ORGANIC LETTERS

2007
Vol. 9, No. 16
3187−3190

Cu-Catalyzed Asymmetric Conjugate Additions of Dialkyl- and Diarylzinc Reagents to Acyclic β-Silyl-α,β-unsaturated Ketones. Synthesis of Allylsilanes in High Diastereo- and Enantiomeric Purity

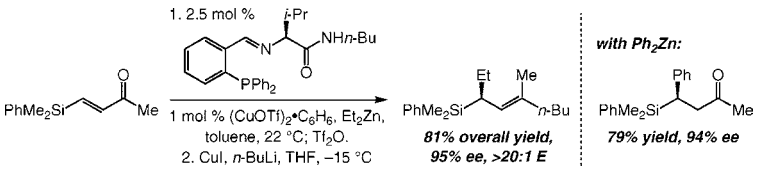
Monica A. Kacprzynski, Stephanie A. Kazane, Tricia L. May, and Amir H. Hoveyda*

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

amir.hoveyda@bc.edu

Received June 5, 2007

ABSTRACT



A readily available and simple (MW = 444.5 g/mol) valine-based chiral phosphine is used to promote highly efficient catalytic asymmetric conjugate additions of dialkyl- and diarylzinc reagents to acyclic β-silyl-α,β-unsaturated ketones. The catalytic asymmetric protocol allows access to versatile allylsilanes that bear a trisubstituted olefin in high diastereo- and enantiomeric purity.

β-Silylcarbonyls are versatile molecules that have significant potential in stereoselective synthesis.[1] The sterically demanding silyl group and the electron-donating (hyperconjugative) attributes of the C−Si bond can induce stereodifferentiation in reactions of neighboring prostereogenic sites (e.g., alkenes or enolates); the C−Si may be converted to a hydroxyl group (oxidation) or an alkane unit (protiodesilylation). The aforementioned attributes of organosilanes have been exploited in the design and development of myriad protocols in stereoselective synthesis.[2] Herein, we report a Cu-catalyzed method for asymmetric conjugate additions (ACA)[3] of dialkyl- and diarylzinc reagents to β-silyl-substituted α,β-unsaturated ketones; these catalytic transformations afford β-silylketones efficiently (59−95% isolated yield) and in high enantiomeric purity (87−96% ee). This study includes, to the best of our knowledge, the first examples of efficient catalytic ACA of di*aryl*zinc reagents to acyclic enones. The chiral ligand is an easily accessible small-molecule phosphine that contains the inexpensive (both antipodes) amino acid valine.

A number of catalytic enantioselective strategies have been reported that deliver β-silylcarbonyls. Among such methods are the Pd-catalyzed 1,4-silylation of α,β-unsaturated ketones

(1) Fleming, I. *Science of Synthesis*; Thieme: Stuttgart, Germany, 2002; Vol. 4; pp 927−946.

(2) (a) Fleming, I.; Barbaro, A.; Walter, D. *Chem. Rev.* **1997**, *97*, 2063−2192. For related Si-based stereoselective strategies developed in these laboratories, see: (b) Hale, M. R.; Hoveyda, A. H. *J. Org. Chem.* **1992**, *57*, 1643−1645. (c) Hale, M. R.; Hoveyda, A. H. *J. Org. Chem.* **1994**, *59*, 4370−4364. (d) Young, D. G. J.; Gomez-Bengoa, E.; Hoveyda, A. H. *J. Org. Chem.* **1999**, *64*, 692−693.

(3) For recent reviews on catalytic asymmetric conjugate addition (ACA) reactions, see: (a) Krause, N.; Hoffmann-Röder, A. *Synthesis* **2001**, 171−196. (b) Alexakis, A.; Benhaim, C. *Eur. J. Org. Chem.* **2002**, 3221−3236. (c) Feringa, B. L.; Naasz, R.; Imbos, R.; Arnold, L. A. in *Modern Organocopper Chemistry*; Krause, N., Ed.; Wiley-VCH: Weinheim, Germany, 2002; pp 224−258.

