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Enantioselective Conjugate Silyl Additions to Cyclic and Acyclic Unsaturated Carbonyls Catalyzed by Cu Complexes of Chiral N-Heterocyclic Carbenes

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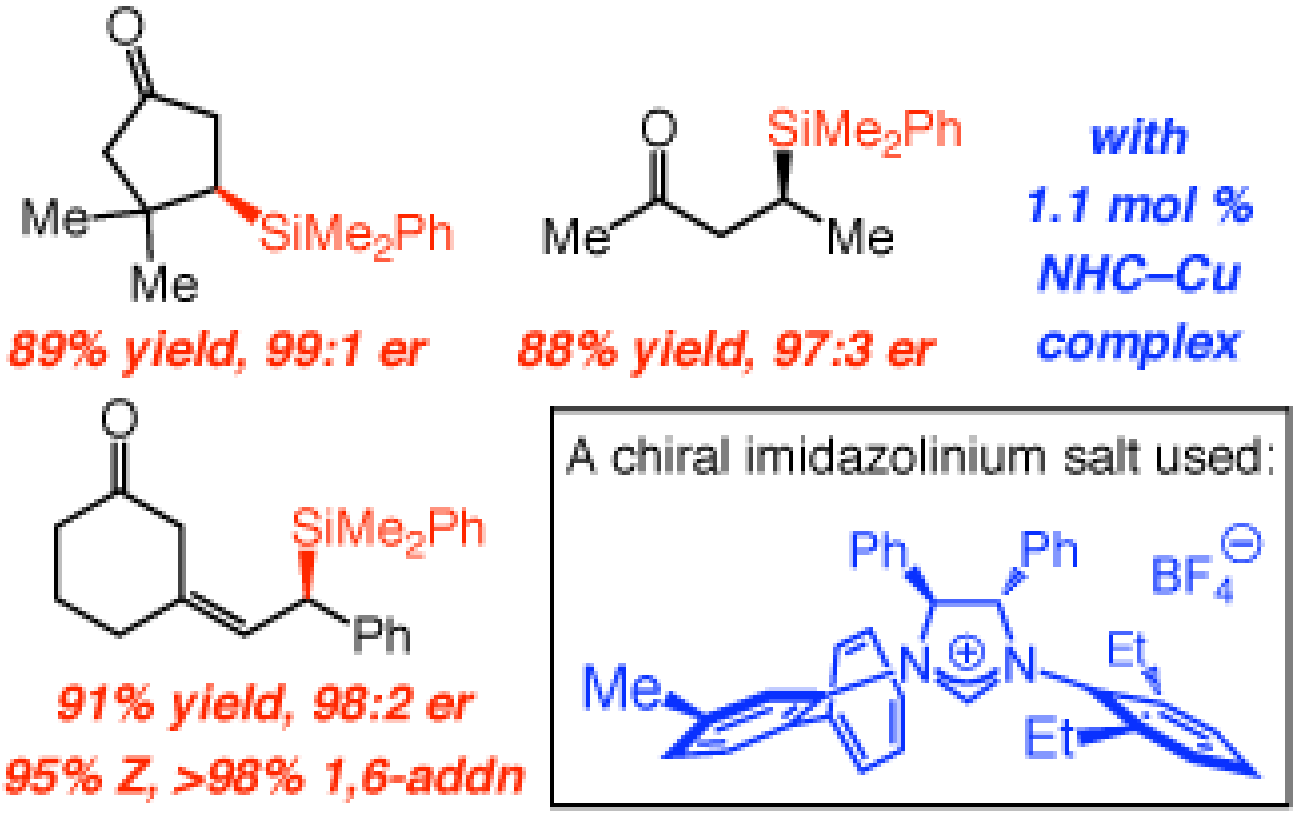
Abstract



An efficient Cu-catalyzed protocol for enantioselective addition of a dimethylphenylsilanyl group to a wide range of cyclic and acyclic unsaturated ketones, esters, acrylonitriles and *α*,*β*,*γ*,*δ*-dienones is disclosed. Reactions are performed in the presence of 1–2 mol % of commercially available and inexpensive CuCl, a readily accessible monodentate imidazolinium salt as well as commercially available (dimethylphenylsilyl)pinacolatoboron. Cu-catalyzed enantioselective conjugate additions proceed to completion within only two hours to afford the desired silanes in 87–97% yield and 90:10–

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Supporting Information Available: Experimental procedures and spectral, analytical data for all products (PDF). This material is available on the web: http://www.pubs.acs.org

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99:1 enantiomeric ratio (er). Use of a proton source (e.g., MeOH) is not required; accordingly, synthetically versatile *α*-silyl boron enolates can be obtained. The special utility of the present protocol, in comparison with the related catalytic enantioselective aldol and boronate conjugate additions, are discussed and illustrated through various functionalizations of the enantiomerically enriched *β*-silylcarbonyls.

