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Enantioselective Alkenylation and Phenylation Catalyzed by a Chiral CuF Complex

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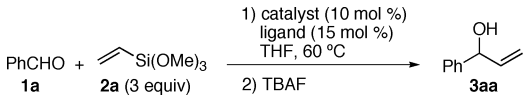
Chiral allylic alcohols are among the most versatile synthetic intermediates. Catalytic enantioselective synthesis of these chiral building blocks currently relies on two main methods; kinetic resolution using the Sharpless epoxidation[1] and asymmetric addition of alkenylzinc reagents to carbonyl compounds.[2] These groundbreaking reactions are reliable and have established new concepts in the history of organic synthesis. Because of the recent demands for safe and sustainable organic synthesis, however, resolution methodology or the use of highly sensitive reagents is not desirable, especially for large-scale synthesis.[3] In this communication, we report a new catalytic method for chiral allylic alcohol synthesis using air-stable and commercially available vinylsilanes as nucleophiles. In addition, the method also allows for a highly enantioselective phenylation of aldehydes, producing another group of valuable chiral building blocks, diarylmethanols.

We previously reported that silylated nucleophiles such as allyltrimethoxysilanes and ketene silyl acetals are activated by a catalytic amount of CuF, producing highly nucleophilic allylcoppers or copper enolates through transmetalation.[4,5] These species are sufficiently reactive to perform catalytic enantioselective allylation and aldol reactions to ketones, when the CuF is modified by chiral phosphine ligands. On the basis of these findings, we planned to use trimethoxyvinylsilane as a nucleophile. Previous reports on CuCl-promoted homo-coupling of alkenylfluorosilanes,[6] as well as stoichiometric Cu(I)-induced protodesilylation[7] and allylation[8] of alkenylsilanes support our expectation that the generation of alkenylcopper through transmetalation between copper and silicon atoms should be possible. On the other hand, the reactivity of the thus-generated vinylcopper to carbonyl compounds and the possibility of catalyst turnover could not be predicted.[9]

Our initial studies focused on the determination of vinylation conditions for aldehydes using achiral CuF complexes, and we first found a dramatic difference in reactivity between allylation and vinylation reactions. When the optimized conditions for catalytic allylation[4a] were applied to catalytic vinylation of benzaldehyde (**1a**) using trimethoxyvinylsilane (**2a**), the reaction did not proceed (Table 1, entries 1 and 2). The allylation was completed in 1 min under the same conditions. During the reaction, the solution color changed from pale yellow (derived from CuF) to dark brown, which might indicate the generation of a vinylcopper via transmetalation. To enhance the reactivity of the generated vinylcopper species, ligand-acceleration effects were investigated (entries 3−7). After systematic screening of diphosphine ligands regarding the electronic and steric factors, dppf was determined to be the optimum achiral ligand (entry 7).[10] The reaction rate was faster in DMF than in THF, and the reaction was completed in 3 h using 5 mol % catalyst (entry 8).[11] To our knowledge, this is the first example of a catalytic intermolecular vinylation of aldehydes using weakly nucleophilic simple vinylsilane as a nucleophile.[12]

Table 1. Optimization of the Vinylation Reaction: Ligand Effects



entry	catalyst	ligand	time (h)	yield (%)
1	CuCl-TBAT[a]	none	24	0
2	CuF·3PPh$_3$·2EtOH	none	24	0
3	CuF·3PPh$_3$·2EtOH	dppe	24	61
4	CuF·3PPh$_3$·EtOH	d(*p*-Cl)ppe[b]	24	47
5	CuF·3PPh$_3$·2EtOH	d(*p*-MeO)ppe[c]	24	57
6	CuF·3PPh$_3$·2EtOH	dppp	24	89
7	CuF·3PPh$_3$·2EtOH	dppf	4	100
8[d]	CuF·3PPh$_3$·2EtOH	dppf	3	100

[a] Tetrabutylammonium difluorotriphenylsilicate. [b] 1,2-Bis(di-*p*-chlorophenylphosphino)ethane. [c] 1,2-Bis(di-*p*-methoxyphenylphosphino)ethane. [d] 5 mol % catalyst and 7 mol % dppf were used. Solvent = DMF.

