ChemPubSoc Europe
DOI: 10.1002/chem.201501371
CHEMISTRY
A European Journal
Communication

Allylic Substitution

Asymmetric Catalysis with Silicon-Based Cuprates: Enantio- and Regioselective Allylic Substitution of Linear Precursors

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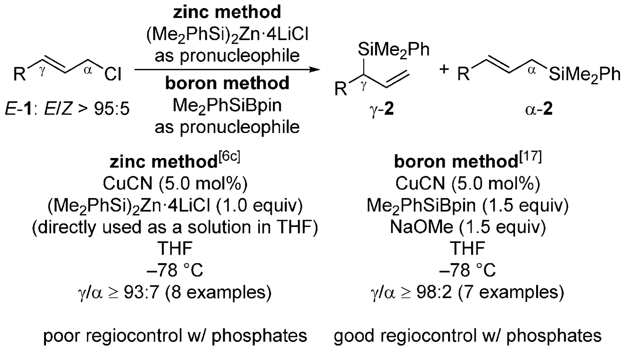
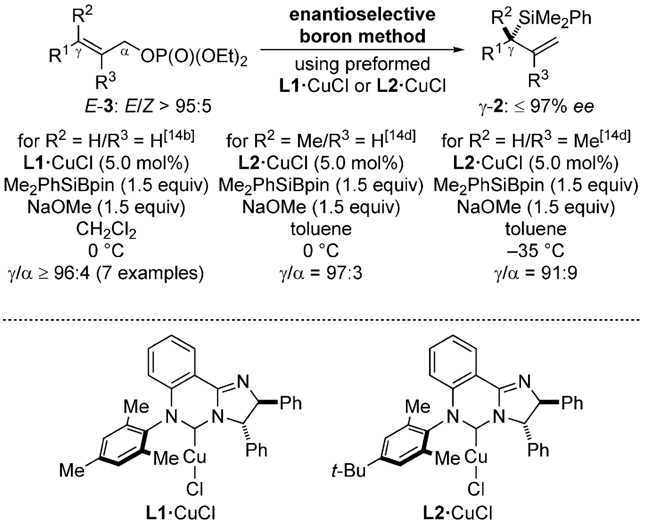
Dedicated to Professor Reinhard Brückner on the occasion of his 60th birthday

Abstract: An enantio- and regioselective allylic silylation of linear allylic phosphates that makes use of catalytically generated cuprate-type silicon nucleophiles is reported. The method relies on soft bis(triorganosilyl) zincs as silicon pronucleophiles that are prepared in situ from the corresponding hard lithium reagents by transmetalation with $ZnCl_2$. With a preformed chiral N-heterocyclic carbene–copper(I) complex as catalyst, exceedingly high enantiomeric excesses are achieved. The new method is superior to existing ones using a silicon–boron reagent as the source of the silicon nucleophile.

Silicon-based cuprates such as Fleming's $(Me_2PhSi)_2CuLi{\cdot}LiX$ or $Me_2PhSiCu{\cdot}LiX$ (X = I or CN) are, despite being stoichiometric in copper(I), established reagents for the formation of carbon–silicon bonds.[1] Catalytic variants had been elusive for decades[2] until our laboratory introduced $(Me_2PhSi)_2Zn{\cdot}4\,LiCl$[3] as a pronucleophile in copper(I) catalysis.[4] Combinations of $(Me_2PhSi)_2Zn{\cdot}4\,LiCl$ and CuX are broadly applicable to common acceptors[5–8] but rendering these copper(I)-catalyzed reactions asymmetric poses a formidable challenge. For example, enantioselective conjugate addition had initially failed, mainly because of the excess LiCl that comes with the silicon pronucleophile.[9] This hypothesis was verified by the use of $(Me_2PhSi)_2Zn{\cdot}4\,KCl$ that is not burdened with overstoichiometric amounts of the lithium Lewis acid, and promising but still low

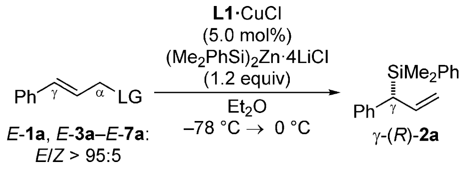


Scheme 1. Racemic copper(I)-catalyzed allylic substitution with zinc- and boron-based silicon pronucleophiles. pin = pinacolato.