Development of practical and efficient methods for catalytic enantioselective formation of C–Si bonds is an important and challenging goal of research in chemical synthesis;[1] transformations delivering *β*-silylcarbonyls are particularly attractive. A Si-based substituent, among other functions, serves as a masked hydroxyl group; it is sufficiently robust to allow for a range of functionalization processes that involve the carbonyl unit without causing decomposition or side reactions (e.g., retro-aldol).[2] If silyl conjugate addition is used,[3,4,5] the resulting enol resides adjacent to a sizeable silyl group and an electron-donating C–Si bond (e.g., **iii**, Scheme 1) and can thus react efficiently and stereoselectively with electrophiles. A number of catalytic enantioselective silyl conjugate additions to *α*,*β*-unsaturated carbonyls have been disclosed.[6,7] Such protocols, promoted by Pd- and Rh-based phosphine complexes, are noteworthy but operate within a relatively narrow substrate range (e.g., require cis alkenes[7b]), at times proceed with low to moderate enantioselectivity[6] or moderate efficiency,[7] or demand reagents (e.g., $Cl_2PhSi–SiMe_3$), which afford products that must be alkylated (MeLi) prior to efficient product isolation. Herein, we outline a Cu-catalyzed protocol for enantioselective addition of a dimethylphenylsilanyl group to unsaturated cyclic and acyclic ketones, lactones, esters, as well as acrylonitriles and cyclic *α*,*β*,*γ*,*δ*-dienones. Reactions proceed in 87–97% yield and 90:10–99:1 er with 1–2 mol % of an inexpensive commercially available Cu salt and silylborane reagent, as well as easily accessible monodentate chiral imidazolinium salts (3–4 steps from diphenylethylenediamine in ~50% overall yield).[8]

Our investigations were initiated partly based on observations by Sadighi and co-workers,[9] who demonstrated that NHC–Cu-alkoxides (e.g., **i**, Scheme 1) react with bis(pinacolato) diboron [$B_2(pin)_2$] to afford the derived NHC–Cu-B(pin). Such a process is likely driven by the formation of the B–O bond in pinacolatoboron alkoxide that is generated as a byproduct. As outlined in Scheme 1, we sought to determine whether an NHC–Cu-alkoxide (**i**) reacts with the sterically more congested (dimethylphenylsilyl)pinacolatoboron to deliver an NHC–Cu-silane (**ii**), which would undergo reaction with an unsaturated carbonyl to effect formation of a C–Si bond (**iii**). We surmised that **ii** would be preferred over NHC–Cu-boronate since formation of a Si–O is energetically less favored than a B–O bond.[10] Reaction of the resulting copper enolate with dimethylphenylsilylpinacolatoboron (**1**, Scheme 1) regenerates **ii**, affording boron enolate **iv**. We have illustrated that NHC–Cu-enolates (e.g., **iii**) react readily with $B_2(pin)_2$ to release the catalytically active NHC–Cu-B(pin).[11] If the same process proceeds with **1**, the catalytic process would not require an alcohol additive (MeOH), which is used to induce turnover in catalytic Cu–B(pin) additions to alkenes.[12] The versatile boron enolate (vs protonated ketone) would thus be obtained as a result of the projected conjugate silane addition.

We began by probing the ability of a number of chiral NHC–Cu complexes in promoting the addition of **1** to cyclohexenone to afford *β*-silylketone **6**; key results are summarized in Table 1. All NHC–Cu complexes, generated in situ from reaction of bidentate Ag-based carbenes **2**[13] and **3**[14] as well as monodentate variants **4**[15] and **5**[8] with CuCl, promote conjugate addition of the silane unit. It should be noted that none of the products derived from the formation of a C–B bond is observed (<2% by 400 MHz ^{1}H NMR), and the presence of a proton source (MeOH) is not required. Moreover, enantioselectivity is significantly higher with monodentate complexes **4** and **5**, with the C_1-symmetric chiral catalyst (**5**) delivering the optimal er (96:4, entry 4).

