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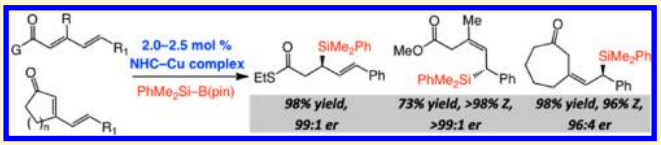
NHC–Cu-Catalyzed Silyl Conjugate Additions to Acyclic and Cyclic Dienones and Dienoates. Efficient Site-, Diastereo- and Enantioselective Synthesis of Carbonyl-Containing Allylsilanes

Kang-sang Lee, Hao Wu, Fredrik Haeffner, and Amir H. Hoveyda*

Department of Chemistry, Merkert Chemistry Center, Boston College, Chestnut Hill, Massachusetts 02467, United States

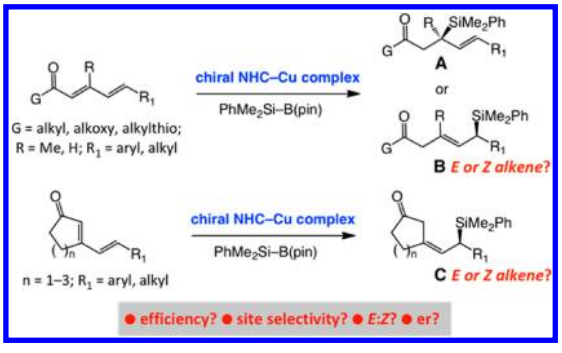
Supporting Information

ABSTRACT: Efficient and highly diastereo- and enantioselective conjugate additions of phenyldimethylsilyl units to acyclic and cyclic dienones and dienoates are disclosed. The C–Si bond forming reactions are catalyzed by 2.0–2.5 mol % of a copper complex of a chiral monodentate N-heterocyclic carbene; the requisite reagent, $PhMe_2Si–B(pin)$, is commercially available or can be easily prepared. Transformations generate allylsilanes in up to 98% yield and >99:1 enantiomeric ratio and proceed with complete 1,4-selectivity, unless the dienone or dienoate carries a trisubstituted alkene conjugated to the carbonyl group; in the latter cases, 1,6-addition products are obtained exclusively and in up to >98% *Z* selectivity.



Silicon-containing organic molecules are of substantial utility in chemical synthesis,[1] and allylsilanes are one of the most useful among them.[2] A valuable subset of chiral allylsilanes consists of those containing a carbonyl unit β to the silyl or the alkene unit (cf. **A** and **B**, Scheme 1);[3] such entities have served

Scheme 1. Enantioselective Synthesis of Carbonyl-Containing Allylsilanes by NHC–Cu-Catalyzed Silyl Conjugate Addition



in enantioselective preparation of several structurally complex natural products.[3,4] One direct approach to accessing the carbonyl-containing allylsilanes in the enantiomerically enriched form[5−10] involves site- and enantioselective silyl conjugate additions to acyclic or cyclic $\alpha,\beta,\gamma,\delta$-unsaturated dienones or dienoates. We envisioned that monodentate chiral N-heterocyclic carbenes[11] (NHCs) and their derived Cu-based complexes, developed recently in these laboratories and used for catalytic enantioselective silyl conjugate additions,[12,13] might be utilized to access allylsilanes represented by **A**–**C** (Scheme 1). If 1,6-addition were to be predominant (i.e., **B** and **C** are formed as major products), we would have to establish whether the alkene, likely to be generated as part of a β,γ-unsaturated carbonyl due to kinetic protonation of dienolate at the α position, is formed with high stereoselectivity.

Herein, we report the results of our investigations regarding the development of an efficient catalytic enantioselective method for silyl conjugate additions to dienones and dienoates. The resulting protocols allow access to an assortment of allylsilanes in 69–98% yield and 94.5:5.5 to more than 99:1 enantiomeric ratio (er). The requisite chiral ligands are prepared in three to four steps in ~50% overall yield;[11] the silylboron reagent ((dimethylphenylsilyl)pinacolatoboron (**1**)) is commercially available or can be prepared easily on a multigram scale.[14] Acyclic unsaturated ketones, esters, and thioesters as well as five-, six-, and seven-membered-ring cyclic dienones can be used as substrates. Depending on the substrate structure, 1,4- or 1,6-modes of addition predominate. In the case of 1,6-addition products,[15] trisubstituted alkenes are obtained with 78% to >98% *Z* selectivity.