Scheme 2. Enantioselective γ-selective copper(I)-catalyzed allylic silylation.

Table 1. Survey of leaving groups.



Entry	Allylic precursor	Leaving group	γ/α[a]	Yield [%][b]	ee [%][c]
1	*E*-**1a**	Cl	> 95:5	80	98
2	*E*-**3a**	$OP(O)(OEt)_2$	> 95:5	80	> 99
3	*E*-**4a**	Br	> 95:5	44	17
4	*E*-**5a**	OC(O)OEt	> 95:5	traces[d]	60
5	*E*-**6a**	OC(O)NHPh	–	–[e]	–
6	*E*-**7a**	OC(O)Me	–	–[e]	–

[a] Determined by GLC and ^1H NMR analysis; [b] combined yield of analytically pure regioisomers after purification by flash chromatography on silica gel; [c] determined by HPLC analysis using a chiral stationary phase; [d] not isolated in analytically pure form; [e] no conversion. LG = leaving group.

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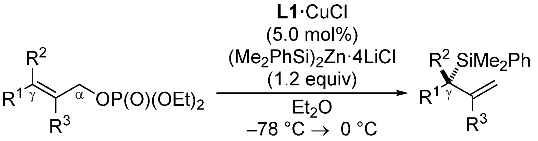
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201501371.

enantioinduction was indeed obtained.[9] Asymmetric allylic substitution was, however, not achieved with this catalytic system.[10] These problems were recently overcome by a novel approach to the catalytic generation of cuprate-type silicon reagents, namely the transmetalation of the silicon–boron bond in $Me_2PhSiBpin$[11] by copper(I) alkoxides.[12] With chiral bidentate phosphines or monodentate N-heterocyclic carbenes (NHCs) as ligands, essentially all typical carbon–silicon bond-forming reactions were accomplished in enantioselective fashion with excellent enantioselectivities.[13–16]

Both the zinc[6c] and the boron[17] methods are perfectly applicable to branched-selective allylic substitution of linear allylic chlorides (Scheme 1). The γ/α ratios are generally higher with the latter and good regioselectivity is also obtained with allylic phosphates. Our group,[14b,d] as well as Hayashi and co-workers,[14c] were recently able to render the boron method enantioselective by using copper(I) complexes with different chiral NHC ligands. By this method, allylic phosphates with and without substitution at the β and γ positions were transformed into α-chiral allylic silanes with high enantiocontrol and excellent γ-selectivity (Scheme 2, top).[14b,d] This was achieved by using preformed NHC–copper(I) complexes **L1**·CuCl and **L2**·CuCl, introduced by McQuade and co-workers (Scheme 2, bottom).[18] We disclose herein that McQuade's catalysts are also applicable to the zinc method. The new protocol is superior to the boron method[14b,d] not only in terms of enantio- and regiocontrol but also with regard to the leaving group of the allylic acceptor. The present work is, to our knowledge, the first example of a highly enantioselective carbon–silicon bond-forming reaction with a catalytically generated silicon-based cuprate reagent.

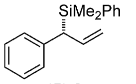
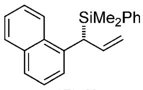
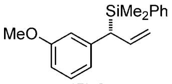
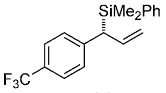
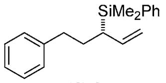
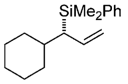
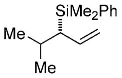
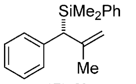
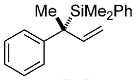
We began with a few control experiments. $(Me_2PhSi)_2Zn\cdot 4\,LiCl$ is made in situ by mixing $Me_2PhSiLi\cdot LiCl$ in THF (2 M) and $ZnCl_2$ in Et_2O (1 M). The disadvantage of this procedure is that it introduces two solvents to a transformation that is known to be highly sensitive toward the solvent, particularly with regard to the regioselectivity.[6c,14d] We nevertheless tested the zinc method with **L1**·CuCl in that solvent system and were delighted to find that both allylic chloride *E*-**1a** and phosphate *E*-**3a** were converted into allylic silane γ-(*R*)-**2a** with 92 % *ee* and 91 % *ee*, respectively (not shown). Moreover, the γ/α ratios were surprisingly high in comparison to the α-selectivity typically seen with complex **L1**·CuCl in THF.[14d,19] A solvent change to Et_2O was achieved by

Table 2. Enantio- and regioselective copper(I)-catalyzed branched-selective allylic silylation of allylic phosphates.