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Imidazolinium salts are more robust (less light sensitive) than the derived monodentate NHC–Ag complexes (e.g., **4**–**5**, Table 1). Accordingly, simultaneous with our efforts to identify an optimal catalyst that can be utilized in lower loading (e.g., 1 mol %), we turned to variants of the aforementioned chiral C_1-symmetric imidazolinium salts. As shown in Scheme 2, ligands where the symmetric NAr unit bears larger substituents deliver lower enantioselectivity (**7**–**9**). Next, we examined candidates containing a 2,4,6-trimethylaniline (NMes; cf. **7**, not shown in Scheme 2)[16] or a 2,6-diethylphenylamine (cf. **8**) along with dissymmetric NAr groups. Optimal enantioselectivities were obtained with **12** (Scheme 2); as before (i.e., with **7**–**8**), the catalyst bearing a smaller *meta* substituent (Me) furnishes higher selectivity (97.5:2.5 vs 91:9 er with **10**).[16] Two additional points merit mention: 1) C_1-Symmetric NHC complexes[17] offer a larger degree of diversity versus C_2-symmetric variants (i.e., each NAr unit can be modified independently), and thus are more advantageous in connection with reaction optimization. 2) The ligands corresponding to **10**–**12**, but bearing an NMes unit, promote less selective conjugate additions,[16,18] indicating cooperativity between the two NAr units of the chiral ligand. The lower er observed with C_2-symmetric **4** versus C_1-symmetric **5** (Table 1) further supports the above notion.

Cyclic unsaturated ketones undergo enantioselective silyl conjugate addition in the presence of 1.1 mol % **12** and 1.0 mol % CuCl (Table 2). Reactions proceed to >98% conversion after only one hour at −78 °C, affording the desired *β*-silylketones in 87–95% yield and 90:10–99:1 er. Five- (entries 1 and 5), six- (entries 2 and 6), as well as seven- (entries 3 and 7) and eight-membered (entry 4) ring enones are effective substrates. Enones that contain sterically congested electrophilic sites readily undergo conjugate silyl addition within one hour (entries 5–6, Table 2). Conjugate addition to an unsaturated lactone is efficient (entry 8, Table 2), but proceeds with lower enantioselectivity (vs the related ketone: 92:8 er vs 97.5:2.5 er in entry 2).

Reactions of acyclic *α*,*β*-unsaturated ketones proceed with equally high efficiency and enantioselectivity (Table 3). Substrates bearing alkyl (entries 1–3, Table 3) as well as aryl (entries 4–7) substituents undergo reaction to afford the desired products in 87–97% yield and up to 98.5:1.5 er. Neither the efficiency nor the enantioselectivity is affected by the electronic attributes (entries 4–6) or the presence of an *ortho* substituent (entry 7).

The Cu-catalyzed protocol extends beyond reactions of alkyl ketones, as illustrated by the formation of **13** (Scheme 3) in 92% yield and 95.5:4.5 er. As the additional cases in Scheme 3 indicate, acrylonitriles (e.g., **14**), a class of substrates that is inert to Rh-catalyzed silyl conjugate additions,[7b] and unsaturated esters (**15** and **16**) are effective substrates.

Our preliminary investigations indicate that the present catalytic protocol can be readily carried out with *α*,*β*,*γ*,*δ*-dienones, affording the 1,6-addition products exclusively (>98% site-selectivity), with effective control of olefin geometry and in high enantioselectivity; the examples in Scheme 4 are illustrative. Several points regarding the observations in Scheme 4 are worthy of note: 1) The optimal catalyst for this class of transformations is derived from C_2-symmetric imidazolinium salt **19** (Scheme 4), since NHC–Cu complex **12** delivers substantially lower *E*/*Z* ratios and levels of enantiomeric purity (**20** in 2:1 *Z*:*E* and 94.5:5.5 and 54:46 er, respectively; **21** in >98% *E* and 69.5:30.5 er). 2) The high alkene stereoselectivity and enantioselectivity with which **21** is formed indicates that reaction likely occurs through an *s*-cis diene. 3) The enantiomerically enriched allylsilanes can be used in reactions with various electrophiles; the diastereoselective oxidation affording **22** is a case in point. Further development of this class of conjugate additions is ongoing in these laboratories.