We began by probing the ability of a selection of NHC–Cu complexes, derived from imidazolinium salts **4**–**6**, to promote conjugate addition of the versatile phenyldimethylsilyl moiety to dienone **2a** through reactions performed in the presence of silylboron reagent **1**. Although reasonable efficiency and enantioselectivity is observed in every case (Table 1), with C_2-symmetric **6b** serving as catalyst precursor, allylsilane **3a** is isolated in 96% yield and 99:1 er, and formation of the 1,4-addition product is strongly favored (<2% δ C–Si bond formation). We then determined that enantioselective synthesis of **3a** can be performed with 2.2 mol % of **6b** (2.0 mol % of CuCl, 4.4 mol % of NaO-*t*-Bu, −78 °C, 2.0 h) with identical efficiency and enantioselectivity (96% yield, 99:1 er). Similar to the NHC–Cu-catalyzed transformations involving $B_2(pin)_2$ to generate

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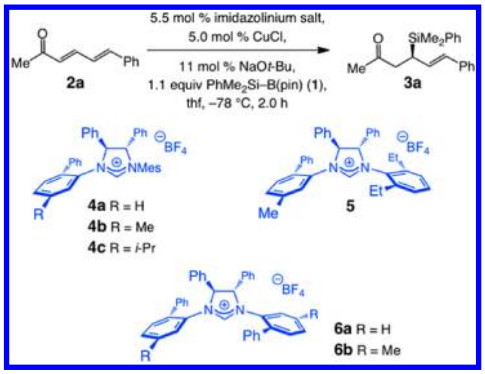
Table 1. Silyl Addition to an Acyclic Dienone: NHC−Cu Screening[a]



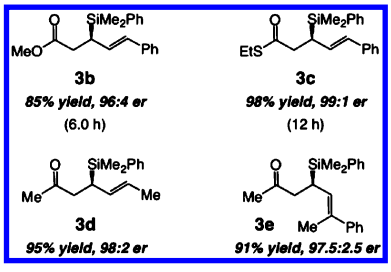
entry	imidazolinium salt	conversn (%)[b]	yield (%)[c]	er[d]
1	**4a**	80	77	86:14
2	**4b**	>98	92	93:7
3	**4c**	88	87	91:9
4	**5**	94	91	96:4
5	**6a**	>98	94	95:5
6	**6b**	*>98*	*96*	*99:1*

[a]Reactions performed under N_2 atmosphere. [b]Determined by analysis of 400 MHz ^{1}H NMR spectra of unpurified mixtures (±2%). [c]Yields of purified products (±5%). [d]Determined by HPLC analysis. See the Supporting Information for details. Mes = 2,4,6-$Me_3C_6H_2$.

tertiary C−B bonds,[16] silyl conjugate additions proceed readily in the absence of MeOH, the presence of which is required in some instances.[17] Thus, the NHC−Cu−enolate appears to be sufficiently able, likely due to the strong donor ability of the heterocyclic ligand,[16] to react with the sizable silylboron reagent in order to regenerate the catalytically active NHC−Cu−$SiMe_2Ph$ species.

The Cu-catalyzed additions have significant scope, as the data presented in Scheme 2 indicate. With 2.7 mol % **6b** (2.5 mol % of CuCl, 5.5 mol % of NaO*t*-Bu, −78 °C), *β*-silyl-substituted carboxylic ester **3b** is formed in 85% yield and 96:4 er, although the transformation is less facile and requires 6 h to proceed to completion. Conjugate addition to the corresponding thioester (cf. **3c**) is still slower (>98% conversion in 12 h at −78 °C), but the desired product is isolated in exceptionally high yield and enantiomeric purity (98% yield, 99:1 er). Cu-catalyzed enantioselective syntheses of *β*-silylketones **3d,e** illustrate that substrates bearing an alkyl-substituted dienes (vs Ph in **3a−c**), or those that contain a sterically demanding trisubstituted olefin, serve as equally effective starting points.