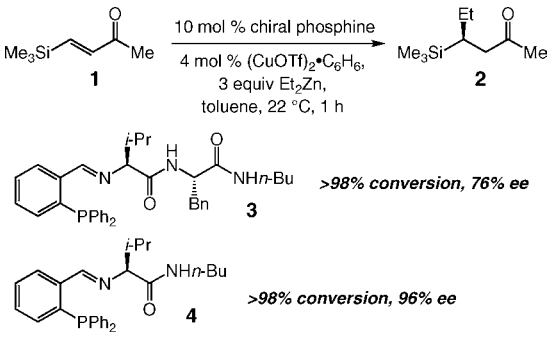
10.1021/ol071331k CCC: $37.00
Published on Web 06/30/2007

with $PhCl_2Si-SiMe_3$,[4] Rh-catalyzed ACA of vinyl- and arylboronic acids to β-silylketones and esters[5] as well as the related processes involving silylboronic acids and cyclic enones.[6] Other protocols of note consist of Al-catalyzed ACA of stabilized carbanions to unsaturated β-silyl imides[7] and Cu-catalyzed hydride additions to trisubstituted olefins of β-silylesters (polymethylhydrosiloxane as hydride source).[8]

We judged that an effective method for Cu-catalyzed ACA of readily available dialkyl and diarylzinc reagents to β-silylketones would be of value. Such a protocol delivers the same class of products as the Pd-catalyzed disilylation and Rh-catalyzed ACA but would benefit from several advantages. The Pd-catalyzed approach requires a less atom-economical disilane that deposits a $PhCl_2Si$ at the β carbon, requiring treatment with MeLi (conversion to a $PhMe_2Si$ group) to access the desired β-silylketone. Moreover, the Rh-catalyzed ACA[5] has not been extended to reactions of *alkyl*boronic acids.

To initiate our investigations, we prepared β-silylenone **1**[9] (Scheme 1) and examined the ability of a select number

Scheme 1. Initial Examination of Chiral Amino Acid-Based Phosphines

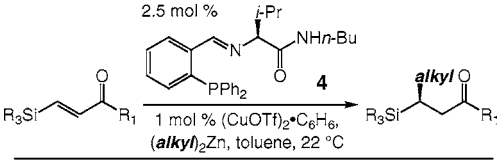


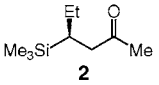
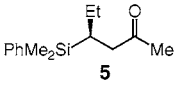
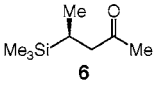
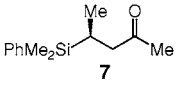
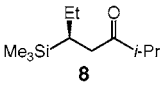
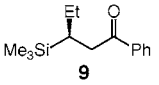
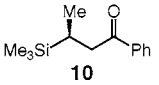
of amino acid-based chiral phosphines, previously developed in these laboratories,[10] to catalyze the corresponding ACA with Et_2Zn. As illustrated in Scheme 1, chiral ligands **3**[10a,h] and **4**[10c,h] (10 mol % used in preliminary screening) promote reaction to >98% conversion to afford β-silylketone **2** at ambient temperature in the presence of 4 mol % $(CuOTf)_2 \cdot C_6H_6$. The simpler chiral phosphine **4**, however, delivers **2** in markedly higher enantioselectivity (96% vs 76% ee). It should be noted that enantioselectivities do not change significantly at lower temperatures. Preliminary examination of chiral N-heterocyclic carbenes,[11] also developed in these laboratories for Cu-catalyzed ACA, indicates that these chiral complexes are less effective for this class of reactions (formation of **2** in <80% ee).

As illustrated in entry 1 of Table 1, with 2.5 mol % of chiral phosphine **4**, 1.0 mol % of $(CuOTf)_2 \cdot C_6H_6$ and 3 equiv of Et_2Zn (22 °C), β-silylketone **2** is obtained in 77% yield and 96% ee. Cu-catalyzed ACA of Et_2Zn with the substrate bearing a dimethylphenylsilyl unit proceeds efficiently to afford **5** in 95% yield and 96% ee (entry 2). Similar efficiency and enantiopurity levels are observed with the less reactive Me_2Zn (entries 3−4, Table 1).

