Organosilanes in Copper-Mediated Conjugate Reductions and Reductive Aldol Reactions

Pauline Chiu*

Department of Chemistry, The University of Hong Kong, Pokfulam Road, Hong Kong, P. R. China
Fax +852(2857)1586; E-mail: pchiu@hku.hk

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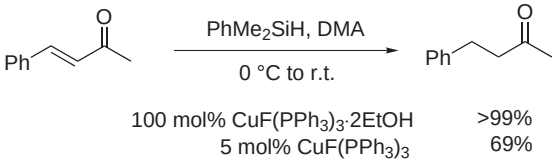
Abstract: Organosilanes have been used to synthesize and regenerate copper hydrides, and have been employed as stoichiometric reductants in the copper-catalyzed reductions of a variety of activated olefins. Reductive aldol condensations and cyclizations using organosilanes and transition metal catalysts, including copper hydrides, have also been achieved.

Key words: organosilanes, copper conjugate reductions, aldol reactions

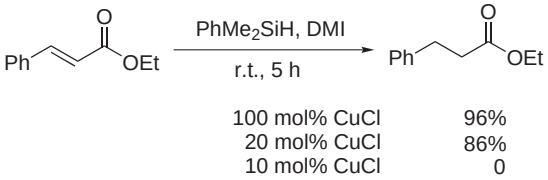
Organosilane Reductions Mediated by Copper

While conjugate reductions of α,β-unsaturated carbonyl compounds by organosilanes mediated by complexes of rhodium, palladium, molybdenum, and platinum are well established,[1,2] the use of copper complexes for the analogous transformation is a comparatively recent development. With the chemoselective conjugate reduction of activated olefins afforded by copper hydrides such as Stryker's reagent ($[Ph_3PCuH]_6$) having been demonstrated,[3] Mori et al. first reported the generation of a copper hydride species for conjugate reduction from organosilanes and $CuF(PPh_3)_3$ in 1997. Using $PhMe_2SiH$ or Et_3SiH with stoichiometric amounts of the copper fluoride complex, the generation of a copper hydride reagent was evidenced by the conjugate reduction of a number of α,β-unsaturated cyclic and acyclic ketones in good yields (Equation 1).[4] Other organosilanes, Ph_2SiH_2 and Cl_2PhSiH, were examined and were found to be inferior or unreactive. The reduction also proceeded with a catalytic amount of $CuF(PPh_3)_3$, but with a clearly diminished yield.



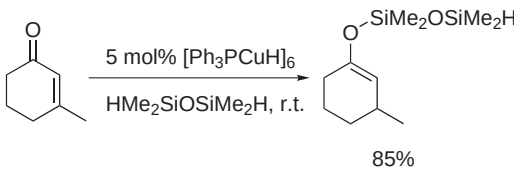
Equation 1

The stoichiometric generation of another copper hydride species from CuCl and $PhMe_2SiH$ in DMI was reported almost contemporaneously by Ito et al.[5] Notably, Ito's copper hydride was not stabilized by phosphine ligands. Transfer of hydride from silane to copper occurred smoothly for $PhMe_2SiH$, Ph_2SiH_2 and Et_3SiH. Both enones and enoates underwent conjugate reduction with high yields. When the copper salt was used catalytically, this reducing system was much less effective, such that a 10 mol percent of CuCl failed to induce any conjugate reduction (Equation 2).



Equation 2

More recently, Lipshutz[6] and Buchwald[7a,b] reported that organosilanes such as phenylsilane, tetramethyldisiloxane, and especially the safe, convenient, and inexpensive polymer polymethylhydrosiloxane (PMHS) are effective stoichiometric reductants in the generation of copper hydrides. Lipshutz showed that a reductive silylation catalytic in Stryker's reagent $[Ph_3PCuH]_6$ could be achieved in very good yields using these organosilanes (Equation 3). In contrast to previous copper catalysts, the conjugate reduction proceeded very efficiently with catalyst loadings at 1–5 mol% of $[Ph_3PCuH]_6$. Using this copper source, however, Et_3SiH proved to be a poor stoichiometric reductant, unable to regenerate the copper hydride at a useful rate.