E-**3a**–*E*-**3i**: *E*/*Z* > 95:5

γ-**2a**–γ-**2i**

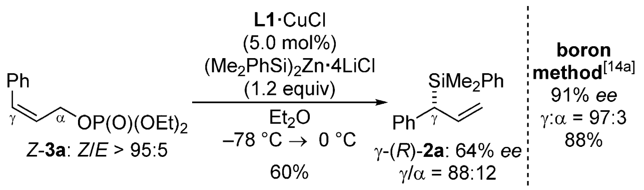
Entry	Phosphate	Allylic silane	γ/α[a]	Yield [%][b]	*ee* [%][c]	*ee* [%][d]
1	*E*-**3a**	 γ-(*R*)-**2a**	> 95:5	80	> 99 (*R*)	96[14b] (*R*)
2	*E*-**3b**	 γ-(*R*)-**2b**	> 95:5	80	97 (*R*)	–
3	*E*-**3c**	 γ-(*R*)-**2c**	> 99:1	74	98 (*R*)	95[14b] (*R*)
4	*E*-**3d**	 γ-(*R*)-**2d**	95:5	94[e]	> 99 (*R*)	93[14b] (*R*)
5	*E*-**3e**	 γ-(*S*)-**2e**	> 99:1	76	96[f] (*S*)	88[14b] (*S*)
6	*E*-**3f**	 γ-(*R*)-**2f**	> 99:1	70	> 99[f] (*R*)	95[14b] (*R*)
7	*E*-**3g**	 γ-(*S*)-**2g**	97:3	70	94 (*S*)	97[14b] (*S*)
8	*E*-**3h**	 γ-(*R*)-**2h**	92:8	65[g]	70[g] (*R*)	78[14b] (*R*)
9	*E*-**3i**	 γ-(*R*)-**2i**	94:6	75	94[h] (*R*)	93[14d] (*R*)

[a] Determined by GLC and ^1H 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] enantiomeric excesses obtained with the boron method in CH_2Cl_2 using precatalyst **L1**·CuCl (cf. Scheme 2);[14b,d] [e] contaminated with disilane; [f] no full baseline separation of the enantiomers achieved by HPLC analysis; [g] not stable on silica gel, and impurities seen in the HPLC analysis; [h] value likely to be higher as minor enantiomer co-elutes with impurity.

evaporation under reduced pressure after the salt metathesis and dissolution of the dark brown residue in Et_2O. The resulting suspension was filtered to remove undissolved LiCl.[6c] Repeating the previous allylic silylations with this ethereal solution of the zinc reagent boosted the enantioselectivity. Allylic chloride *E*-**1a** afforded γ-(*R*)-**2a** with 98% *ee* and allylic phosphate *E*-**3a** yielded γ-(*R*)-**2a** with a superb >99% *ee* (Table 1, entries 1 and 2). Unexpectedly,[6c] allylic bromide *E*-**4a** reacted with little enantioinduction in moderate yield (Table 1, entry 3). Other acceptors such as *E*-**5**–*E*-**7a**, with oxygen leaving groups that are displaced α-selectively in the racemic series,[6c] showed poor conversion or did not react at all (Table 1, entries 4–6). It is also worth noting that **L1**·CuCl (>99% *ee*) was again superior to **L2**·CuCl (70% *ee*, not shown) in the reaction of the allylic phosphate, in agreement with earlier findings.[14d]

Owing to the excellent enantiomeric excess obtained with *E*-**3a**, we decided to continue with allylic phosphates as substrates (Table 2). For comparison, we have included the enantiomeric excesses achieved with the boron method (Table 2, column 7).[14b,d] As a general observation with linear acceptors *E*-**3a**–**f**, the enantioselectivities are substantially higher with the zinc method at similar levels of regiocontrol (Table 2, entries 1–6); *E*-**3g** is an exception with a slightly lower enantiomeric excess (Table 2, entry 7). Acceptors with substitution at either the β or γ position, such as *E*-**3h** and *E*-**3i**, afforded dramatically improved γ/α ratios with comparable enantioselectivities. The regioselectivity for β-methyl-substituted *E*-**3h** increased from 65:35[14b] to 92:8 (Table 2, entry 8) and for γ-methyl-substituted *E*-**3i** from 73:27[14d] to 94:6 (Table 2, entry 9), again demonstrating the superiority of the zinc over the boron method.

