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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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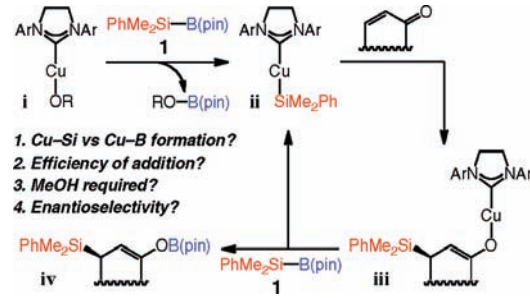
Development of practical and efficient methods for catalytic enantioselective formation of C−Si bonds is an important and challenging goal of research in chemical synthesis;[1] transformations delivering β-silylcarbonyls are particularly attractive. A Si-based substituent, among other functions, serves 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,[3−5] the resulting enol resides adjacent to a sizable 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 β-dihalosilylcarbonyls 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, and acrylonitriles as well as cyclic $\alpha,\beta,\gamma,\delta$-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 catalyzing the addition of **1** to cyclohexenone to afford β-silylketone **6**; key results are summarized in Table 1. All Cu-based carbenes, 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 are observed (<2% by 400 MHz ^{1}H NMR), and the presence of a proton source (MeOH) is not required. Moreover, enantioselectivity is higher with monodentate complexes **4** and **5**, with the C_1-symmetric chiral catalyst (**5**) delivering the optimal er (96:4, entry 4).

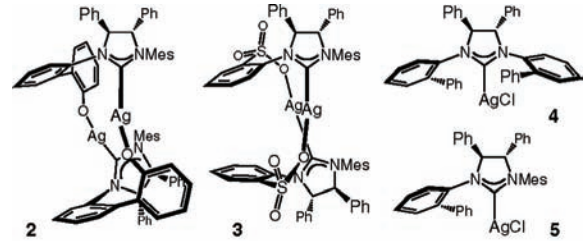
Imidazolinium salts are more robust (less light sensitive) than the derived monodentate NHC−Ag complexes (e.g., **4**−**5**, Table 1). Accordingly, simultaneous with our efforts to identify an optimal catalyst that can be utilized in lower loading (e.g., 1 mol %), we

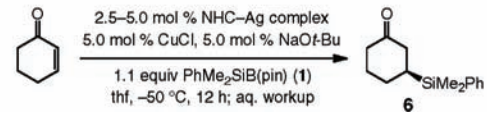
Scheme 1. Catalytic Cycle for Silane Conjugate Additions Promoted by a NHC-Cu Complex[a]



[a] B(pin) = pinacolatoboron.

Table 1. Initial Examination of Various Chiral NHC Complexes[a]



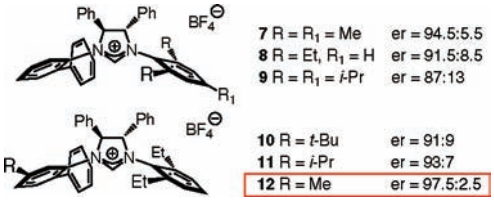


entry	NHC–Ag; mol %	conv (%)[b]	yield (%)[c]	er[d]
1	**2**; 2.5	>98	91	87:13
2	**3**; 2.5	>98	94	89:11
3	**4**; 5.0	>98	90	92.5:7.5
4	**5**; 5.0	>98	92	96:4

[a] Under N_2 atmosphere. [b] Determined by analysis of 400 MHz ^{1}H NMR spectra of unpurified mixtures. [c] Yields of purified products. [d] By HPLC analysis; see the Supporting Information (SI) for details. Mes = 2,4,6-trimethylphenyl.

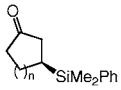
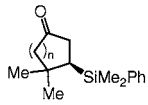
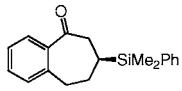
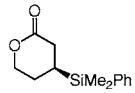
10.1021/ja910989n

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).

Table 2. NHC-Cu-Catalyzed Enantioselective Conjugate Additions of Silanes to Cyclic α,β-Unsaturated Carbonyls[a]

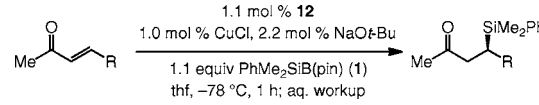
entry	product		yield (%)[b]	er[c]
1		n = 1	87	90:10
2		n = 2	92	97.5:2.5
3		n = 3	95	97:3
4		n = 4	95	98:2
5		n = 1	89	99:1
6		n = 2	94	99:1
7			91	96.5:3.5
8[d]			95	92:8

[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*t-Bu) used for 12 h.

turned to variants of the aforementioned 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), and seven- (entries 3 and 7) as well as eight-membered (entry 4) ring enones are effective substrates. Unsaturated ketones that contain sterically congested electrophilic sites readily undergo conjugate silyl addition within 1 h (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).

