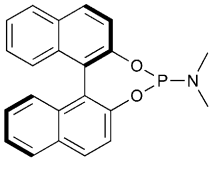

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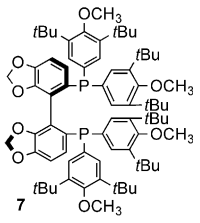

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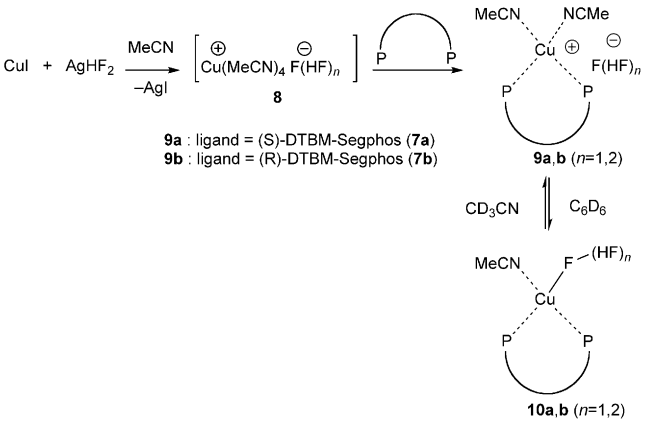
We found that diphosphine ligands, (*rac*)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (binap) and MeO-biphep (**5**; see Table 1 for structure), when used with **3** also promoted the 1,2-addition, but a prolonged reaction time was required (Table 1, entries 2 and 3). Moreover, no significant enantioselectivity was observed with chiral ligands, because the reaction was much faster with PPh_3 as the ligand (Table 1, entry 3). Therefore, we decided to change the catalytic system. When diphosphine **5** was used in combination with the CuCl/NaO*t*Bu system, the reaction did not give the desired product **4a** (Table 1, entry 4). When we used the P–N ligand **6**, a 12% yield was obtained, but we observed a modest increase in enantioselectivity up to 20%. The use of the sterically hindered ligand DTBM-Segphos (**7**) considerably improved the enantioselectivity (Table 1, entry 6). Finally, the addition of methanol led to significant improvement of both the yield and enantioselectivity, which suggests that methanol plays a significant role in regenerating the catalyst (Table 1, entry 7). The optimized conditions were found to be: CuCl (5 mol%), NaO*t*Bu (5 mol%), MeOH (4 equiv), and (*R*)-DTBM-Segphos (10 mol%) at room temperature in THF. The desired product was obtained in 46% yield and 97% *ee*. However, we found that these conditions gave fairly irreproducible results, both for yields and enantioselectivities, with significant drops (down to 65% from 97%) in the enantioselection.

Recently, our group developed a new pathway to unprecedented N-heterocyclic carbene (NHC) copper(I) bifluoride complexes, which proved to be excellent catalysts for nucleophilic transfer to electrophilic double bonds, aldehydes, and chiral imines.[19] Furthermore, hydrogen bifluoride (FHF^-) is a unique anion, as it features the strongest known hydrogen bond.[18] This anion is also an anhydrous source of fluoride that can activate the Si–B reagent **2**, thus avoiding the need for co-catalysts such as alkoxides. These observations prompted us to design a new family of well-defined diphosphine copper(I) complexes bearing a bifluoride counteranion, which might lead to better control of the formation of the copper–nucleophile active species, and thus reproducible experiments. The original procedure was then modified and we found that the reaction of copper(I) iodide with silver(I) hydrogen fluoride in acetonitrile gave, after the removal of silver iodide by filtration, the tetrakis(acetonitrile) copper(I) hydrogen bifluoride intermediate (**8**) in situ. The complex was identified by a sharp singlet at $\delta = -166$ ppm by ^{19}F NMR analysis (in CD_3CN) and an acidic proton at $\delta =$ 14.1 ppm by ^1H NMR analysis, but could not be isolated by crystallization. However, the addition of ligands **7a**,**b** gave, after removal of the solvent, the new cationic complexes **9a**,**b** (Scheme 1) in excellent yield. We found that, depending on the quality of the starting commercial silver bifluoride, the bifluoride anion could be contaminated with dihydrogen trifluoride anion (see the Supporting Information for details), albeit without any detrimental effect on their catalytic activity. Furthermore, ^{19}F NMR analysis suggested that those complexes can exist either in cationic form in coordinating solvents such as acetonitrile (one sharp peak around $\delta = -165.5$ ppm) or as neutral copper-fluoride-bound complexes in non-coordinating solvents such as benzene ($d =$