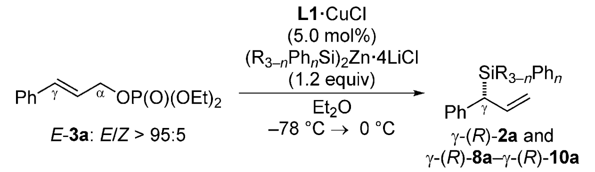
Another feature of the boron method is its stereoconvergence with *E*-**3a** and *Z*-**3a** furnishing identical regioselectivities and enantioselectivities in the same order of magnitude.[14b] That stereoconvergence was also found for the zinc method yet with significantly deteriorated levels of regio- and enantiocontrol (Scheme 3). This comparison underscores once more that the reagent cocktails of the boron and zinc methods indeed lead to different product distributions.



Scheme 3. Stereoconvergence of the zinc versus boron method.

A convenience of the zinc over the boron method is the straightforward reagent preparation. Reductive metalation of an aryl-substituted chlorosilane, typically $R_{3-n}Ph_nSiCl$ with $n = 1$–3, with sodium-rich lithium metal followed by salt metathesis with $ZnCl_2$ produces the ready-to-use zinc reagent,[4] possibly requiring a solvent change. The same reductive metalation is utilized in the preparation of the boron reagent but the intermediate anion then reacts with a pinacolborane derivative to afford the distillable and storable Si–B compound.[11] However, applications of the boron method have to date been largely limited to $Me_2PhSiBpin$,[12,16a] despite the availability of the common substitution patterns at the silicon atom.[11] The ease of the preparation of the zinc reagent allowed us to test three other silicon nucleophiles in the allylic silylation (Table 3).

Table 3. Survey of silyl groups.



Entry	$R_{3-n}Ph_nSi$	Allylic silane	γ/α[a]	Yield [%][b]	*ee* [%][c]
1	Me_2PhSi	γ-(*R*)-**2a**	>95:5	80	>99
2	$MePh_2Si$	γ-(*R*)-**8a**	>99:1	78	96
3	Ph_3Si	γ-(*R*)-**9a**	>99:1	60	68
4	$tBuPh_2Si$	γ-(*R*)-**10a**	88:12	60	44

[a] Determined by GLC and ^1H 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.

The key finding is that both the enantioselectivity and, to a lesser extent, the regioselectivity decrease with increasing steric bulk at the silicon atom (e.g., $MePh_2Si$ vs. $tBuPh_2Si$; Table 3, entries 2 and 4). With the Ph_3Si group the γ/α ratio remained unaffected while the enantiomeric excess collapsed (Table 3, entry 3).

In summary, we have reported herein the first application of silicon-based cuprates in asymmetric catalysis. Exceedingly high enantioselectivities were achieved in branched-selective allylic silylations of linear allylic phosphates, and the method was also shown to work with chloride as leaving group.[20] Unlike previously reported methods that relied on a silicon–boron reagent as the silicon pronucleophile,[14] the new procedure makes use of soft bis(triorganosilyl) zincs that are formed in situ from the corresponding hard lithium reagents by transmetalation with $ZnCl_2$. The zinc method is superior in terms of regio- and particularly enantiocontrol. Although both the established boron method and the new zinc method are likely to involve similar silicon–copper complexes, the individual salt additives lead to different results. NaOMe brings in Lewis basic methoxide, whereas LiCl is Lewis acidic.

Acknowledgements

M.O. is indebted to the Einstein Foundation (Berlin) for an endowed professorship.

Keywords: allylic substitution · asymmetric catalysis · copper · silicon · zinc

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Received: April 8, 2015