Enantioselective synthesis of *iso*-propylketone **8** (entry 5) and phenyl- substituted ketones **9** and **10**, generated in 75−

Table 1. Cu-Catalyzed ACA of Dialkylzinc Reagents to Acyclic β-Silyl-α,β-Unsaturated Enones[a]



entry	$(alkyl)_2Zn$	product	yield (%)[b]	ee (%)[c]
1	Et_2Zn	 **2**	77	96
2	Et_2Zn	 **5**	95	96
3	Me_2Zn	 **6**	59[d]	95
4	Me_2Zn	 **7**	96	96
5	Et_2Zn	 **8**	75	95
6	Et_2Zn	 **9**	91	89
7	Me_2Zn	 **10**	77	93

[a] All reactions carried out under N_2 atm with 3 equiv $(alkyl)_2Zn$. Reactions times: 1 h with Et_2Zn (3 h for entry 5) and 6 h with Me_2Zn. [b] Isolated yields after purification; >98% conversion in all cases. [c] Determined by chiral GLC or HPLC analysis; see the Supporting Information for details. [d] Lower isolated yield is due to product volatility.

(4) (a) Hayashi, T.; Matsumoto, Y.; Ito, Y. *J. Am. Chem. Soc.* **1998**, *110*, 5579−5581. (b) Matsumoto, Y.; Hayashi, T. *Tetrahedron* **1994**, *50*, 335−346.

(5) Shintani, Y.; Okamoto, K.; Hayashi, T. *Org. Lett.* **2005**, *7*, 4757−4759.

(6) Walter, C.; Auer, G.; Oestreich, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 5675−5677.

(7) Balskus, E. P.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2006**, *128*, 6810−6812.

(8) Lipshutz, B. H.; Tanaka, N.; Taft, B. R.; Lee, C.-T. *Org. Lett.* **2006**, *8*, 1963−1966.

(9) See the Supporting Information for experimental details.

(10) (a) Degrado, S. J.; Mizutani, H.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2001**, *123*, 755−756. (b) Mizutani, H.; Degrado, S. J.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2002**, *124*, 779−781. (c) Degrado, S. J.; Mizutani, H.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2002**, *124*, 13362−13363. (d) Luchaco-Cullis, C. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2002**, *124*, 8192−8193. (e) Hird, A. W.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 1276−1279. (f) Mampreian, D. M.; Hoveyda, A. H. *Org. Lett.* **2004**, *6*, 2829−2832. (g) Wu, J.; Mampreian, D. M.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2005**, *127*, 4584−4585. (h) Brown, M. K.; Degrado, S. J.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2005**, *44*, 5306−5310. (i) Hird, A. W.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2005**, *127*, 14988−14989.

(11) (a) Lee, K.-s.; Brown, M. K.; Hird, A. W.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2006**, *128*, 7182−7184. (b) Brown, M. K.; May, T. L.; Baxter, C. A.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2007**, *46*, 1097−1100.

91% isolated yields and 89−95% ee, indicate that the Cu-catalyzed ACA can be performed with substrates that bear a sterically hindered carbonyl substituent. Two additional points merit mention: (1) All reactions were carried out with commercial grade dialkylzinc reagents. (2) All efforts to establish conditions for efficient Cu-catalyzed ACA of longer chain (e.g., $(n\text{-Bu})_2Zn$, $(i\text{-Pr})_2Zn$) or functionalized (e.g., $[AcO(CH_2)_4]_2Zn$) dialkylzinc reagents proved unsuccessful; <5% conversion was observed in such cases.[12]

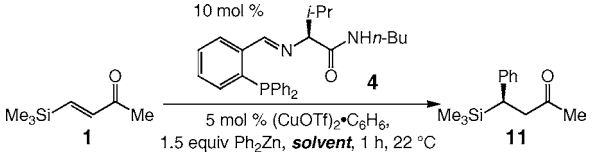
Next, we considered the possibility of using diarylzinc reagents. We judged this critical to our investigations, not only because of the aforementioned limitation vis-à-vis dialkylzinc reagents but also since examples of catalytic ACA involving arylmetals are scarce.[13] To the best of our knowledge, there are no reports of diarylzinc reagents used in catalytic ACA of acyclic α,β-unsaturated carbonyls.[14]

As illustrated in entry 1 of Table 2, under the conditions shown in Scheme 1, β-silyl-α,β-unsaturated ketone **1** undergoes ACA to afford β-phenyl ketone **11** but in only 17% ee. Control experiments indicated that low selectivity is likely due to competitive uncatalyzed addition: treatment of Ph_2Zn with enone **1** in toluene results in >98% conversion to *rac*-**11** in 1 h (22 °C). To minimize direct addition, we investigated Cu-catalyzed ACA in coordinating solvents; we surmised that, under such conditions, carbonyl activation by the Lewis acidic Zn salts that give rise to uncatalyzed conjugate addition would be avoided. With THF as the solvent, catalytic ACA proceeds (>98% conversion, 1 h) with significant improvement in enantioselectivity: **11** is obtained in 83% ee. Further screening (see Table 2) led to identification of DME as the optimal medium (entry 5, >98% conversion, 88% ee).