Scheme 1. Synthesis of new diphosphine copper(I) bifluoride complexes.

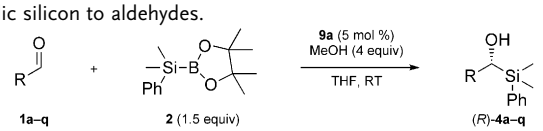
-139.6 ppm for Cu-F-H-*F* and $\delta = -192.4$ ppm for Cu-*F*-H-F). This was confirmed by crystallization in toluene/*n*-hexane which afforded crystals of X-ray quality for analysis. The structure confirmed the formation of a neutral complex bearing a σ-bonded $H_2F_3^-$ anion. Finally, we were delighted to find that those complexes are very air and moisture stable, both in the solid state and in solution, and display excellent reactivity in our model reaction.

These new complexes **9a**,**b** were tested in the copper-catalyzed 1,2-addition of a silicon nucleophile to aldehydes. Reaction of **1a** with **2** and copper complex **9a** (5 mol%) under the previously established optimized conditions, was completed in 16 h to afford the (*R*)-α-hydroxysilane (*R*)-**4a** in >99% *ee* and 87% yield of isolated product. The use of copper complex **9b** afforded the (*S*)-α-hydroxysilane (*S*)-**4a** in >99% *ee* and 82% yield of isolated product (Table 2, entries 1 and 2). The absolute configuration of compound **4a** is based on literature data.[8d]

The optimized reaction conditions were then applied to various aromatic and aliphatic aldehydes **1a**–**q** (Table 2). Regarding aromatic aldehydes, both electron-donating as well as electron-withdrawing groups were well tolerated. Yields of isolated products were good to high and the corresponding α-hydroxysilanes were obtained with excellent enantioselectivity. The electronic substitutions on the aromatic ring did not affect the enantioselectivity. However, aromatic aldehydes with functional groups at the *ortho*-position proved to be less reactive and gave the product in moderate yield (Table 2, entries 3 and 16), as a consequence of the steric hindrance at the *ortho* position. To our delight, we found that aliphatic aldehydes reacted well (Table 2, entries 9, 12, and 13). However, propionaldehyde gave the desired product in only 87% *ee* (Table 2, entry 12). This result suggests that the aldehyde is not bulky enough to obtain good selectivity. Neither aromatic aldehydes with reactive functional groups in the *para* position (NO_2 and OH groups) nor pyridine-4-carboxaldehyde yielded the desired α-hydroxysilane.

Finally, we decided to check the reactivity of more challenging substrates, such as α,β-unsaturated aldehydes, for which competition between 1,2- and 1,4- addition could be expected. Citral **10**[20] reacted with $Me_2PhSiBpin$ in the

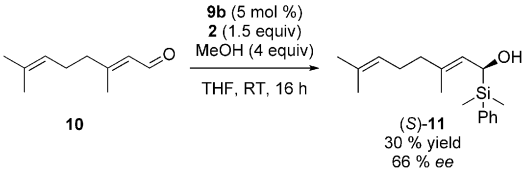
Table 2: Substrate scope of the copper-catalyzed 1,2-addition of nucleophilic silicon to aldehydes.