Equation 3

Since organosilanes had been shown to be able to regenerate Stryker's reagent, it followed that silanes can also be used for the synthesis of this stable and well-characterized copper hydride. Previously, the laboratory syntheses of Stryker's reagent employed hydrogen as the reductant. Thus from CuCl, and sodium or potassium *t*-butoxide, $[Ph_3PCuH]_6$ was synthesized in the presence of hydrogen

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and an excess of triphenylphosphine.[8] This heterogeneous reaction was typically an overnight reaction, yielding about 50–65% of Stryker's reagent. When organosilanes were used instead of hydrogen as the reductant, thus rendering the reduction a homogenous reaction, the generation of copper hydride was nearly instantaneous as indicated by the appearance of the characteristic deep red color of the reagent (Equation 4).[9] By following the progress by ^{1}H NMR, it was found that the rate of copper hydride formation induced by organosilanes was extremely fast, such that 90% of the maximum yield of Stryker's reagent was achieved in 30 minutes. Although a variety of reactive silanes could induce this reduction, including PMHS and tetramethyldisiloxane, phenyldimethylsilane was found to generate $[Ph_3CuH]_6$ in the purest form upon isolation. The reaction time for the synthesis of Stryker's reagent was thus reduced to within an hour, which greatly facilitated the laboratory preparation of this useful reagent.

$$PPh_3 + CuCl + KO\textit{t}\text{-}Bu \xrightarrow[PhH,\ 1\text{–}2\ h]{\text{organosilanes}} [Ph_3PCuH]_6$$

Equation 4

Preparation of $[Ph_3PCuH]_6$ on a 10 mmol Scale[9]

Copper (I) chloride (0.993 g, 10.03 mmol), potassium *t*-butoxide (1.124 g, 10.02 mmol) and PPh_3 (5.246 g, 20.00 mmol) were weighed inside a dry-box. The flask was charged with benzene (50 mL, distilled and degassed) and the contents were stirred for 30 min under Ar to produce a slightly cloudy, yellow solution. $PhMe_2SiH$ (3 mL, 19.57 mmol) was added and the color of the reaction mixture changed instantaneously from yellow to red, to very dark red. After stirring for 2 h, the mixture was transferred via cannula to a large Schlenk filter containing 1 cm celite. The reaction flask and the celite pad were rinsed with anhyd benzene (4 × 10 mL). The red filtrate was concentrated in vacuo to a volume of ca 20 mL. Anhyd, degassed MeCN (40 mL) was slowly layered onto the top of the benzene solution via cannula to induce crystallization of the product. After standing overnight, the red crystals thus obtained were isolated by filtration under Ar, washed with anhyd MeCN (3 × 10 mL) and dried under vacuum to give 2.5–2.9 g (76–88%) of bright to dark red crystals of $[Ph_3PCuH]_6$.

^{1}H NMR (400 MHz, C_6D_6): δ = 7.67 (t, *J* = 8.1 Hz, 36 H), 6.95 (t, *J* = 7.3 Hz, 18 H), 6.74 (t, *J* = 7.5 Hz, 36 H), 3.51 (s, 6 H).

This same procedure could be conveniently adapted for the synthesis of $[Ph_3PCuD]_6$, which has been utilized in labeling experiments, by substituting the deuterated silane Ph_2SiD_2 as the reducing agent.