The Cu-catalyzed enantioselective silane conjugate additions described herein are of substantial utility and complement the related processes involving boronates,[19] which, upon

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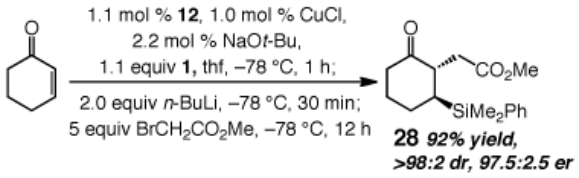
oxidation, can also furnish the corresponding *β*-hydroxy carbonyls. The present set of protocols, however, offers distinct advantages; two examples are illustrated in Scheme 5. First, whereas the boron enolate derived from catalytic boronate conjugate addition to six-membered ring enones undergoes facile aldol addition,[11,19d] the corresponding enolates from reactions of cyclopentenone or cycloheptenone are unreactive.[20] In contrast, as depicted in Scheme 5, the boron enolates of all ring sizes (only five- and seven-membered rings shown) obtained through catalytic silyl additions react readily with aldehydes to afford the desired *β*-silyl,*β*-hydroxyketones **23** and **24**. The neighboring donor C–Si bonds likely enhances the nucleophilicity of the boron enolates through hyperconjugative effects;[21] in contrast, the low-lying C–B *σ** in the related boronate addition products can diminish enolate nucleophilicity.

Second, pinacolatoboronates are sensitive to common organometallics such as aryl- or alkyllithiums as well as the derived Grignard reagents. In contrast, *β*-silylketones can be easily functionalized, often with high diastereoselectivity, through reaction with such reagents. The example in Scheme 5 (→**26**) is representative; the *β*-boronate ketones are converted to unidentifiable products.[22] As also presented in Scheme 5, subsequent oxidation[23] (→**27**) furnishes the enantiomerically enriched *syn*-1,3-diol. A similar procedure with a boronate product would require prior oxidation and protection of the resulting carbinol (to avoid retro-aldol upon treatment with arylmetal).

The Cu-catalyzed additions should prove to be of utility in complex molecule synthesis. For example, ketoester **28** (eq 1), accessed through a racemic synthesis followed by HPLC separation of the enantiomers, was recently utilized in an approach to biologically active natural product (+)-erysotramidine.[24] As shown in eq 1, the desired intermediate can now be easily synthesized by a one-pot procedure in 92% yield, as a single diastereomer and in 97.5:2.5 er. The stability of the silyl group towards *n*-BuLi (see above) allows for conversion of the boron enolate to its more nucleophilic Li-based derivative.



(1)

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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16. See the Supporting Information for details regarding these screening studies.
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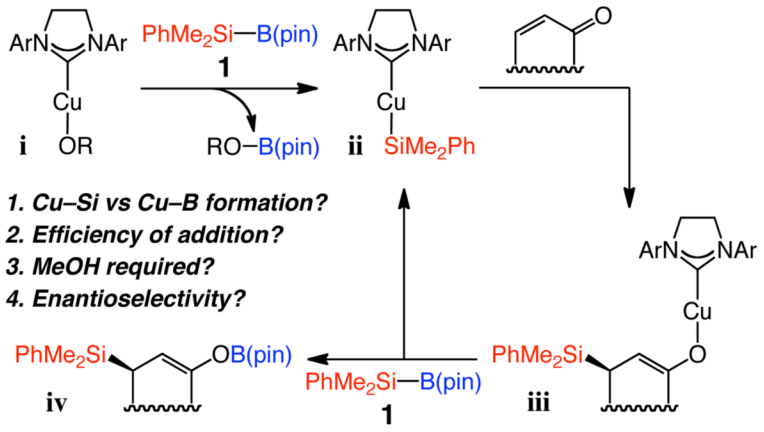

Scheme 1.

Catalytic Cycle for Silane Conjugate Additions Promoted by a NHC–Cu Complex[a]

[a] B(pin) = pinacolatoboron.

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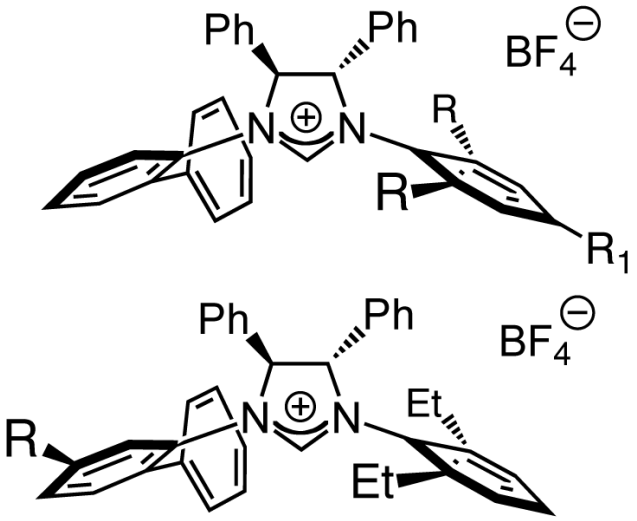