The Cu-catalyzed ACA of commercially available Ph_2Zn (1.5 equiv) to β-silylenone **1**, shown in entry 1 of Table 3, proceeds to >98% conversion within 6 h when performed in DME at 0 °C in the presence of 2.5 mol % **4** and 1 mol % Cu salt; β-silylketone **11** is isolated in 81% yield and 92% ee. As depicted in entry 2, under identical conditions, **12** is obtained in 79% yield and 94% ee. Catalytic transformation with $(p\text{-MeOC}_6H_4)_2Zn$ is more sluggish (>98% conv in 16 h, entry 3), delivering **13** in 82% isolated yield and 87% ee. As noted in entry 4 of Table 3, when $(p\text{-CF}_3C_6H_4)_2Zn$ is used, ACA is significantly less efficient: 10 mol % **4** and 5 mol % $(CuOTf)_2{\cdot}C_6H_6$ is required for >98% conversion in 48 h; β-silylketone **14** is obtained in 66% yield and 87% ee.

In addition to the widely appreciated oxidations that yield β-hydroxyketones,[15] enantiomerically enriched β-silylenones can be utilized to access a number of useful organic

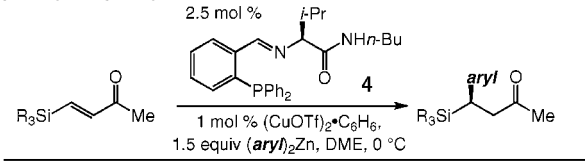
Table 2. Screening of Solvents in Cu-Catalyzed ACA of Ph_2Zn to Enone **1**[a]

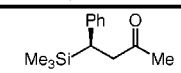
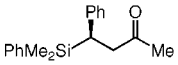
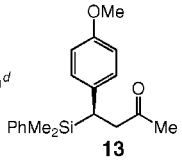
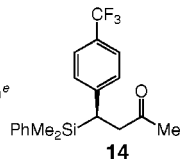


entry	solvent	conversion (%)[b]	ee (%)[c]
1	toluene	>98	17
2	THF	>98	83
3	1,4-dioxane	>98	59
4	Et_2O	>98	68
5	**DME**	**>98**	**88**

[a] All reactions carried out under N_2 atm. [b] Determined by analysis of 400 MHz ^1H NMR spectra. [c] Determined by chiral HPLC analysis; see the Supporting Information for details.

Table 3. Cu-Catalyzed ACA with Diarylzinc Reagents and Acyclic β-Silyl-α,β-unsaturated Enones[a]



entry	$(aryl)_2Zn$	product	time (h)	yield (%)[b]	ee (%)[c]
1	Ph_2Zn	 **11**	6	81	92
2	Ph_2Zn	 **12**	6	79	94
3	$(p\text{-OMeC}_6H_4)_2Zn$[d]	 **13**	16	82	87
4	$(p\text{-CF}_3C_6H_4)_2Zn$[e]	 **14**	48	66	87

[a] All reactions carried out under N_2 atm. [b] Isolated yields after purification; >98% conversion in all cases. [c] Determined by chiral GLC or HPLC analysis; see the Supporting Information for details. [d] Reaction run with 2.0 equiv Ar_2Zn. [e] Reaction run in the presence of 10 mol % catalyst.