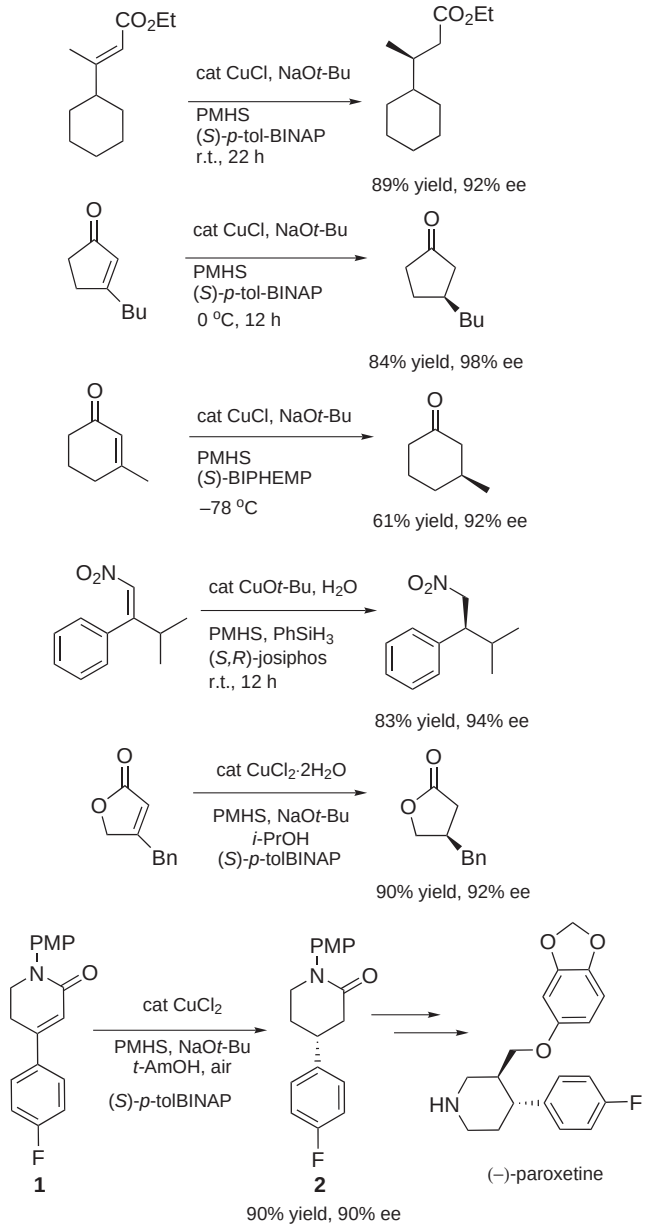
Enantioselective Copper-Catalyzed Conjugate Reductions Using Organosilanes

Employing the reagents for the in situ generation of Stryker's reagent, and replacing the ligand by chiral bisphosphines such as (*S*)-*p*-tol-BINAP, (*S*)-BIPHEMP, and (*S*,*R*)-JOSIPHOS,[10] the enantioselective 1,4-reductions of prochiral α,β-unsaturated esters,[7a] ketones,[7b,c] lactones,[7d] lactams,[7d] and nitroalkenes[7e] have been realized, culminating in a family of powerful catalytic asymmetric transformations for the synthesis of chiral intermediates (Scheme 1). These enantioselective reductions have the hallmarks of reactions that will find wide applicability in synthesis. These reactions are relatively tolerant of moisture, and the addition of hydroxylic solvents has been found to actually increase the rate of the reduction as well as improve the product yield. The reactions occur efficiently using inexpensive PMHS as the stoichiometric hydride source. Very low catalyst loadings of 0.1–1 mol% copper are viable. Most of these reactions attained high enantioselectivities in the range of 90–98% ee. This methodology has already enabled the synthesis of chiral cyclopentanones bearing β-stereocenters with enantiomeric excesses surpassing the complementary asymmetric conjugate nucleophilic additions to cyclopentenone.[7b] The conjugate reduction of δ-lactams have in fact been found to be accelerated when the reaction is run open to air.[7d] The application of this catalytic asymmetric reduction to hydropyridone **1** to confer the key stereochemistry in lactam **2** was seminal in accomplishing a concise synthesis of the anti-depressant (–)-paroxetine.

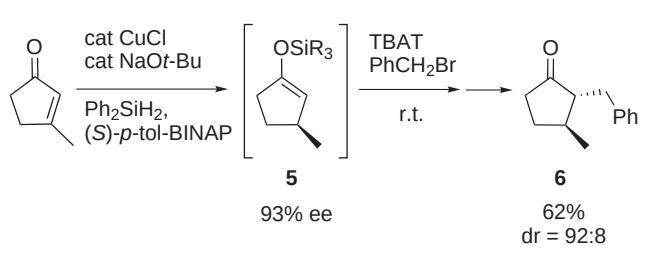
Tandem Copper-Catalyzed Conjugate Reduction-Alkylation Reactions Using Organosilanes

