Allylic Alkylation

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Enantioselective Synthesis of Allylsilanes Bearing Tertiary and Quaternary Si-Substituted Carbons through Cu-Catalyzed Allylic Alkylations with Alkylzinc and Arylzinc Reagents**

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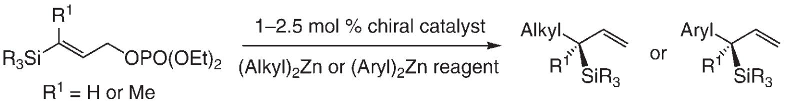
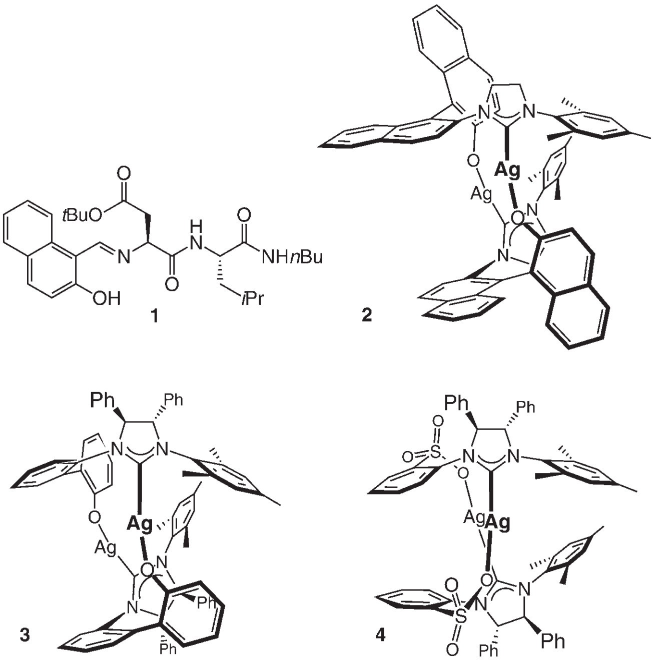
Allylsilanes are widely used in stereoselective organic synthesis.[1] Design and development of efficient catalytic asymmetric methods that furnish chiral allylsilanes in high enantiomeric purity would significantly expand the utility of these versatile nucleophiles. Herein, we report an efficient method for enantioselective synthesis of a range of allylsilanes by Cu-catalyzed asymmetric allylic alkylation (AAA)[2] of Si-substituted unsaturated phosphates with dialkyl- and diarylzinc reagents [Eq. (1)]. Transformations are promoted by 1–2.5 mol% of chiral N-heterocyclic carbene based (NHC-based) catalysts and afford enantiomerically enriched allylsilanes in up to 98% *ee* and over 70% yield. Catalytic asymmetric reactions that afford tertiary as well as those that deliver quaternary Si-substituted carbon stereogenic centers are presented. To the best of our knowledge, this disclosure puts forth the first method for catalytic asymmetric synthesis of quaternary carbon stereogenic centers that bear a silyl group,[3,4] as well as the first catalytic AAA that utilizes arylmetal reagents.[5]



(1)

A number of protocols for catalytic enantioselective synthesis of allylsilanes have been developed. Such transformations include enantioselective couplings of 1-(silyl)-alkyl Grignard reagents with vinyl halides,[6] hydrosilylations of 1,3-dienes,[7] silylations of allylic chlorides,[8] hydride additions to silyl-substituted allylic carbonates,[9] and silaborations of allenes.[10] These processes, all Pd-catalyzed, largely involve formation of C−Si or C−H bonds (with the exception of cross-coupling reactions)[11] and deliver an array of synthetically useful allylsilanes in the non-racemic form. In many cases, however, products are obtained in less than optimal enantiomeric purity (< 90% *ee*). To address such complications and identify a more efficient method, we investigated the possibility of accessing allylsilanes of high enantiomeric purity through catalytic AAA of organozinc reagents to electrophilic Si-substituted alkenes [Eq. (1)]. Such transformations would be catalyzed by chiral Cu complexes generated in situ from amino acid based[12] or bidentate NHC-based[13,14] ligands developed in these laboratories (see Scheme 1). Our interest was further fueled by the realization that, thus far, all catalytic AAA involving hard alkylmetals have been with substrates that carry a C-based substituent (i.e., versus a silyl group in this study).



