Allylic Substitution

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Asymmetric Synthesis of α-Chiral Allylic Silanes by Enantioconvergent γ-Selective Copper(I)-Catalyzed Allylic Silylation[**]

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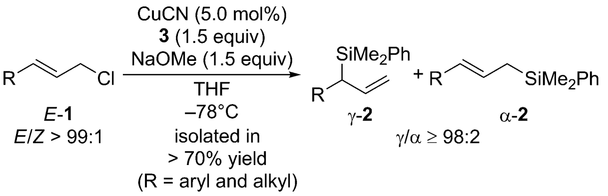
Dedicated to Professor Larry E. Overman on the occasion of his 70th birthday

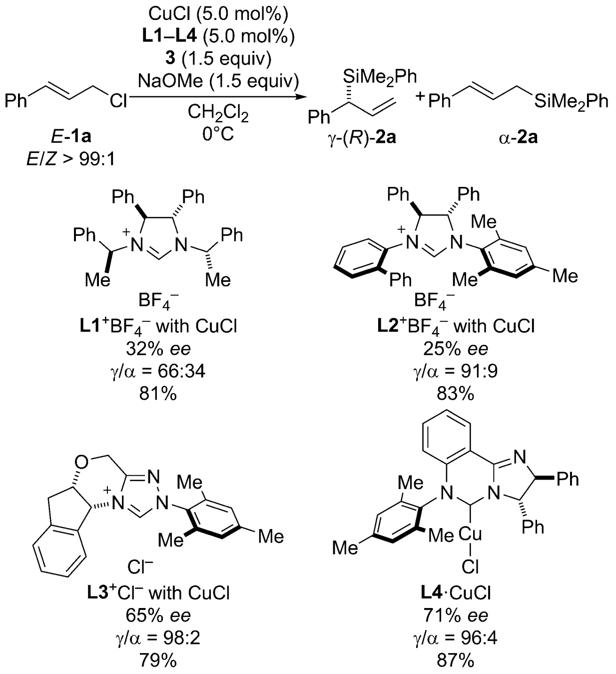
Transmetalation of the Si–B linkage with selected transition metal–oxygen bonds releases silicon nucleophiles that are transferred to various acceptors under carbon–silicon bond formation.[1,2] An impressive number of monofunctionalizations based on this activation mode has been developed in the past few years,[1] but catalytic asymmetric variants are available for just a handful of those.[3] These are essentially limited to conjugate additions[4] using either chiral diphosphine–{Rh^I-O}[5] or NHC–{Cu^I-O}[6] complexes.[7] Just recently, an enantioselective 1,2-addition using a preformed chiral diphosphine–{Cu^I-F} complex was reported.[8,9] The copper(I)-catalyzed transmetalation approach is remarkably general,[1,2,6–8,10,11] and we had elaborated a branched-selective allylic substitution of linear allylic chlorides, yielding α-chiral allylic silanes in racemic form (*E*-**1**→γ-**2**, Scheme 1).[10] An enantioselective procedure for this highly regioselective transformation is particularly attractive as it provides direct access to these prevalent chiral reagents[12] from non-silicon-containing precursors. We present herein an enantio- and regioselective allylic substitution of linear allylic chlorides[13,14a] and phosphates[14b,c] catalyzed by a copper(I) complex containing a chiral N-heterocyclic carbene (NHC) ligand.[15,16]



Scheme 1. Branched-selective allylic substitution of allylic chlorides involving copper(I)-catalyzed activation of the Si–B bond in Suginome's $Me_2PhSiBpin$[17] (**3**).[10a]

When we presented the racemic procedure for the above γ-selective allylic displacement,[10a] we had already tested achiral and chiral phosphine ligands, but these merely slowed down the reaction rate (minutes at −78 °C versus hours at 0 °C). No or little asymmetric induction had been obtained with commercially available diphosphine ligands.[18,19] We then decided to use chiral NHCs as ligands because these have emerged as effective in γ-selective allylic substitution involving the related copper(I)-catalyzed B–B bond activation.[20] Also, enantioselective 1,4-addition of either silicon or boron nucleophiles released from Si–B[6] and B–B[21] compounds, respectively, were shown to be catalyzed by NHC–{Cu^I-O} complexes.

We selected C_2-symmetric **L1** and C_1-symmetric **L2** as representative chiral NHCs, and we also included Bode's triazolium ion-derived NHC **L3**[22] into our survey (Scheme 2). **L1** (allylic substitution with carbon nucleophiles)[23] and **L2** (allylic substitution and conjugate addition



Scheme 2. Chiral NHCs as ligands in the copper(I)-catalyzed, regio- and enantioselective allylic silyl transfer to an allylic chloride (NHCs were generated with KO*t*Bu prior to the addition of the reactants).