The conjugate reduction of unsaturated ketones by organosilanes constitutes an overall reductive silylation, yielding silyl enol ethers as products. Regiospecific generation of silyl enol ethers of unsymmetrical ketones is possible due to the position of the olefin determining the site of enolate formation. This transformation is an alternative strategy to the synthesis of silyl enol ethers using stoichiometric base. Having these versatile intermediates in hand, rather than simply subjecting them to hydrolysis, the silyl enol ethers could be induced to react in a subsequent operation to achieve multiple transformations in one pot. Lipshutz has subjected the silyl enol ether obtained upon reductive silylation to Mukaiyama aldol reaction and benzylation to give diastereomeric mixtures of alkylated products **3** and **4** (Scheme 2).[6b]

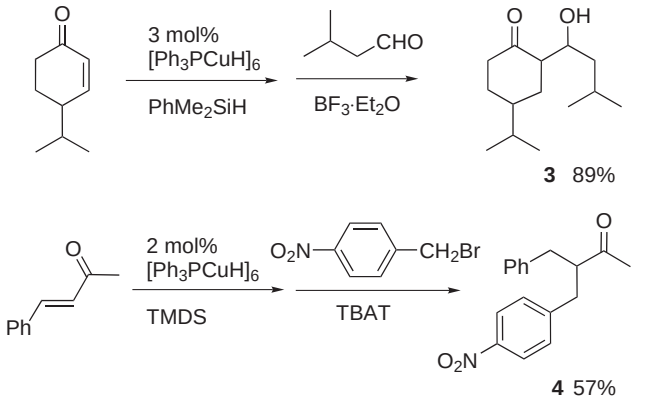
Exploiting the stereoselectivity in vicinally substituted cyclopentanones, Buchwald has engaged chiral silyl enol ethers such as **5** in a benzylation reaction to afford, after equilibration, 2,3-dialkylated cyclopentanone **6** with excellent diastereo- and enantioselectivity (Equation 5).[11]



Scheme 1



Equation 5

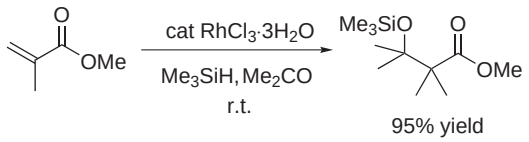


Scheme 2

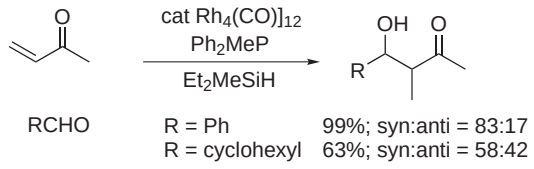
Catalytic Reductive Aldol Reactions Using Organosilanes as Stoichiometric Reductants

The direct reductive aldol coupling of α,β-unsaturated ketones in the presence of the electrophilic partners poses significant challenges for current synthetic methodology. In terms of chemoselectivity, the electrophiles, either aldehydes or ketones, must be inert toward the reductive conditions. The metathesis reaction of the enolate and the organosilane must be slow relative to the aldol carbon-carbon bond forming reaction; otherwise, the silyl enol ether is trapped, or in the presence of Lewis acids, a classical Mukaiyama reaction ensues. The relative rates of these reactions will have a significant bearing on the diastereoselectivity and the potential enantioselectivity of such a process.

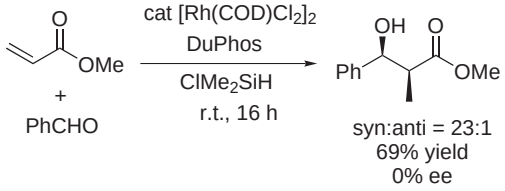
Based on precedented 1,4-hydrosilylations catalyzed by rhodium and palladium, the earliest transition metal catalyzed reductive aldol reactions also involve complexes of these metals. The direct coupling of enones and ketones in reductive aldol reactions using organosilanes and rhodium was first reported by Revis and Hilty (Equation 6).[12] Successive work by the groups of Matsuda and Morken progressively improved the diastereoselectivity of this rhodium-catalyzed process (Equations 7 and 8).[13,14]