7 R = R_1 = Me er = 94.5:5.5
8 R = Et, R_1 = H er = 91.5:8.5
9 R = R_1 = *i*-Pr er = 87:13

10 R = *t*-Bu er = 91:9
11 R = *i*-Pr er = 93:7
12 R = Me er = 97.5:2.5

Scheme 2.
Enantioselective Synthesis of *β*-Silylketone **6** with Various Chiral C_1-Symmetric NHC Complexes[a]
[a] Under conditions in Table 1, except with 1.0 mol % CuCl, 1.1 mol % **7**–**12**, 2.2 mol % NaO*t*-Bu. All conv >98% by analysis of 400 MHz ^{1}H NMR spectra of unpurified mixtures. Enantiomeric ratios by HPLC analysis (see the SI for details).

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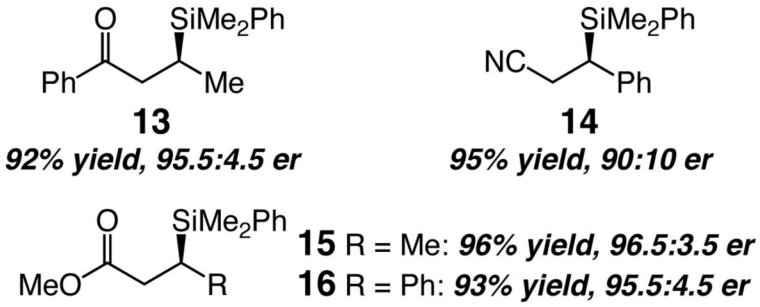

Scheme 3.

a

[a] See Table 2 for reaction conditions.

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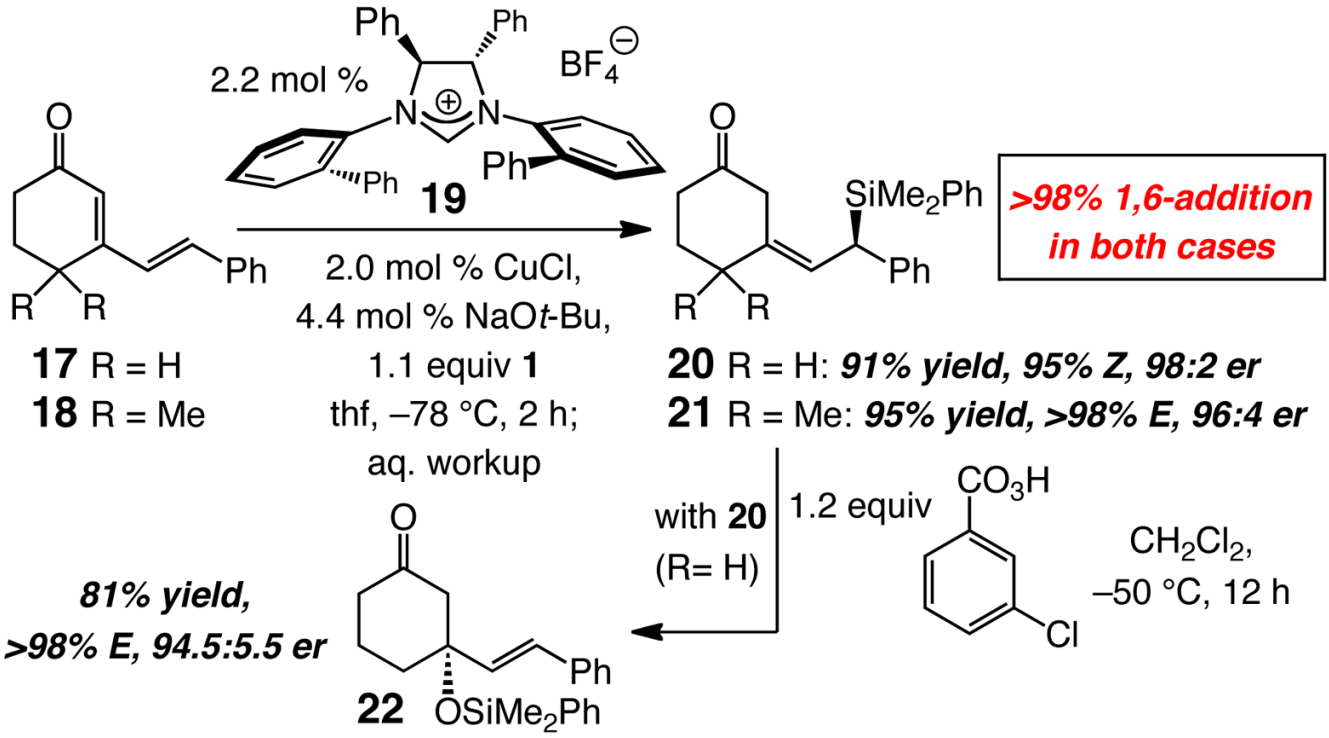