Entry	Aldehyde	R	Product	Yield [%][a]	*ee* [%][b]
1	**1a**	Ph	(*R*)-**4a**	87	>99
2[c]	**1a**	Ph	(*S*)-**4a**	82	>99
3	**1b**	2-MeC_6H_4	**4b**	51	99
4	**1c**	2-thiophene	**4c**	99	>99
5	**1d**	4-MeC_6H_4	**4d**	78	96
6	**1e**	4-(MeO)C_6H_4	**4e**	53	96
7	**1f**	3,4-(MeO)C_6H_4	**4f**	80	95
8	**1g**	4-PhC_6H_4	**4g**	95	95
9	**1h**	Cy	**4h**	67	>99
10	**1i**	1-naphtyl	**4i**	60	96
11	**1j**	3-(MeO)C_6H_4	**4j**	99	96
12	**1k**	CH_3CH_2	**4k**	60	87
13	**1l**	Ph$(CH_2)_2$	**4l**	88	>99
14	**1m**	4-(CN)C_6H_4	**4m**	98	95
15	**1n**	3-ClC_6H_4	**4n**	99	94
16	**1o**	2-BrC_6H_4	**4o**	66	93
17	**1p**	4-FC_6H_4	**4p**	98	98
18	**1q**	4-$CF_3C_6H_4$	**4q**	65	>99

[a] Yield of isolated product after flash chromatography on silica gel. [b] Determined by HPLC analysis on a chiral stationary phase. [c] With catalyst **9b**. Cy = cyclohexyl.

presence of copper complex **9b** under the optimized conditions to afford the (*S*)-α-hydroxysilane (*S*)-**11** in 66% *ee* and 30% yield of isolated product (Scheme 2). Such structures are particularly attractive, as they can be employed in various useful transformations, such as the Ireland–Claisen rearrangement.[6a]



Scheme 2. Copper-catalyzed silyl 1,2-addition to citral **10**.

In conclusion, we have reported the first example of the highly reactive and enantioselective addition of a silicon nucleophile to aldehydes, catalyzed by newly developed copper(I) complexes **9a**,**b**. A series of aromatic and aliphatic aldehydes were converted into the corresponding α-hydroxysilanes in excellent *ee* and good to high yields. Thus, this method provides a new and practical route to producing chiral silane compounds from readily available aldehydes. Mechanistic investigations are in progress.

Experimental Section

General procedure for the synthesis of α-hydroxysilane: Copper(I) complex **9a** or **9b** (0.05 equiv) was loaded into a flame-dried Schlenk flask. The vessel was then sealed and flushed with three vacuum/argon cycles, then THF (3 mL) was added. After the solids were dissolved, freshly distilled aldehyde (0.5 mmol, 1 equiv) was added. $Me_2PhSiBpin$ **2** (1.2 equiv) was then added dropwise. Finally, MeOH (4 equiv) was added and the mixture was stirred at room temperature overnight. $NaBO_3$ (4 equiv), Et_2O (1 mL) and water (3 mL) were added, and the mixture stirred for 3 h. Et_2O (5 mL) was then added and the phases separated. The aqueous phase was extracted with Et_2O (3 × 5 mL). The combined organic phases were then sequentially washed with sat. aq. NH_4Cl (15 mL), sat. aq. $NaHCO_3$ (15 mL), and brine (15 mL), then dried over $MgSO_4$ and concentrated under reduced pressure. Finally, the product was purified by flash chromatography on silica gel. For further details, see the Supporting Information.

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[1] For recent reviews of copper- and rhodium-catalyzed Si–B bond activation, see: a) M. Oestreich, E. Hartmann, M. Mewald, *Chem. Rev.* **2013**, DOI: 10.1021/cr3003517; b) E. Hartmann, M. Oestreich, *Chim. Oggi* **2011**, *29*, 34–36; c) E. Hartmann, D. J. Vyas, M. Oestreich, *Chem. Commun.* **2011**, *47*, 7917–7932; d) for an earlier attempt at the copper(I)-catalyzed enantioselective transfer of a silyl nucleophile to aldehydes, see Ref. [21] in: D. J. Vyas, M. Oestreich, *Angew. Chem.* **2010**, *122*, 8692–8694; *Angew. Chem. Int. Ed.* **2010**, *49*, 8513–8515.