Equation 6

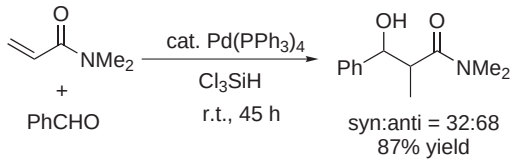


Equation 7



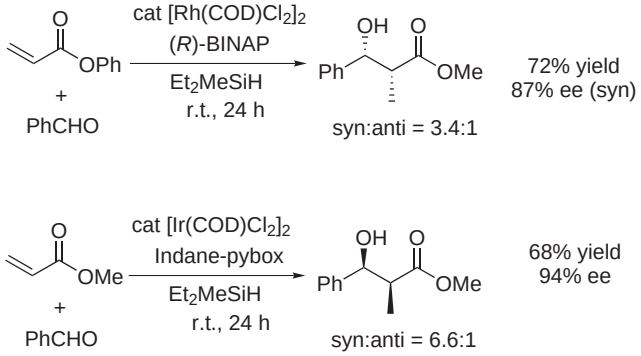
Equation 8

Kiyooka et al. employed palladium as the catalyst in the direct reductive coupling of acrylamides with aryl aldehydes (Equation 9). With acrylate esters, the yield was significantly diminished, and this reaction did not proceed with aliphatic aldehydes.[15]



Equation 9

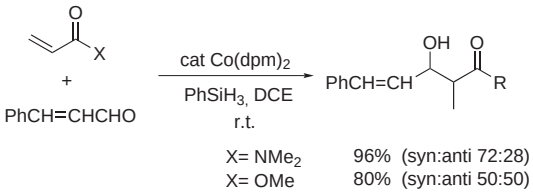
The successful development of diastereoseletive reductive aldol reactions led to advances in enantioselective reductive couplings using chiral ligands[10] (Scheme 3).[16]



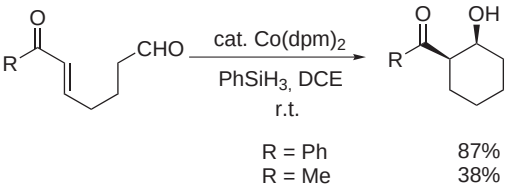
Scheme 3

The phenylsilane reduction catalyzed by $Co(dpm)_2$ (dpm = dipivaloylmethane) successfully induced intermolecular reductive aldol reactions, albeit with low diastereoselectivity (Equation 10).[17] However, the same reducing system, in the context of an intramolecular reaction, an overall cycloreduction, has been found to be highly diastereoselective (Equation 11).[18] The *syn*:*anti* selectivity is greater than 99:1, and the cyclization is general for five-, six- and seven-membered ring formation, although the latter occurred with diminished yield (35%). Aliphatic enones underwent this reaction with lower yields. Significantly, this methodology allowed the chemoselective formation of the ketone enolate in the presence of the more acidic aldehyde for reaction.

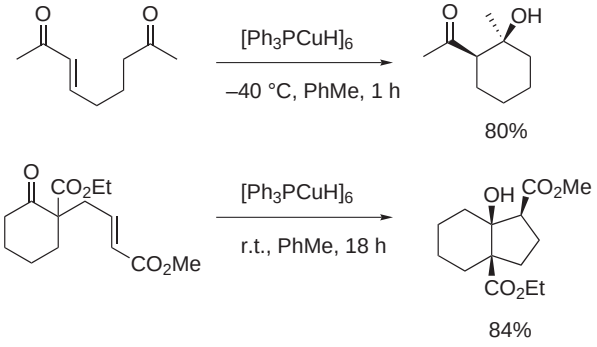
We have previously demonstrated that stoichiometric Stryker's reagent induced a highly *syn*-selective intramo-