Scheme 2. Enantiomerically Enriched Acyclic Carbonyl-Containing Allylsilanes[a]



[a]Reactions were performed with 2.7 mol % of **6b**, 2.5 mol % of CuCl and 5.5 mol % of NaO*t*-Bu under a N_2 atmosphere (2.0 h unless otherwise noted). Yields are of isolated and purified products (±5%). Enantioselectivities were determined by HPLC analysis. See the Supporting Information for details.

Examining the reactions of acyclic dienones that contain a methyl substituent at their *β* carbon came next (cf. **7**, Table 2).

Table 2. Addition to a *β*-Substituted Acyclic Dienone: NHC−Cu Screening[a]

entry	imidazolinium salt	conversn (%)[b]	*Z*:*E*[b]	er[c]
1	**6a**	>98	91:9	95:5
2	**6b**	77	80:20	83:17
3	**9**	*81*	*93:7*	>99:1

[a−c]See Table 1; er values correspond to *Z* product isomers.

The question here was whether the NHC−Cu-catalyzed additions would occur at the C4 site to generate a Si-substituted quaternary carbon stereogenic center, or if C−Si bond formation occurs at the *δ* site. In both cases, there is only 1,6-addition and the *β*,*γ*-unsaturated ketone is formed exclusively. Unlike transformations with the less substituted dienone **2a**, the Cu complex derived from imidazolinium salt **6a** promotes a more efficient reaction and delivers the desired product (**8a**) with higher enantiomeric purity (entries 1 and 2, Table 1: 95:5 vs 83:17 er). Although both processes furnish the *Z* trisubstituted olefin predominantly, the reaction with **6a** is more stereoselective (91% vs 80% *Z*). As mentioned above, a hallmark of chiral monodentate NHC ligands is the ease with which their structure can be modified.[11,12] Accordingly, further screening led us to establish that use of C_2-symmetric imidazolinium salt **9** (entry 3, Table 2) leads to the formation of **8a** with superior *Z* selectivity and enantioselectivity (93% *Z*, >99:1 er).

Enantioselective synthesis of **8a** proceeds to >98% conversion with 2.5 mol % **9** within 6 h, under the conditions shown in Table 3; the allylsilane is generated in 93% *Z* selectivity and >99:1 er (entry 1). As the findings in entries 2 and 3 of Table 3 indicate, variations in the electronic attributes of the aryl substituent do not strongly affect *Z* selectivity or enantioselectivity. Formation of alkyl-substituted allylsilanes **10a,b** (entries 4 and 5, Table 3) is equally efficient and exceptionally enantioselective (>99:1 er), but the degree of alkene stereoisomeric purity is somewhat diminished (89% *Z*). Conjugate additions to the corresponding carboxylic and alkylthio esters, as shown in entries 6 and 7 of Table 3, generate the expected allylsilanes with complete *Z* selectivity and enantioselectivity (<2% *E* and ≥99:1 er); the conjugate addition with the S-containing substrate, however, demands higher temperatures (−50 vs −78 °C) and longer reaction times (48 vs 12 h) to proceed to completion.

The final segment of our investigation entailed a more extensive study of additions to cyclic dienones, two examples of which, involving six-membered-ring substrates in entries 2 and 7 of Table 4, were reported to occur with high *Z* selectivity and enantioselectivity in our initial disclosure.[12a] We were particularly keen on establishing whether the reactions are sensitive to different

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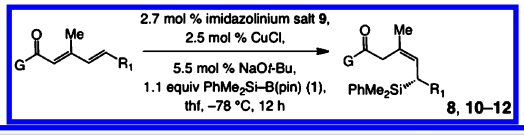
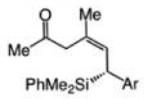
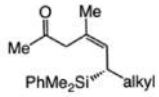
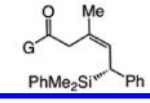
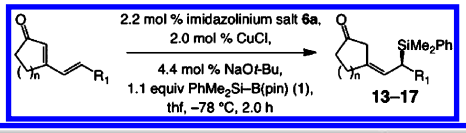
Table 3. Additions to β-Substituted Acyclic Dienones: Scope[a]