[2] For copper-catalyzed 1,4-addition, see: a) K.-S. Lee, A. H. Hoveyda, *J. Am. Chem. Soc.* **2010**, *132*, 2898–2900; b) A. Welle, J. Petrignet, B. Tinant, J. Wouters, O. Riant, *Chem. Eur. J.* **2010**, *16*, 10980–10983; c) I. Ibrahem, S. Santoro, F. Himo, A. Cordova, *Adv. Synth. Catal.* **2011**, *353*, 245–252; for copper-catalyzed 1,2-addition, see: d) D. J. Vyas, R. Fröhlich, M. Oestreich, *Org. Lett.* **2011**, *13*, 2094–2097; for a recent summary of Si–B chemistry, see: T. Ohmura, M. Suginome, *Bull. Chem. Soc. Jpn.* **2009**, *82*, 29–49.

[3] P. F. Cirillo, J. S. Panek, *Org. Prep. Proced. Int.* **1992**, *24*, 553–582.

[4] I. Fleming, A. Barbero, D. Walter, *Chem. Rev.* **1997**, *97*, 2063–2192.

[5] For reactions using chiral aliphatic and benzylic α-hydroxysilanes, see: a) J. D. Buynak, J. B. Strickland, G. W. Lamb, D. Khasnis, S. Modi, D. Williams, H. Zhang, *J. Org. Chem.* **1991**, *56*, 7076–7083; b) R. J. Linderman, A. Ghannam, I. Badejo, *J. Org. Chem.* **1991**, *56*, 5213–5216; c) J. R. Huckins, S. D. Rychnovsky, *J. Org. Chem.* **2003**, *68*, 10135–10145.

[6] For reactions using chiral allylic α-hydroxysilanes, see: a) R. E. Ireland, M. D. Varney, *J. Am. Chem. Soc.* **1984**, *106*, 3668–3670; b) M. A. Avery, C. Jennings-White, W. K. M. Chong, *J. Org. Chem.* **1989**, *54*, 1789–1792; c) J. S. Panek, M. A. Sparks, *J. Org. Chem.* **1990**, *55*, 5564–5566; d) P. F. Cirillo, J. S. Panek, *J. Org. Chem.* **1994**, *59*, 3055–3063; e) K. Sakaguchi, H. Mano, Y. Ohfune, *Tetrahedron Lett.* **1998**, *39*, 4311–4312; f) A. Kamimura, Y. Kaneko, A. Ohta, K. Matsuura, Y. Fujimoto, A. Kakehi, S. Kanemasa, *Tetrahedron* **2002**, *58*, 9613–9620; g) P. A. Jacobi, C. Tassa, *Org. Lett.* **2003**, *5*, 4879–4882; h) K. Sakaguchi, M. Higashino, Y. Ohfune, *Tetrahedron* **2003**, *59*, 6647–6658; i) I. Izzo, E. Avallone, L. D. Corte, N. Maulucci, F. De Riccardis, *Tetrahedron: Asymmetry* **2004**, *15*, 1181–1186; j) S. Perrone, P. Knochel, *Org. Lett.* **2007**, *9*, 1041–1044.

[7] For reactions using chiral propargyllic α-hydroxysilanes, see: B. K. Guintchin, S. Bienz, *Organometallics* **2004**, *23*, 4944–4951.

[8] a) J. D. Buynak, J. B. Strickland, T. Hurd, A. Phanm, *J. Chem. Soc. Chem. Commun.* **1989**, 89–90; b) J. A. Soderquist, C. L.

Anderson, E. I. Miranda, I. Rivera, G. W. Kabalka, *Tetrahedron Lett.* **1990**, *31*, 4677 – 4680; c) K. Takeda, Y. Ohnishi, T. Koisumi, *Org. Lett.* **1999**, *1*, 237 – 239; d) N. Arai, K. Suzuki, S. Sugisaki, H. Sorimachi, T. Ohkuma, *Angew. Chem.* **2008**, *120*, 1794 – 1797; *Angew. Chem. Int. Ed.* **2008**, *47*, 1770 – 1773; e) J.-I. Matsuo, Y. Hattori, H. Ishibashi, *Org. Lett.* **2010**, *12*, 2294 – 2297; for selected examples of enzymatic methods, see: f) R. Tacke, H. Hengersberg, H. Zilch, B. Stumpf, *J. Organomet. Chem.* **1989**, *379*, 211 – 216; g) I. An, E. N. Onyeozili, R. E. Maleczka, Jr., *Tetrahedron: Asymmetry* **2010**, *21*, 527 – 534.