Equation 10



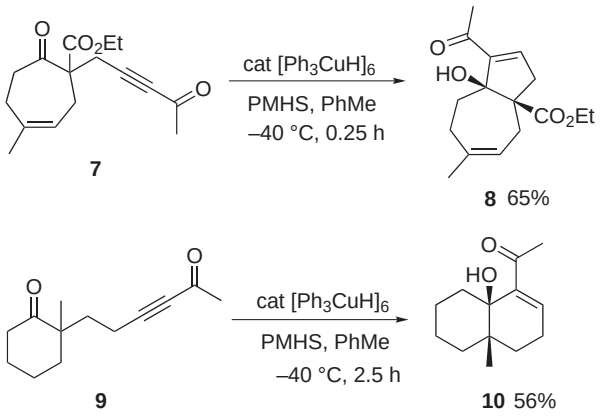
Equation 11



Scheme 4

lecular reductive aldol cyclization (Scheme 4).[19] Although aldehydes cannot be used in this reaction due to their competitive reduction by Stryker's reagent,[3] this methodology allowed the generation and reaction of ester enolates in the presence of the more acidic ketones. In our continuing studies of this reducing system, we have found that a catalytic amount of Stryker's reagent with PMHS induced reductive aldol cyclizations of alkynediones such as **7** and **9** at low temperatures with good diastereoselectivities (Scheme 5).[20] Both five and six-membered ring cyclizations occurred readily to generate highly functionalized β-hydroxyalkenones such as **8** and **10** as products, which interestingly resemble products from intramolecular Baylis–Hillman reactions. While over-reduction is clearly a side reaction, β-hydroxyalkenones have been obtained as the major products in all cases examined, the alkynones being significantly more reactive toward reduction than the hindered alkenone products.

The achievement of these diastereoselective, catalytic processes using organosilanes as reductants should pave the way for the future developments of additional novel organosilane reducing systems and enantioselective transformations for organic synthesis.



Scheme 5

Reactions were carried out under argon atmosphere employing standard inert atmosphere techniques, using glassware oven-dried at 120 °C for at least 4 h. Prior to use in reactions, solvents were dried according to standard procedures and were degassed by bubbling in argon for 30 min. Commercially available compounds were used without further purification. IR spectra were recorded on a Bio-Rad FT-IR spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on Bruker DRX 300 or AV 400 spectrometers, and are reported downfield from TMS at δ = 0.00 ppm for ^{1}H NMR spectra and relative to $CDCl_3$ at δ = 77.03 ppm for ^{13}C NMR spectra. Low and high resolution mass spectra were recorded on a Finnigan MAT90 mass spectrometer.

(3a*R,8a*S**)-1-Acetyl-8a-hydroxy-6-methyl-4,7,8,8a-tetrahydro-3H-azulene-3a-carboxylic acid ethyl ester (8): Catalytic Reductive Aldol Cyclization; General Procedure**

$[Ph_3PCuH]_6$ (4.0 mg, 0.012 mmol) was transferred into an oven-dried flask in a dry-box. The flask was capped with a septum and removed from the dry-box. Anhydrous and degassed toluene (1.0 mL) was added and the solution was cooled to –40 °C. To the solution was added PMHS (0.014 mL, 0.233 mmol), followed by substrate **7** (32.2 mg, 0.117 mmol) in toluene (1.0 mL). After 15 min, the reaction was quenched by adding sat. aq NH_4Cl (1 mL), and stirring for 2 h further, open to air. The resulting mixture was filtered through a silica gel plug, which was washed with EtOAc (10 mL). The organic layer was separated, and the aqueous layer was back-extracted with EtOAc (2 × 5 mL). The combined organics were dried over $MgSO_4$ and concentrated. Flash chromatography (0–20% EtOAc in hexane) of the residue gave **8** (21.1 mg, 65%); R_f 0.30 (30% EtOAc in hexane).

IR (CH_2Cl_2): 3692, 3055, 2998, 1722, 1656, 1551, 1376, 1197, 1179, 1097, 1030cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.98 (t, *J* = 2.7 Hz, 1 H), 5.17 (m, 1 H), 4.13 (qd, *J* = 7.1, 2.0 Hz, 2 H), 3.72 (br s, 1 H), 3.07 (d, *J* = 13.5 Hz, 1 H), 3.01 (dd, *J* = 19.4, 3.1 Hz, 1 H), 2.67 (dd, *J* = 19.4, 2.4 Hz, 1 H), 2.54 (m, 1 H), 2.32 (s, 3 H), 2.15 (m, 3 H), 1.75 (m, 1 H), 1.58 (s, 3 H), 1.22 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 197.7, 174.4, 147.4, 143.7, 139.0, 119.3, 88.3, 61.5, 60.7, 39.4, 34.4, 31.4, 29.9, 27.2, 25.3, 14.1.

LRMS (20 eV): *m*/*z* = 278 (30) [M$^+$], 260 (30), 214 (15), 187 (100), 171 (17), 143 (24).