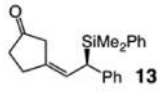
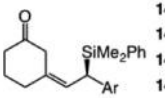
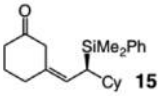
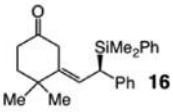
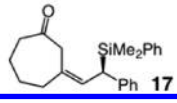


entry	allylsilane product		yield (%);[b]	Z:E[c]	er[d]
1[e]		**8a** Ar = Ph	81	93:7	>99:1
2		**8b** Ar = *p*-MeOC$_6$H$_4$	81	95:5	99:1
3		**8c** Ar = *p*-F$_3$CC$_6$H$_4$	75	91:9	>99:1
4		**10a** alkyl = *n*-Pr	85	89:11	>99:1
5		**10b** alkyl = Cy	72	89:11	>99:1
6		**11** G = OMe	73	>98:2	>99:1
7[f]		**12** G = SEt	69	>98:2	99:1

[a]Reactions performed under a N_2 atmosphere; >98% conversion, <2% α,β-unsaturated carbonyl product, and >98% 1,6-addition in all cases. [b]Yields of purified products (±5%). [c]Determined by analysis of 400 MHz ^{1}H NMR spectra of unpurified mixtures (±2%). [d]Determined by HPLC analysis; er values correspond to the *Z* alkene product. [e]Reaction time = 6.0 h. [f]Performed at −50 °C for 48 h. See the Supporting Information for details.

Table 4. Additions to β-Substituted Cyclic Dienones[a]



entry	allylsilane product		yield (%)[b]	Z:E[c]	er[d]
1[e]	 **13**		85	78:12	95:5
2		**14a** Ar = Ph	91	95:5	98:2
3		**14b** Ar = *p*-MeC$_6$H$_4$	95	>98:2	95:5
4		**14c** Ar = *p*-MeOC$_6$H$_4$	91	>98:2	97:3
5		**14d** Ar = *p*-F$_3$CC$_6$H$_4$	88	>98:2	94.5:5.5
6	 **15**		92	95:5	98:2
7	 **16**		95	<2>98	96:4
8	 **17**		98	96:4	96:4

[a–d]See Table 3. [e]Product mixture contained 15–20% of the isomerized α,β-unsaturated ketone. See the Supporting Information for details.

ring sizes and variations in the steric or electronic attributes of the alkene substituent.

Five- as well as seven-membered-ring dienones serve as effective substrates, delivering the desired allylsilanes in 85% and 98% yields, respectively (entries 1 and 8, Table 4).[18] Both products (**13** and **17**, Table 4) are obtained with high enantioselectivity (95:5 and 96:4 er, respectively), but the degree of *Z* selectivity with the cyclopentenyl system is diminished (78% vs 96% *Z*). Additionally, for the transformation in entry 1 of Table 4, the product mixture contains 15–20% of the derived α,β-unsaturated cyclopentenone (inseparable from **13**), formed presumably as a result of adventitious isomerization. Electronic alterations within the aryl substituent do not cause any significant variations in the *Z* selectivity or enantioselectivity of the silyl conjugate additions, as demonstrated by reactions shown in entries 2–5 of Table 4. Moreover, conjugate addition to the cyclic dienone in entry 6, carrying an alkyl substituent, is equally efficient and stereoselective, affording **15** in 92% yield, 95% *Z* selectivity, and 98:2 er.[19]

The NHC–Cu·dienone ensembles in Figure 1 provide a stereochemical model regarding the outcome of the 1,6-silyl conjugate

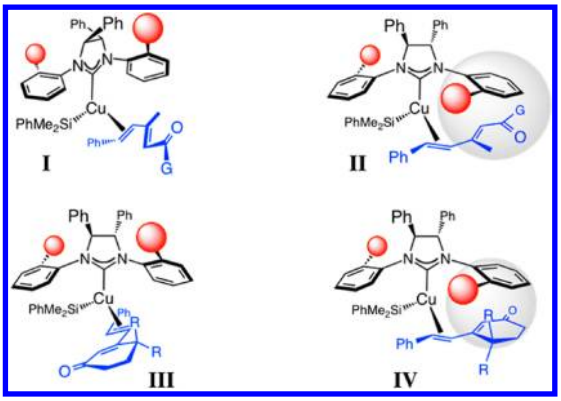


Figure 1. Proposed stereochemical models.