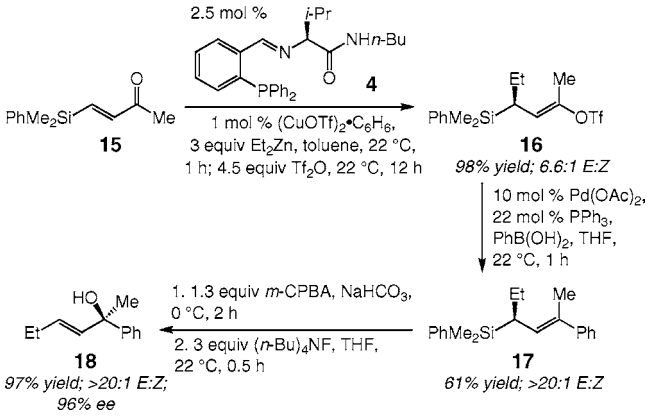
(12) Attempts to promote reactions of longer chain alkylzinc reagents with the more active chiral bidentate N-heterocyclic carbenes (cf. ref 11) results in >98% conversion and only a complex mixture of products. Studies to address this shortcoming are in progress.

(13) One example of Cu-catalyzed ACA of PhMgBr to an α,β-unsaturated methyl ketone has been reported. See: (a) López, F.; Harutyunyan, A.; Minnaard, A. J.; Feringa, B. L. *J. Am. Chem. Soc.* **2004**, *126*, 12784−12785. For an example involving a cyclic enone, see: (b) Martin, D.; Kehrli, S.; d'Augustin, M.; Clavier, H.; Mauduit, M.; Alexakis, A. *J. Am. Chem. Soc.* **2006**, *128*, 8416−8417.

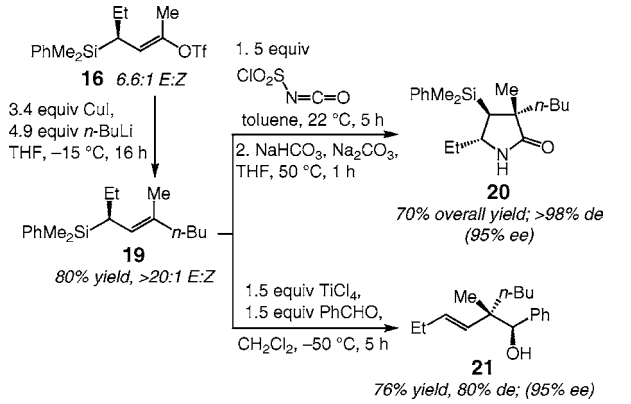
(14) For Cu-catalyzed ACA of diarylzinc reagents to cyclic enones, see: (a) Reference 11a. (b) Schinneri, M.; Seitz, M.; Kaiser, A.; Reiser, O. *Org. Lett.* **2001**, *3*, 4259−4262. (c) Pena, D.; Lopez, F.; Harutyunyan, S. R.; Minnaard, A. J.; Feringa, B. L. *Chem. Commun.* **2004**, 1836−1837. (d) Shi, M.; Wang, C.-J.; Zhang, W. *Chem.−Eur. J.* **2004**, *10*, 5507−5516. For asymmetric allylic alkylations processes, see: (e) Kacprzynski, M. A.; May, T. L.; Kazane, S. A.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2007**, *46*, 4554−4558.

(15) For example, subjection of β-silylketone **6** (entry 3, Table 1) to $HBF_4{\cdot}Et_2O$, followed by KF, $KHCO_3$, and H_2O_2 affords the corresponding β-hydroxyketone in 76% overall yield (95% ee).

Scheme 2. Synthesis of Enantiomerically Enriched Trisubstituted Allylsilanes and Tertiary Alcohols from Catalytic ACA Products



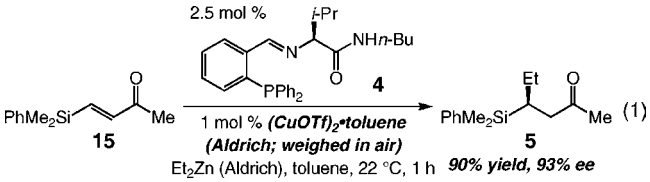
Scheme 3. Stereoselective Functionalizations of Enantiomerically Enriched and Diastereomerically Pure Allylsilane **19**



molecules. As illustrated in Scheme 2, when the product from catalytic ACA of Et_2Zn and β-silylenone **15** is subjected to 4.5 equiv of Tf_2O (at 22 °C, 12 h), enol triflate **16** is obtained in 98% isolated yield as a 6.6:1 mixture of *E*:*Z* isomers. Treatment of the mixture with Pd-catalyzed cross coupling reactions,[16] as illustrated in Scheme 2, leads to the formation of allylsilane **17** in 61% yield as a single olefin isomer (>20:1 *E*:*Z*).[17] Thus, only the *E* enol triflate undergoes catalytic cross coupling (81% yield based *E* isomer).[18] Enantiomerically enriched allylsilane **17** can be used in stereoselective processes.[19] The two-step sequence in Scheme 2 is representative: diastereoselective epoxidation and fluoride-mediated desilylation/epoxide cleavage generates tertiary allylic alcohol **18**[20] in 97% overall yield and 96% ee.