Scheme 1. Chiral ligands and complexes used for in situ generation of chiral Cu-based catalysts.

We began by examining the reaction of vinylsilane **5** with Et_2Zn in the presence of amino acid based ligand **1**, shown to be highly effective in promoting Cu-catalyzed AAA of alkylzinc reagents to di- and trisubstituted alkenes.[12c] As shown in entry 1 of Table 1, with 10 mol% **1** and 5 mol% $(CuOTf)_2{\cdot}C_6H_6$ (−15 °C, 24 h) there is only 50% conversion

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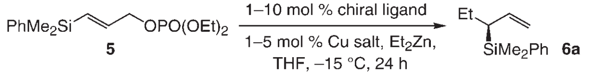
Table 1: Initial catalyst screening.[a]



Entry	Ligand; mol %	Cu salt; mol %	Conv. [%][b]	S_N2'/ S_N2[b]	*ee* [%][c]
1	**1**; 10	$(CuOTf)_2{\cdot}C_6H_6$; 5	50	> 98:2	69
2	**2**; 1	$(CuOTf)_2{\cdot}C_6H_6$; 1	> 98	> 98:2	98
3	**3**; 1	$(CuOTf)_2{\cdot}C_6H_6$; 1	> 98	> 98:2	94
4	**4**; 1	$(CuOTf)_2{\cdot}C_6H_6$; 1	98	> 98:2	92
5	**2**; 1	$(CuOTf)_2$·toluene; 1	> 98	> 98:2	98
6	**2**; 1	CuOAc; 2	70	> 98:2	98
7	**2**; 1	CuCl; 2	80	> 98:2	98
8	**2**; 1	$Cu(OTf)_2$; 2	12	> 98:2	70
9	**2**; 1	$Cu(OAc)_2$; 2	20	> 98:2	95
10	**2**; 1	$CuCl_2{\cdot}2H_2O$; 2	25	> 98:2	95

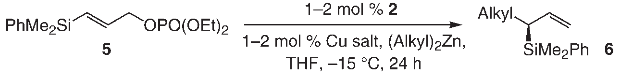
[a] Reactions performed under N_2 atmosphere. [b] Conversions and S_N2'/S_N2 ratios determined by analysis of 400-MHz ^1H NMR spectra. [c] Enantioselectivities determined by chiral GLC and HPLC analysis; see the Supporting Information for details.

to the desired allylsilane; although over 98 % S_N2'/S_N2 selectivity is observed, **6a** is generated in 69 % *ee*. In contrast, with 1 mol % NHC·Ag^I complex **2**[13a] and 1 mol % $(CuOTf)_2{\cdot}C_6H_6$ (entry 2, Table 1), the reaction proceeds to over 98 % conversion, affording **6a** in 98 % *ee* (> 98 % S_N2'/S_N2). As illustrated in entries 3 and 4 of Table 1, complexes **3**[13b] and **4**[14] furnish similar reactivity and regioselectivity levels but enantioselectivities are slightly diminished (94 % *ee* and 92 % *ee*, respectively). Commercially available $(CuOTf)_2$·toluene can also be used under otherwise identical conditions to afford the desired allylsilane **6** in over 98 % conversion and 98 % *ee* (entry 5, Table 1,). Although high activity is provided by $(CuOTf)_2{\cdot}C_6H_6$, as the data in entries 6 and 7 of Table 1 indicate, air-stable CuOAc and CuCl (commercial samples, not purified) can be used to promote the catalytic AAA in 98 % *ee*; the latter transformations, however, proceed to 70 % and 80 % conversion, respectively, under the same reaction conditions [vs. > 98 % conv. with $(CuOTf)_2{\cdot}C_6H_6$]. Finally, as the data in entries 8–10 in Table 1 show, Cu^{II} salts provide significantly lower activity, although in two instances, **6a** is isolated in 95 % *ee*.