additions. The NHC–Cu–SiMe$_2$Ph complex is generated in situ by the pathways described before.[12a] Such a complex can coordinate with the γ,δ-alkene of the substrate, as illustrated by **I**–**IV**, with the high *Z* selectivity indicating the involvement of the *s-cis* conformers. Preliminary DFT calculations indicate that although, as expected, the *s-trans* dienes are energetically favored (by ≥2.0 kcal/mol), reaction through the intermediacy of an NHC–Cu-*s-cis* complex is favored.[20] Elucidation of the precise reason for such a preference requires additional studies but might partially be attributable to the η^4 nature of the Cu–diene coordination.[20] The observed enantioselectivity can arise from the minimization of steric repulsion between the substrate and the catalyst, forcing the more sterically demanding enone moiety to be oriented as depicted in **I** and **III** (Figure 1). The relatively low *Z* selectivity observed for the addition to cyclopentenone **13** (entry 1, Table 4) is difficult to explain. However, the proposed scheme is consistent with the lower *Z* selectivity delivered for the more sluggish and relatively nonselective transformations with to dienone *Z*-**18** (eq 1). In the latter instance, the resulting allylic strain likely

raises substantially the energy of the substrate's *s-cis* conformer, rendering the derived NHC–Cu–diene complex less accessible. As a result, alternative complexes, such as the corresponding *s-trans* dienone or that derived from coordination through the other enantiotopic face of the olefin, become competitive, causing diminution in *Z* selectivity and enantioselectivity.

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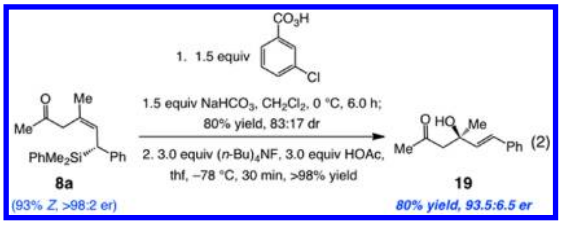
The protocols described here offer a convenient and direct route to a variety of enantiomerically enriched allylsilanes. The high *Z* selectivity in instances where 1,6-addition is dominant is a noteworthy aspect of the NHC−Cu-catalyzed transformations; in the corresponding processes with C-based nucleophiles, only moderate stereoselectivity is observed (≤85% of one alkene isomer favored).[15] Furthermore, attempts to perform NHC-catalyzed (Cu-free) silyl conjugate additions[12b] to representative substrates mentioned above (e.g., **2a**) resulted in <10% yield of the desired allylsilanes and a complex mixture of unidentifiable entities. The above attributes, together with the high efficiency and stereoselectivity observed in the aforementioned processes, should render the present class of Cu-catalyzed protocols of utility in chemical synthesis. The example shown in eq 2, involving the synthesis of β-hydroxy



ketone **19**, the product of an enantioselective ketone aldol addition[21] to an α,β-unsaturated ketone, is illustrative.

■ ASSOCIATED CONTENT

Supporting Information

Text, tables, and figures giving experimental procedures, spectral and analytical data for all products, and data for the theoretical calculations. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: amir.hoveyda@bc.edu.

Notes

The authors declare no competing financial interest.

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(18) Similar yields and enantioselectivities are obtained with the Cu complex derived from **9**. For instance, **16** is obtained in 79% yield (>98% conversion) and 96:4 er with the latter species.

(19) The minor *E* isomers are likely generated enantioselectivity (e.g., *E*-**15** in 79% yield and 91:9 er).

(20) See the Supporting Information for details.

(21) Broadly applicable, efficient, and highly enantioselective catalytic protocols for aldol additions to ketones remain lacking. For key reports, see: (a) List, B.; Shabat, D.; Zhong, G.; Turner, J. M.; Li, A.; Bui, T.; Anderson, J.; Lerner, L. A.; Barbas, C. F. *J. Am. Chem. Soc.* **1999**, *121*, 7283. (b) Denmark, S. E.; Fan, Y.; Eastgate, M. D. *J. Org. Chem.* **2005**, *70*, 5235. For a recent review on Cu-catalyzed ketone aldol processes, see: (c) Shibasaki, M.; Kanai, M. *Chem. Rev.* **2008**, *108*, 2853. For Ag-catalyzed aldol adition to α-keto esters, see: (d) Akullian, L. C.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2006**, *128*, 6532.