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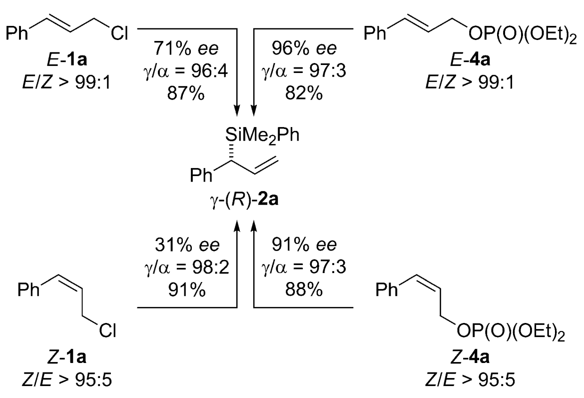
with boron nucleophile)[20a,21a] were used before as ligands in copper(I) catalysis, whereas **L3** is a rather unusual choice for a transition-metal-catalyzed reaction. The racemic procedure (Scheme 1) was slightly modified: CH_2Cl_2 as solvent secured better azolium salt solubility and 0 °C as reaction temperature allowed for reasonable reaction rate (E-**1a**→γ-(R)-**2a**, Scheme 2). While both regio- and enantioselectivity were poor with **L1**, the γ/α ratios were, however, excellent with **L2** and **L3**. NHC **L3** induced a promising 65 % *ee*. In situ formation of these NHC complexes might be an issue, and we had already known from our previous work that the ligand-free catalysis is fast.[10a] To avoid a racemic background reaction, we turned to preformed NHC complexes and selected six-membered NHC-copper(I) complex **L4**·CuCl that was introduced by McQuade.[24] Its successful application to conjugate addition[21d] and allylic substitution[20b] involving B−B bond activation had also attracted our attention. Gratifyingly, γ/α = 96:4 and 71 % *ee* at a high yield of isolated product were obtained with **L4**·CuCl, whereas its in situ formation resulted in irreproducible enantiomeric excess values.

The procedure applied to the other alkene isomer resulted in significantly lower enantiomeric excess yet same absolute configuration (E-**1a** and Z-**1a**→γ-(R)-**2a**, Scheme 3).

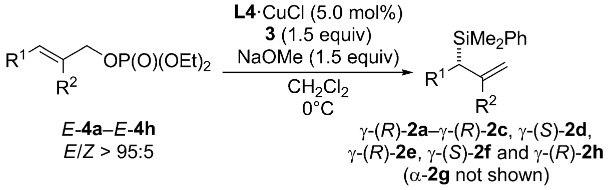


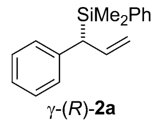
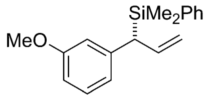
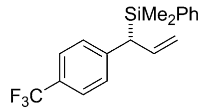
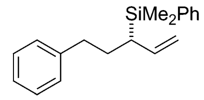
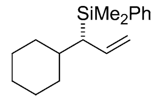
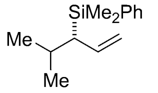
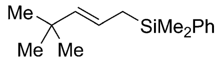
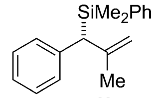
Scheme 3. Enantioconvergent allylic substitution of allylic chlorides and phosphates. Reaction conditions: **L4**·CuCl (5.0 mol %), **3** (1.5 equiv), NaOMe (1.5 equiv), CH_2Cl_2, 0 °C.

McQuade and co-workers had discovered this peculiar enantioconvergence in their enantioselective preparation of branched allylic boronates from linear allylic aryl ethers, but enantiomeric excesses were on a similar order of magnitude.[20b] We also tested phosphate as leaving group (γ/α = 91:9 in the racemic series[10a]), and were delighted to see that McQuade's observations were confirmed in our allylic silylation (E-**4a** and Z-**4a**→γ-(R)-**2a**, Scheme 3). The level of enantiocontrol was excellent, and both alkene geometries transformed into R configuration with more than 90 % *ee*.

We then continued with representative allylic phosphates having E alkene configuration (Table 1). Aryl-substituted E-**4a**–E-**4c** reacted cleanly with excellent enantiomeric excesses that are independent of the electronic nature of the substituent at the aryl group (entries 1–3). Likewise, yields and asymmetric induction were superb with primary and secondary alkyl-substituted E-**4d**–E-**4f** (entries 4–6). The γ/α ratios were all synthetically useful, except for a tertiary alkyl group at the alkene, where the ratio was essentially reversed (entry 7). It is worthy of note that conversion and yield was poor with the *tert*-butyl-substituted acceptor, affording α-**2g** in 35 % yield. That result might be viewed as support for the notion that **L4**·CuCl strongly favors the γ carbon atom, and if that is not accessible, α attack is not a competing alternative.