As illustrated by the data summarized in Table 2, a range of tertiary allylsilanes (**6a**–**e**) may be obtained in 92–98 % *ee*, with greater than 98 % site-selectivity (S_N2'/S_N2) and in over 70 % yields with 1–2 mol % catalyst loading. A variety of alkylmetals, including the less reactive Me_2Zn (entry 4, Table 2), heteroatom-containing (entry 5) as well as secondary (entries 7 and 8) dialkylzinc reagents may be used with high efficiency. Catalytic alkylations can be readily performed with easy-to-handle and air-stable Cu salts (entries 2, 3, and 8, Table 2); higher catalyst loadings (2 mol % **2** and 4 mol % Cu salt) are required, however, to attain complete conversion. Moreover, Cu-catalyzed AAA can be carried out in undistilled THF and on the bench top: the Cu-catalyzed AAA in entry 2 of Table 2 proceeds to afford **6a** in 98 % *ee* and 79 % yield under such user-friendly conditions (0.8-mmol scale).

A unique attribute of the chiral catalysts developed in these programs is the ability to promote additions to sterically congested trisubstituted olefins, furnishing quaternary carbon stereogenic centers efficiently and in high *ee*.[12a,c,d,13a–c] We thus sought to determine whether chiral NHC·Cu complexes initiate efficient AAA of trisubstituted allylic phosphate **7** in spite of the increased steric hindrance projected by the Si-based substituent, an attribute that might be offset by a longer C–Si bond (vs. a C–C bond). The results of these studies, summarized in Table 3, illustrate that different dialkylzinc reagents, including the sterically demanding iPr_2Zn can be

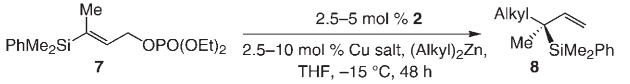
Table 2: Cu-catalyzed enantioselective synthesis of tertiary alkyl-substituted allylsilanes.[a]



Entry	$(Alkyl)_2Zn$; equiv	Cu salt	**2** [mol %]; Cu salt [mol %]	Prod.	S_N2'/ S_N2[b]	Yield [%][c]	*ee* [%][d]
1	Et_2Zn; 3	$(CuOTf)_2{\cdot}C_6H_6$	1; 1	**6a**	> 98:2	72	98
2	Et_2Zn; 3	CuOAc	2; 4	**6a**	> 98:2	84	95
3	Et_2Zn; 3	CuCl	2; 4	**6a**	> 98:2	80	92
4	Me_2Zn; 6	$(CuOTf)_2{\cdot}C_6H_6$	1; 1	**6b**	> 98:2	94	96
5	$[AcO(CH_2)_4]_2Zn$; 2	$(CuOTf)_2{\cdot}C_6H_6$	1; 1	**6c**	> 98:2	76	92
6	$[Me_2CH(CH_2)_3]_2Zn$; 2	$(CuOTf)_2{\cdot}C_6H_6$	1; 1	**6d**	> 98:2	74	98
7	iPr_2Zn; 3	$(CuOTf)_2{\cdot}C_6H_6$	1; 1	**6e**	> 98:2	75	96
8	iPr_2Zn; 3	CuOAc	2; 4	**6e**	> 98:2	75	97

[a] Reactions performed under N_2 atmosphere; > 98 % conversion in all cases. [b] Conversions and S_N2'/S_N2 ratios determined by analysis of 400-MHz ^1H NMR spectra. [c] Yields of isolated purified products. [d] Enantioselectivities determined by chiral GLC and HPLC analysis; see the Supporting Information for details.