Scheme 4.
Cu-Catalyzed Enantioselective Additions to Cyclic Dienones

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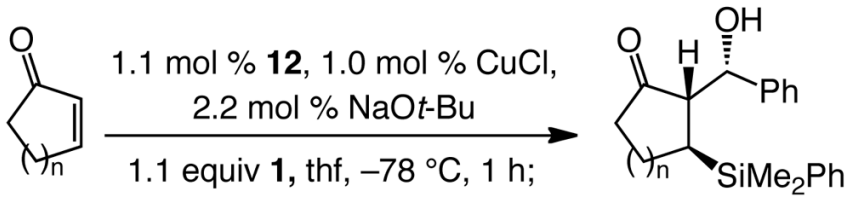
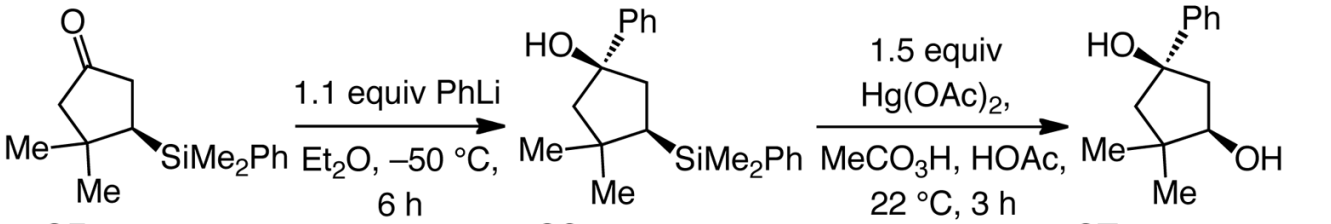
1. Boron enolate Reactions with C-based Electrophiles:



The corresponding boronates (vs silanes) are unreactive towards aldehydes.

23 n = 1 ***91% yield, 6:1 dr***, *(90:10 er)*
24 n = 3 ***92% yield, 3:1 dr***, *(95.5:4.5 er)*

2. β-Silylketone Reactions with Organometallic Reagents:



25 (99:1 er)

26 ***85% yield, >98:2 dr***

27 ***84% yield, >98:2 dr, 98:2 er***

The boronate (vs silane) undergoes decomposition with PhLi or PhMgBr.