Enantiomerically enriched enol triflate **16** (96% ee) can be stereoselectively alkylated with a cuprate reagent;[21] synthesis of allylsilane **19** (Scheme 3), generated in 80% isolated yield in >20:1 *E*:*Z* selectivity,[22] is a case in point. Enantiomerically enriched allylsilane **19** participates in a highly diastereoselective cycloaddition with chlorosulfonyl isocyanate.[23] The two-step sequence gives rise to lactam **20**, bearing an all-carbon quaternary stereogenic center,[20] in 70% overall yield and >98% de (95% ee). Reaction of **19** with benzaldehyde furnishes secondary alcohol **21**, containing an allylic quaternary stereogenic center, in 76% yield and 80% de (95% ee). Thus, the ability to control the stereochemistry of the trisubstituted alkene of the enantiomerically enriched enol triflates (e.g., **16**) and higher reactivity of the major *E* isomer is translated to application of the catalytic ACA method to stereoselective syntheses of quaternary carbons (cf. **18**, **20**, and **21**).

We thus introduce an efficient method for Cu-catalyzed ACA of dialkyl- and diarylzinc reagents to β-silylenones. Reactions require a simple (MW = 444.5 g/mol) chiral phosphine, prepared from commercially available *o*-diphenylphosphine benzaldehyde (Aldrich) and an inexpensive amino acid. We have previously shown[10c] that chiral ligand **4** can be prepared by and used directly without purification. As the example in eq 1 indicates, commercially available $(CuOTf)_2$•toluene can be used in a practical manner (weighed out on a bench top) to promote catalytic ACA.



Development of new catalysts and methods that initiate C−C bond forming reactions of β-silyl enones with a wider range of alkylmetal reagents is in progress.

Acknowledgment. Financial support was provided by the NIH (Grant GM-47480). M.A.K. and S.A.K. were Novartis Graduate and Undergraduate Fellows, respectively.

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

OL071331K

(16) For a review on the utility of enol triflates in synthesis, see: Ritter, K. *Synthesis* **1993**, 735−762.

(17) Willis, M. C.; Claverie, C. K. *Tetrahedron Lett.* **2001**, *42*, 5105−5107.

(18) Unreacted enol triflate *Z* isomer was detected in the 400 MHz ^{1}H NMR of the unpurified mixture.

(19) For utility of allylsilanes in organic synthesis, see: (a) Masse, C. E.; Panek, J. S. *Chem. Rev.* **1995**, *95*, 1293−1316. (b) Fleming, I.; Barbero, A.; Walter, D. *Chem. Rev.* **1997**, *97*, 2063−2192. (c) Barbero, A.; Pulido, F. J. *Acc. Chem. Res.* **2004**, *37*, 817−825. For a recent catalytic asymmetric method for synthesis of allylsilanes, see ref 14e. For a diastereoselective method used for synthesis of enantiomerically enriched allylsilanes, see: (d) S. Schmidtmann, E.; Oestrich, M. *Chem. Commun.* **2006**, 3643−3645.

(20) *Quaternary Stereocenters: Challenges and Solutions for Organic Synthesis*; Christophers, J., Baro, A., Eds.; Wiley-VCH: Weinheim, Germany, 2006.

(21) McMurry, J. E.; Scott, W. J. *Tetrahedron Lett.* **1980**, *21*, 4313−4316.

(22) On the basis of previous studies (McMurry, J. E.; Scott, W. J. *Tetrahedron Lett.* **1980**, *21*, 4313−4316) it is likely that, at least to some extent, the cuprate derived from the minor *Z* enol triflate isomerizes to the more reactive *E* vinylcopper reagent, which undergoes cross coupling.

(23) Woerpel, K. A.; Romero, A. *Org. Lett.* **2006**, *8*, 2127−2130 and references cited therein.