Having established the new catalytic vinylation conditions, extension to a catalytic enantioselective reaction was investigated using chiral diphosphines. Screening available chiral diphosphines led us to determine that DTBM−SEGPHOS (**4**) was the best ligand;[13] reaction of **1a** was completed in 0.5 h using 3 mol % catalyst (generated via in situ reduction of CuF_2·$2H_2O$ by excess chiral phosphine), and the product was obtained in 99% yield with 94% ee (Table 2, entry 1).

The substrate generality of this reaction is summarized in Table 2. Excellent enantioselectivity was generally produced from a wide range of aldehydes. As for enolizable aliphatic aldehyde **1h**, the typical procedure afforded mainly undesired product via self-aldol condensation.[14] In this case, however, simple tuning of the reaction conditions using dimethoxymethylvinylsilane (**2b**) as a nucleophile in toluene solvent gave the vinylation product in high chemical yield (entry 8). Alkenylsilane **2c** with a longer alkyl chain, which was conveniently synthesized through olefin cross metathesis,[15] can be utilized as a nucleophile (entries 9 and 10). The reaction proceeded even using an internal alkenylsilane **2d**, which was synthesized through Trost's ruthenium-catalyzed regioselective hydrosilylation of the corresponding alkyne[16] (entry 11). Although yield and enantioselectivity require further improvement in this case, the result is noteworthy because products containing 1,1′-disubstituted alkenes are not accessible by reactions using alkenylzinc, which is normally generated through a terminal position-selective hydroboration−transmetalation sequence.[2] The reaction proceeded chemoselectively with an activated ketone **1i**, giving the chiral tertiary allylic alcohol with high enantioselectivity (entry 12).[17] Moreover, this methodology can be extended to a catalytic enantioselective phenylation[18] using dimethoxydiphenylsilane (**2e**) as a nucleophile (entries 13 and 14).

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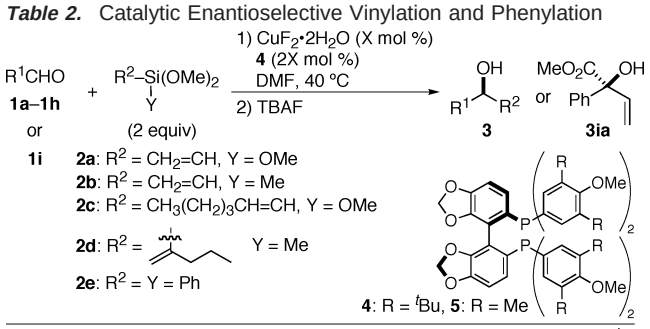
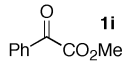
Table 2. Catalytic Enantioselective Vinylation and Phenylation



entry	substrate (R^1)	nucleophile	catalyst (X mol %)	time (h)	yield[a] (%)	ee[b] (%)
1	Ph (**1a**)	**2a**	3	0.5	99	94[f]
2	*p*–Cl-C_6H_5 (**1b**)	**2a**	3	2	99	97[f]
3	*p*–Me-C_6H_5 (**1c**)	**2a**	3	8	99	99[f]
4	*p*–MeO-C_6H_5 (**1d**)	**2a**	10	1	99	92[f]
5	2-Thienyl (**1e**)	**2a**	10	0.5	99	91[f]
6	(*E*)–PhCH=CH (**1f**)	**2a**	10	1	73	83[f]
7	$PhCH_2C(CH_3)_2$ (**1g**)	**2a**	10	40	99	99
8[c]	*c*–Hex (**1h**)	**2b**	10	16	84	98[f]
9	**1a**	**2c**	10	2.5	91	90[f]
10	**1g**	**2c**	10	50	90	97
11[d]	**1a**	**2d**	10	17	48	52
12[e]	 **1i**	**2a**	10	22	76	84[f]
13	**1b**	**2e**	3	1	81	92[f]
14	**1c**	**2e**	5	3	83	90[f]

[a] Isolated yield. [b] Determined by chiral HPLC. [c] The reaction was performed at room temperature in toluene. [d] The reaction was performed at 60 °C in the presence of 10 mol % TBAT as an additive. In the absence of TBAT, the reaction did not proceed. [e] The reaction was performed at room temperature. [f] The absolute configuration was determined to be (*S*).