Scheme 5.
β-Silylketones versus the Corresponding Boronates

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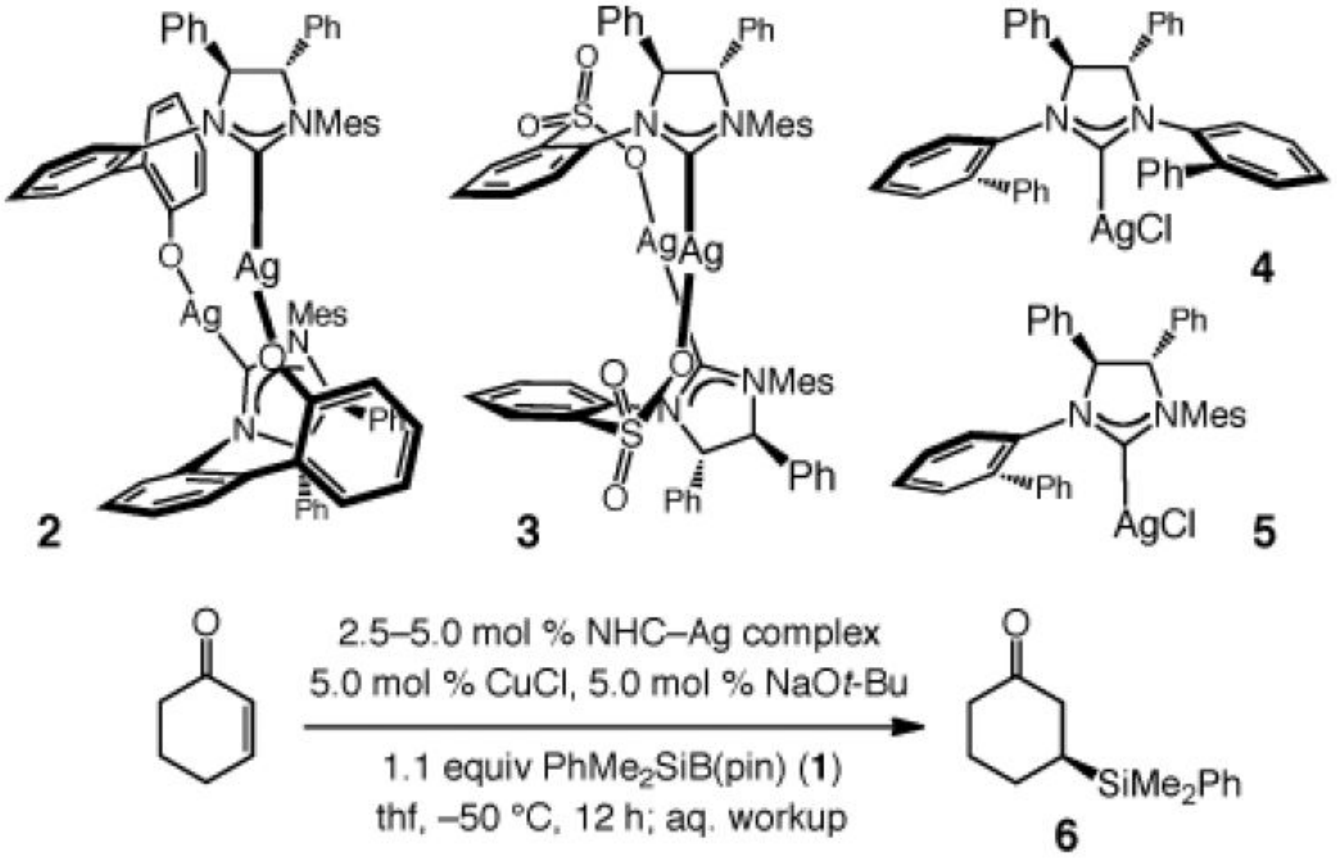
Table 1

Initial Examination of Various Chiral NHC Complexes[a]



entry	NHC–Ag; mol %	conv (%)[b]	yield (%)[c]	er[d]
1	**2**; 2.5	>98	91	87:13
2	**3**; 2.5	>98	94	89:11
3	**4**; 5.0	>98	90	92.5:7.5
4	**5**; 5.0	>98	92	96:4

see the Supporting Information for details. Mes = 2,4,6-trimethylphenyl.

[a] Under N_2 atm.

[b] Determined by analysis of 400 MHz ^{1}H NMR spectra of unpurified mixtures.

[c] Yields of purified products.

[d] By HPLC analysis;