[9] a) L. Panella, B. L. Feringa, J. G. de Vries, A. J. Minnaard, *Org. Lett.* **2005**, *7*, 4177 – 4180; b) S. Bain, S. Ijadi-Maghsoodi, T. J. Barton, *J. Am. Chem. Soc.* **1988**, *110*, 2611 – 2614.

[10] a) P. C. Bulman Page, S. S. Klair, S. Rosenthal, *Chem. Soc. Rev.* **1990**, *19*, 147 – 195; b) R. B. Lettan II, B. C. Milgram, K. A. Scheidt, *Org. Synth.* **2007**, *84*, 22 – 31; c) R. B. Lettan II, B. C. Milgram, K. A. Scheidt, **2009**, *Org. Synth. Coll. Vol. 11*, 197 – 204.

[11] a) T. Hiyama, M. Obayashi, I. Mori, H. Nozaki, *J. Org. Chem.* **1983**, *48*, 912 – 914; b) the 1,2-addition of a silylated nucleophile to benzaldehyde with a NHC ligand is described in footnote 17 of: J. M. O'Brien, A. H. Hoveyda, *J. Am. Chem. Soc.* **2011**, *133*, 7712 – 7715.

[12] A. G. M. Barrett, J. M. Hill, E. M. Wallace, J. A. Flygare, *Synlett* **1991**, 764 – 770.

[13] a) A. G. M. Barrett, J. M. Hill, *Tetrahedron Lett.* **1991**, *32*, 3285 – 3288; b) M. B. Berry, R. J. Griffith, M. J. Sanganee, P. G. Steel, D. K. Welligan, *Org. Biomol. Chem.* **2004**, *2*, 2381 – 2392; c) C.-C. Chang, Y.-H. Kuo, Y.-M. Tsai, *Tetrahedron Lett.* **2009**, *50*, 3805 – 3808; d) L. Rösch, G. Altnau, W. H. Otto, *Angew. Chem.* **1981**, *93*, 607 – 608; *Angew. Chem. Int. Ed. Engl.* **1981**, *20*, 581 – 582.

[14] For an usual 1,2-addition using a tantalum reagent, see: J. Arnold, T. D. Tilley, *J. Am. Chem. Soc.* **1987**, *109*, 3318 – 3322.

[15] C. Kleeberg, E. Feldmann, E. Hartmann, D. J. Vyas, M. Oestreich, *Chem. Eur. J.* **2011**, *17*, 13538 – 13543.

[16] M. Suginome, T. Matsuda, Y. Ito, *Organometallics* **2000**, *19*, 4647 – 4649.

[17] D. J. Gulliver, W. Levason, M. Webster, *Inorg. Chim. Acta* **1981**, *52*, 153 – 159.

[18] Strong hydrogen bonds are typically characterized by A – B separations that are at least 0.25 Å less than the sum of the van der Waals radii; see: F. Hibbert, J. Emsey, *Adv. Phys. Org. Chem.* **1990**, *26*, 255 – 379.

[19] T. Vergote, F. Nahra, A. Welle, M. Luhmer, J. Wouters, N. Mager, O. Riant, T. Leyssens, *Chem. Eur. J.* **2012**, *18*, 793 – 798.

[20] S. Tsuboi, N. Ishii, T. Sakai, I. Tari, M. Utaka, *Bull. Chem. Soc. Jpn.* **1990**, *63*, 1888 – 1893; J. M. Bobbitt, *J. Org. Chem.* **1998**, *63*, 9367 – 9374.