Table 3: Cu-Catalyzed enantioselective synthesis of quaternary alkyl-substituted allylsilanes.[a]

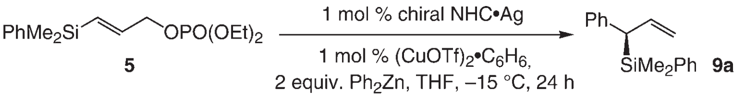


Entry	$(Alkyl)_2Zn$; equiv	Cu salt	**2** [mol %]; Cu salt [mol %]	Prod.	S_N2'/ S_N2[b]	Yield [%][c]	*ee* [%][d]
1	Et_2Zn; 3	$(CuOTf)_2{\cdot}C_6H_6$	2.5; 2.5	**8a**	> 98:2	75	91
2	Et_2Zn; 3	CuOAc	5; 10	**8a**	> 98:2	87	91
3	$[Me_2CH(CH_2)_3]_2Zn$; 2	$(CuOTf)_2{\cdot}C_6H_6$	2.5; 2.5	**8d**	> 98:2	78	91
4	iPr_2Zn; 3	$(CuOTf)_2{\cdot}C_6H_6$	2.5; 2.5	**8e**	> 98:2	81	92

[a] Reactions performed under N_2 atmosphere; > 98 % conversion in all cases. [b] Conversions and S_N2'/S_N2 ratios determined by analysis of 400-MHz ^1H NMR spectra. [c] Yields of isolated purified products. [d] Enantioselectivities determined by chiral GLC and HPLC analysis; see the Supporting Information for details.

used in the enantioselective synthesis of allylsilanes **8a**, **8d**, and **8e** in 91–92% *ee* and 75–87% yields. The corresponding achiral S_N2 product remains undetected (> 98% S_N2' by 400-MHz ^{1}H NMR analysis).

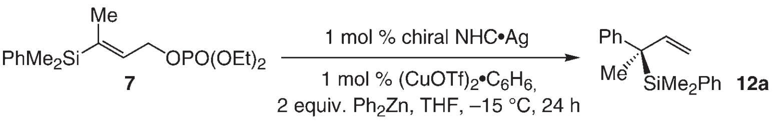
Next, we focused our attention on catalytic AAA involving diarylzinc reagents. Initial studies, summarized in Equation (2) indicated that, in contrast to reactions with dialkylzinc reagents, chiral NHC complex **3** is significantly more effective in promoting the reaction of **5** with commercially available Ph_2Zn. Thus, in the presence of 1 mol% **3**, AAA proceeds to over 98% conversion to afford **9a** in 90% *ee* and with greater than 98% S_N2' selectivity. With NHC complex **2**, there is only 50% conversion, affording **9a** in 65% *ee*, and with the typically more reactive carbene complex **4**, although greater than 98% conversion is obtained, the desired product is formed in 77% *ee*. As illustrated in entries 1–3 of Table 4, reactions with Ph_2Zn proceed readily with 1 mol% **3** to afford the desired allylsilanes **9a** and **11a** in 90–92% *ee* and over 80% yield as a single regioisomer (> 98% S_N2'). Cu-catalyzed AAA with $(p\mathrm{OMeC_6H_4})_2Zn$ is equally efficient and selective (entry 4, Table 4). When $(p\mathrm{CF_3C_6H_4})_2Zn$ is employed as the alkylating agent, although the reaction remains highly efficient (1 mol% **3**, > 98% conversion, 77% yield), **9c** is obtained in 57% *ee* and, for the first (and only) time, we can detect the undesired S_N2 addition product (11:1 S_N2'/S_N2).



(2)

NHC•Ag complex **2** = 50% conv., >98:2 S_N2'/S_N2, 65% *ee*
NHC•Ag complex **3** = >98% conv., >98:2 S_N2'/S_N2, 90% *ee*
NHC•Ag complex **4** = >98% conv., >98:2 S_N2'/S_N2, 77% *ee*

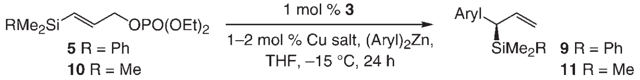
The advantages that arise from availability of a range of sterically and electronically distinct chiral NHC complexes are further highlighted by the initial studies in connection with AAA of trisubstituted alkene **7** by Ph_2Zn. As shown in Equation (3), it is now chiral complex **4** (Scheme 1), recently shown to be optimal in asymmetric conjugate additions of organozinc reagents to cyclic γ-ketoesters,[14] that is optimal (> 98% conversion, 67% *ee*). As the data in entry 1 of Table 5 indicate, when the reaction is performed at −78°C [vs. −15°C in Eq. (3)], in the presence of 1 mol% **4**, **12a** is isolated in 72% yield and 85% *ee* (> 98% S_N2');