To gain insight into the reaction mechanism, several observations were made. First, generation of an alkenylcopper was strongly supported by the observation of an ^{19}F NMR signal corresponding to $(MeO)_3SiF$, when the CuF−dppf complex was mixed with **2a** in a 1:3 ratio.[11,19] Second, enantioselectivity was not affected by the substituents of the silicon atom of alkenylsilane.[11] Thus, the silicon species is not relevant to the enantiodifferentiating addition step. Third, the catalytic cycle can start from a copper alkoxide−DTBM−SEGPHOS complex with the same enantioselectivity as that of the chiral CuF complex.[11] These results, combined with kinetic studies,[20] suggested two key factors: (1) an alkenylcopper (or a phenylcopper) generated through transmetalation works as an active nucleophile, and (2) the diphosphine ligands facilitate the rate-determining catalyst turnover step (regeneration of the alkenylcopper from an intermediate copper alkoxide).

In conclusion, we developed a new catalytic enantioselective method for chiral allylic alcohol and diarylmethanol synthesis using air- and moisture-stable alkenylsilanes and phenylsilane as nucleophiles. Detailed mechanistic studies are in progress.

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Supporting Information Available: Experimental procedures and characterization of the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) The allylcopper species generated through transmetalation from allylsilane demonstrated completely different reactivity and stability from that prepared through a conventional method (transmetalation from allyllithium or allylmagnesium reagents). For example, CuF-catalyzed allylation proceeded with complete 1,2-selectivity to enones at room temperature (ref 4a).

(10) Steric congestion around the copper atom appeared to be more important for the ligand-acceleration effects than the electronic factors (for electronic effects, see Table 1, entries 3−5; for steric effects, see Table 1, entries 3, 6, and 7 and reactivity comparison between Et- and ^{i}Pr-DuPHOS described in ref 13), and steric effects). The difference between DTBM-SEGPHOS (**4**) and DMM-SEGPHOS (**5**) under optimized conditions for enantioselective reaction is also consistent with this tendency: CuF−**5** complex (3 mol % in DMF) gave **3aa** in only 31% yield for 3 h, while the reaction was completed in 0.5 h using **4** (Table 2, entry 1). This acceleration effect might be due to stabilization of a hypothetical monomeric, active copper species and/or acceleration of the rate-determining ligand exchange (see text) to regenerate the active vinylcopper. For examples of acceleration effects by sterically hindered ligands, see: (a) Littke, A. F.; Schwarz, L.; Fu, G. C. *J. Am. Chem. Soc*. **2002**, *124*, 6343. (b) Strieter, E. R.; Blackmond, D. G.; Buchwald, S. L. *J. Am. Chem. Soc*. **2003**, *125*, 13978. (c) Yamasaki, S.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc*. **2001**, *123*, 1256.

(11) For the substrate scope using the CuF-dppf catalyst, results of mechanistic studies, and the proposed catalytic cycle, see Supporting Information for details.

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(13) See Supporting Information for the effects of chiral ligands and the catalyst preparation method. Briefly, *p*-tol-BINAP, Et-DuPHOS, and ^{i}Pr-DuPHOS-complexes (10 mol %) gave **3aa** in 47% with 61% ee (24 h), in 51% with 38% ee (24 h), and in 87% with 64% ee (5 h), respectively.

(14) The self-aldol reaction might be promoted by CuOMe, which is generated through competitive methoxy ligand transfer from silicon to copper, instead of the desired vinyl transfer. For a use of copper alkoxide as a Brønsted base catalyst for direct aldol reaction, see: Suto, Y.; Kumagai, N.; Matsunaga, S.; Kanai, M.; Shibasaki, M. *Org. Lett.* **2003**, *5*, 3147.

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(17) Simple ketones did not give the addition product at the current stage.

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(19) Interestingly, no such signal was observed using CuF·3PPh_3 or TBAT as a fluoride source, which demonstrated no catalyst activity.

(20) The rate-determining step was identified on the basis of kinetic studies. The order dependencies of the initial reaction rate were 1, 0, and 0.5 regarding CuF, aldehyde, and vinylsilane, respectively.

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