Table 1: Enantio- and regioselective copper(I)-catalyzed S_N2' allylic silylation of allylic phosphates.



Entry	Phosphate	Allylic silane	γ/α ratio[a]	Yield [%][b]	*ee* [%][c]
1	E-**4a**	 γ-(R)-**2a**	97:3	82	96[d]
2	E-**4b**	 γ-(R)-**2b**	96:4	92	95
3	E-**4c**	 γ-(R)-**2c**	97:3	93	93
4	E-**4d**	 γ-(S)-**2d**	97:3	81	88[d]
5	E-**4e**	 γ-(R)-**2e**	98:2	88	95[e]
6	E-**4f**	 γ-(S)-**2f**	97:3	91	97[d]
7	E-**4g**	 α-**2g**	6:94	35	–
8	E-**4h**	 γ-(R)-**2h**	65:35	25	78

[a] Determined by GLC and ^{1}H NMR analysis. [b] Combined yield of analytically pure regioisomers after purification by flash chromatography on silica gel. [c] Determined by HPLC analysis using chiral stationary phases. [d] Absolute configuration assigned by comparison with the optical rotation of reported allylic silanes.[14b,25] [e] Value likely to be higher but full baseline separation of the enantiomers was not achieved.

Likewise, a substituent at C2 as in *E*-**4h** eroded both the γ/α ratio and the enantiomeric excess, and the yield of isolated product was again poor (entry 8).

Allylic silanes γ-(*R*)-**2a** with an aryl as well as γ-(*S*)-**2d** and γ-(*S*)-**2f** with an alkyl group were prepared and fully characterized before,[14b,25] and we assigned the absolute configuration as *R* and *S*, respectively by comparison of the optical rotations. These configurations are in accordance with the model proposed by McQuade for his copper(I)-catalyzed, enantioconvergent allylic substitution with a boron nucleophile,[20b] and the same analysis might apply to our catalysis with the silicon nucleophile ($\mathbf{I}_E$ and $\mathbf{I}_Z$, Figure 1, upper). However, enantioconvergence is also an indication of the catalysis passing through a common intermediate starting from diastereomeric allylic acceptors; that is, the η^3 π-allyl copper(III) complex **II** (Figure 1, lower). Neither McQuade nor we are presently able to rule out either pathway.

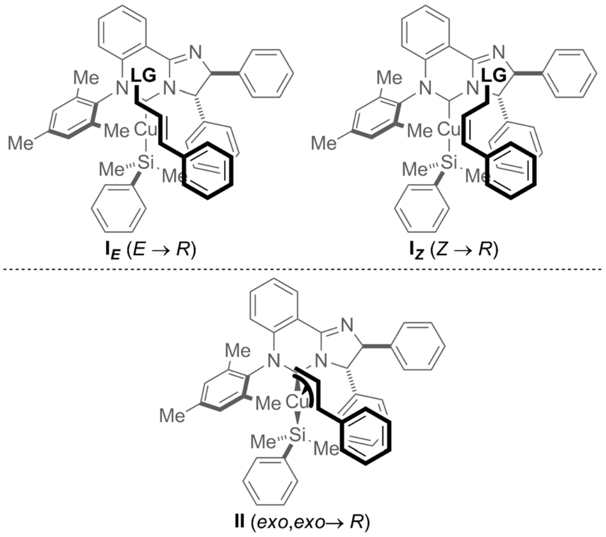
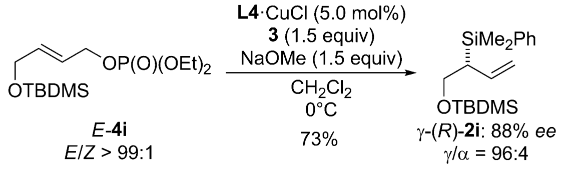


Figure 1. McQuade's model[20b] (upper) or η^3 π-allyl copper(III) intermediate (lower) to rationalize enantioconvergence (LG = leaving group).

The allylic substitution of δ-hydroxy allylic phosphate is a particularly interesting transformation (*E*-**4i**→γ-(*R*)-**2i**, Scheme 4). It produces a protected β-hydroxy α-chiral allylic silane that cannot be easily made by allylation of formaldehyde with Roush's γ-silicon-substituted allylic boronates.[26]

In summary, we reported herein a solution to the longstanding challenge of accessing α-chiral allylic silanes from linear acceptors by regio- and enantioselective allylic substitution with a silicon nucleophile. This was achieved by using McQuade's NHC–copper(I) complex **L4**·CuCl as catalyst. Aside from Hayashi's seminal work,[13] the present method finally provides a reliable way to directly make α-chiral allylic silanes in high enantiomeric excesses from simple linear acceptors derived from allylic alcohols.



Scheme 4. Selective transformation of a δ-hydroxy allylic phosphate into an β-hydroxy α-chiral allylic silane.

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