(3)

NHC•Ag complex **2** = 35% conv., >98:2 S_N2'/S_N2, 26% *ee*
NHC•Ag complex **3** = >98% conv., >98:2 S_N2'/S_N2, 57% *ee*
NHC•Ag complex **4** = >98% conv., >98:2 S_N2'/S_N2, 67% *ee*

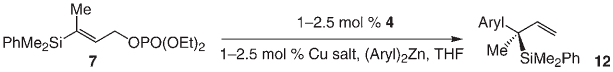
Table 4: Cu-catalyzed AAA of diarylzinc reagents to disubstituted vinylsilanes.[a]



Entry	Substrate	(Aryl)$_2$Zn; equiv	Cu salt	**3** [mol%]; Cu salt [mol%]	Product	S_N2'/S_N2[b]	Yield [%][c]	*ee* [%][d]
1	**5**	Ph_2Zn; 2	$(CuOTf)_2{\cdot}C_6H_6$	1; 1	**9a**	> 98:2	82	90
2	**10**	Ph_2Zn; 2	$(CuOTf)_2{\cdot}C_6H_6$	1; 1	**11a**	> 98:2	91	92
3	**10**	Ph_2Zn; 2	CuOAc	1; 2	**11a**	> 98:2	86	91
4	**5**	$p\mathrm{OMeC_6H_4}$; 2	$(CuOTf)_2{\cdot}C_6H_6$	1; 1	**9b**	> 98:2	88	91
5	**5**	$p\mathrm{CF_3C_6H_4}$; 2	$(CuOTf)_2{\cdot}C_6H_6$	1; 1	**9c**	11:1	77	57

[a] Reactions performed under N_2 atmosphere; > 98% conversion in all cases. [b] Conversions and S_N2'/S_N2 ratios determined by analysis of 400-MHz ^{1}H NMR spectra. [c] Yields of isolated purified products. [d] Enantioselectivities determined by chiral GLC and HPLC analysis; see the Supporting Information for details.

Table 5: Cu-catalyzed AAA of trisubstituted vinylsilanes by diarylzinc reagents.[a]

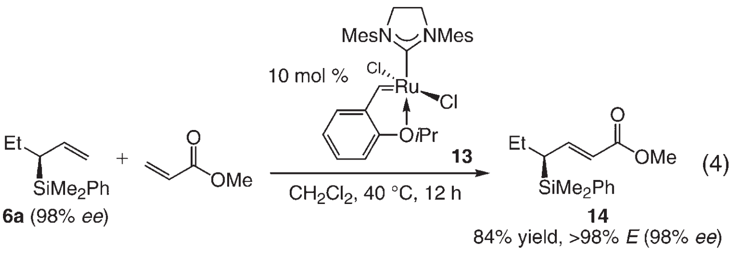


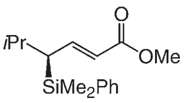
Entry	(Aryl)$_2$Zn; equiv	Cu salt	**4** [mol%]; Cu salt [mol%]	*T* [°C]; *t* [h]	Product	S_N2'/S_N2[b]	Conv. [%][b]; Yield [%][c]	*ee* [%][d]
1	Ph_2Zn; 2	$(CuOTf)_2{\cdot}C_6H_6$	1; 1	−78; 24	**12a**	> 98:2	> 98; 72	85
2	Ph_2Zn; 2	CuOAc	1; 2	−78; 24	**12a**	> 98:2	> 98; 77	84
3	$p\mathrm{OMeC_6H_4}$; 2	$(CuOTf)_2{\cdot}C_6H_6$	2.5; 2.5	−78; 48	**12b**	> 98:2	30; 25	90
4	$p\mathrm{OMeC_6H_4}$; 2	$(CuOTf)_2{\cdot}C_6H_6$	2.5; 2.5	−15; 24	**12b**	> 98:2	> 98; 80	76

[a] Reactions performed under N_2 atmosphere; > 98% conversion in all cases. [b] Conversions and S_N2'/S_N2 ratios determined by analysis of 400-MHz ^{1}H NMR spectra. [c] Yields of isolated purified products. [d] Enantioselectivities determined by chiral GLC and HPLC analysis; see the Supporting Information for details.