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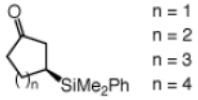
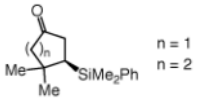
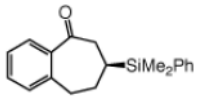
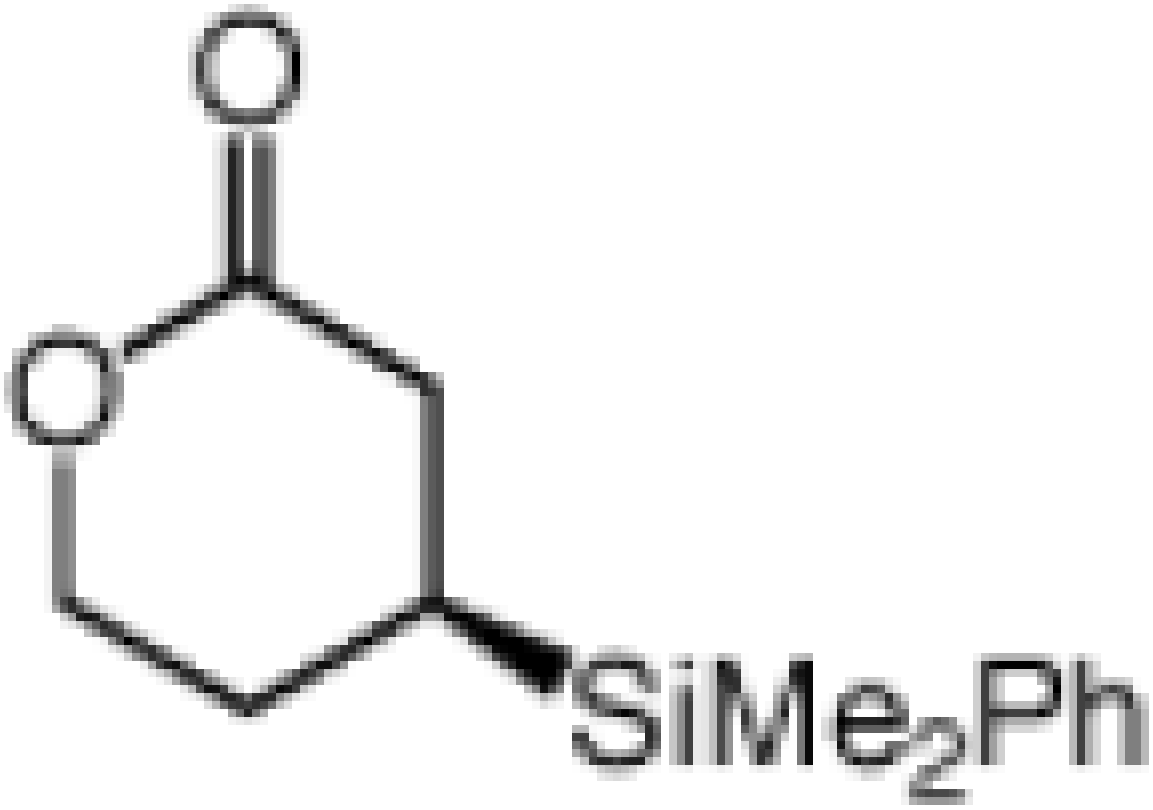
Table 2

NHC–Cu-Catalyzed Enantioselective Conjugate Additions of Silanes to Cyclic α,β-Unsaturated Carbonyls[a]

entry	product	yield (%)[b]
1	 n = 1	87
2	n = 2	92
3	n = 3	95
4	n = 4	95
5	 n = 1	89
6	n = 2	94
7		91
8[d]		95

[a] Under N_2 atm with 1.1 mol % **12**, 1 mol % CuCl and 2.2 mol % NaO*t*-OBu at −78 °C for 1 h; >98% conv in all cases.

[b] Yields of purified products.

[c] By HPLC analysis; see the SI for details.

[d] Imidazolinium salt **11** (2.2 mol % with 2.0 mol % CuCl and 4.4 mol % NaO*t*-Bu) used for 12 h.

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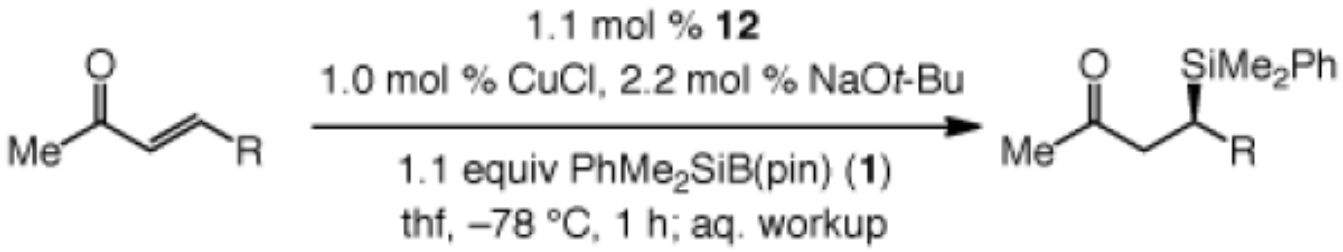
Table 3

NHC–Cu-Catalyzed Enantioselective Conjugate Additions of Silanes to Acyclic α,β-Unsaturated Enones[a]



entry	R	yield (%)[b]	er[c]
1	Me	88	97:3
2	*n*-pent	96	98:2
3	*i*-Pr	87	97:3
4	Ph	91	98.5:1.5
5	*p*-$OMeC_6H_4$	94	97:3
6	*p*-$CF_3C_6H_4$	97	96:4
7	*o*-MeC_6H_4	96	93.5:6.5

[a] See Table 2.

[b] See Table 2.

[c] See Table 2.