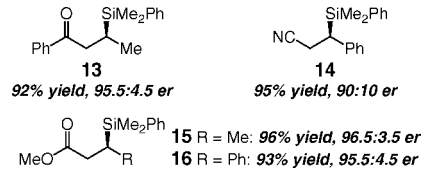
Table 3. NHC−Cu-Catalyzed Enantioselective Conjugate Additions of Silanes to Acyclic α,β-Unsaturated Enones[a]



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$_6$H$_4$	94	97:3
6	*p*-CF$_3$C$_6$H$_4$	97	96:4
7	*o*-MeC$_6$H$_4$	96	93.5:6.5

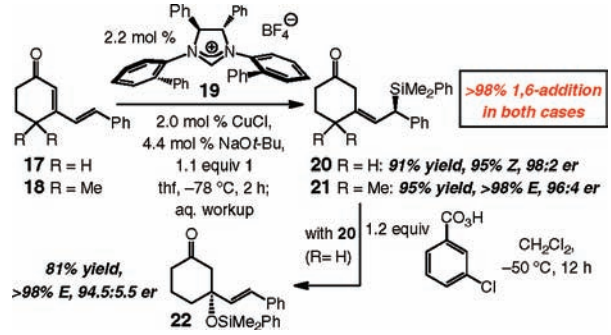
[a−c] See Table 2.

Scheme 3[a]



[a] See Table 2 for reaction conditions.

Scheme 4. Cu-Catalyzed Enantioselective Additions to Cyclic Dienones

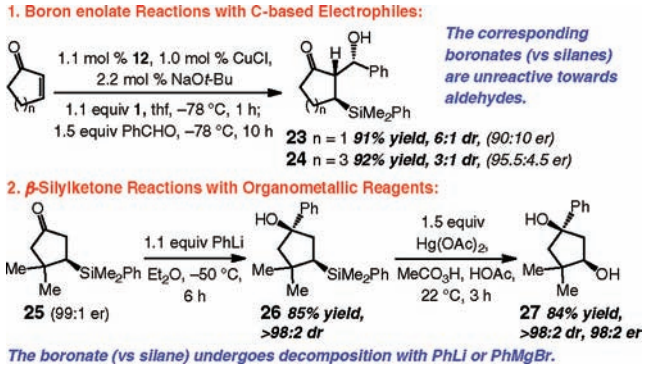


Reactions of trans acyclic α,β-unsaturated ketones proceed with equally high efficiency and enantioselectivity (Table 3) as when cis olefins of cyclic enones are involved. Substrates bearing alkyl (entries 1−3, Table 3) or aryl (entries 4−7) substituents undergo reaction to afford the desired products 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 $\alpha,\beta,\gamma,\delta$-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

Scheme 5. β-Silylketones versus the Corresponding Boronates

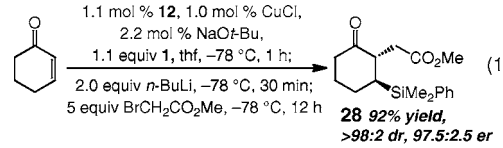


complex **12** delivers substantially lower *E*/*Z* ratios and levels of enantiomeric purity (**20** in 2:1 *Z*:*E* and 94.5:5.5 and 54:46 er, respectively; **21** in >98% *E* and 69.5:30.5 er). (2) The high alkene stereoselectivity and enantioselectivity with which **21** is formed indicates that reaction 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 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 enhance 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 toward *n*-BuLi (see above) allows for conversion of the boron enolate to its more nucleophilic Li-based derivative.



(1)

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Supporting Information Available: Experimental procedures and spectral, analytical data for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) See the Supporting Information for details regarding these screening studies.
(17) For design of C_1-symmetric monodentate chiral NHC-Cu complexes and comparison of their utility vs C_2-symmetric variants, see ref 8.
(18) For example, the NMes-containing derivative of **12** promotes formation of β-silylketone **6** in >98% conversion and 91:9 er (vs 97.5:2.5 er).
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