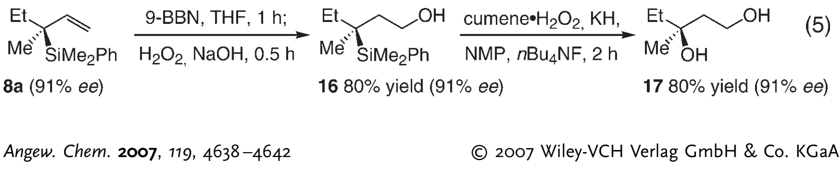
similar results are obtained with the more robust CuOAc (entry 2, Table 5). Catalytic AAA reactions involving $(p\text{OMeC}_6\text{H}_4)_2\text{Zn}$ (entries 3 and 4, Table 5) are less efficient. Thus, at −78 °C, high enantioselectivity (90 % *ee*, entry 3) is at the cost of low conversion (30 % conversion, 25 % yield); to achieve complete reaction, the temperature must be raised to −15 °C, an adjustment that causes diminution of selectivity (76 % *ee*, entry 4 in Table 5). It is possible that the lower efficiency of the above process is partly due to stabilization of the intermediate Cu^{III} complex by the electron-donating *p*-OMe substituent (leading to a slower rate of reductive elimination)[15] as well as the more sterically demanding olefinic site (vs. disubstituted alkenes in Table 4).

As mentioned previously, the utility of allylsilanes as chiral reagents for Lewis acid catalyzed additions to carbonyl- and imine-based electrophiles, is well appreciated.[1,2] Nonetheless, additional examples are presented below. As exemplified by the reaction shown in Equation (4), tertiary allylsilanes, such as **6a** (98 % *ee*), undergo catalytic cross-metathesis in the presence of Ru catalyst **13**[16] to afford functionalized allylsilanes in high yields to afford γ-substituted α,β-unsaturated carbonyls **14** [Eq. (4)] and **15**. Two additional points are worthy of note: 1) Cross-metathesis reactions[17] with PCy_3-bearing second-generation Grubbs catalyst[18] are significantly less efficient (< 40 % conversion, under identical conditions). 2) Attempts to promote cross-metathesis with substrates bearing a quaternary Si-substituted carbon center proved unsuccessful (< 5 % conversion, under identical conditions), a finding that points to the need for significantly more effective olefin metathesis catalysts. Another representative functionalization, involving an allylsilane with a quaternary carbon stereogenic center, is illustrated in Equation (5). Hydroboration (with 9-borabicyclo[3.3.1]nonane, 9-BBN) of the terminal alkene in **8a** (91 % *ee*) proceeds smoothly to afford the corresponding enantiomerically enriched primary carbinol **16** in 80 % yield. Subsequent oxidation (with *N*-methyl-2-pyrollidone, NMP)[19] furnishes tertiary alcohol **17** with greater than 98 % retention of stereochemistry and in 80 % yield.





15
>98% yield, >98% *E* (96% *ee*)



We thus introduce an efficient catalytic method for enantioselective synthesis of allylsilanes, including those that contain a quaternary Si-substituted carbon stereogenic center. The present study further underlines the rapidly emerging and significant utility of chiral bidentate NHC complexes in asymmetric catalysis and enantioselective synthesis. These investigations illustrate the significance of the availability of a diverse set of chiral NHCs to the development of catalytic asymmetric alkylations that can be effected on a range of substrates and with alkyl- as well as arylmetal nucleophiles.[20]

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Keywords: allylation · allylsilanes · asymmetric catalysis · N-heterocyclic carbenes · quaternary stereocenters

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