HRMS (EI): *m*/*z* [M$^+$] calcd for $C_{16}H_{22}O_4$: 278.1518; found: 278.1516.

Acknowledgment

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References

(1) (a) Ojima, I. *Catalytic Asymmetric Synthesis*; VCH: New York, **1993**, Chap 6. (b) Larock, R. C. *Comprehensive Organic Transformations*, 2nd ed; Wiley-VCH: New York, **1999**, 13–26.
(2) For a review on the complementary hydrosilylation of carbonyl compounds by organosilanes, see: Carpentier, J. F.; Bette, V. *Curr. Org. Chem.* **2002**, *6*, 913.
(3) Mahoney, W. S.; Brestensky, D. M.; Stryker, J. M. *J. Am. Chem. Soc.* **1988**, *110*, 291.
(4) Mori, A.; Fujita, A.; Nishihara, Y.; Hiyama, T. *Chem. Commun.* **1997**, 2159.
(5) Ito, H.; Ishizuka, T.; Arimoto, K.; Miura, K.; Hosomi, A. *Tetrahedron Lett.* **1997**, *38*, 8887.
(6) (a) Lipshutz, B. H.; Keith, J.; Papa, P.; Vivian, R. *Tetrahedron Lett.* **1998**, *39*, 4627. (b) Lipshutz, B. H.; Chrisman, W.; Noson, K.; Papa, P.; Sclafani, J. A.; Vivian, R. W.; Keith, J. M. *Tetrahedron* **2000**, *56*, 2779.
(7) (a) Appella, D. H.; Moritani, Y.; Shintani, R.; Ferreira, E. M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9473. (b) Moritani, Y.; Appella, D. H.; Jurkauskas, V.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 6797. (c) Lipshutz, B. H.; Servesko, J. M. *Angew. Chem. Int. Ed.* **2003**, *42*, 4789. (d) Hughes, G.; Kimura, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 11253. (e) Czekelius, C.; Carreira, E. M. *Angew. Chem. Int. Ed.* **2003**, *42*, 4793.
(8) (a) Mahoney, W. S.; Stryker, J. M. *J. Am. Chem. Soc.* **1989**, *111*, 8818. (b) Goeden, G. V.; Caulton, K. G. *J. Am. Chem. Soc.* **1981**, *103*, 7354. (c) Brestensky, D. M.; Huseland, D. E.; McGettigan, C.; Stryker, J. M. *Tetrahedron Lett.* **1988**, *29*, 3749.
(9) Chiu, P.; Li, Z.; Fung, K. C. M. *Tetrahedron Lett.* **2003**, *44*, 455.
(10) *p*-Tol-BINAP: 2,2′-bis(di-*p*-tolylphosphino)-1,1′-binaphthyl; BIPHEMP: 2,2′-bis(diphenylphosphino)-6,6′-dimethyl-1,1′-biphenyl; JOSIPHOS: 1-[2-diphenyl]-phosphanyl]ferrocenyl]ethyldicyclohexyl-phosphane; BINAP: 2,2′-bis(dipenylphosphino)-1,1′-binaphthyl; DuPhos: 1,2-bis(2,5)-dimethylphosphalano)benzene, pybox: 2,6-bis(oxazolinyl)pyridine.
(11) Yun, J.; Buchwald, S. L. *Org. Lett.* **2001**, *3*, 1129.
(12) Revis, A.; Hilty, T. K. *Tetrahedron Lett.* **1987**, *28*, 4809.
(13) Matsuda, I.; Takahasi, K.; Sato, S. *Tetrahedron Lett.* **1990**, *31*, 5331.
(14) Taylor, S. J.; Morken, J. P. *J. Am. Chem. Soc.* **1999**, *121*, 12202.
(15) Kiyooka, S.; Shimizu, A.; Torii, S. *Tetrahedron Lett.* **1998**, *39*, 5237.
(16) (a) Taylor, S. J.; Duffey, M. O.; Morken, J. P. *J. Am. Chem. Soc.* **2000**, *122*, 4528. (b) Zhao, C. X.; Bass, J.; Morken, J. P. *Org. Lett.* **2001**, *3*, 2839. (c) Zhao, C. X.; Duffey, M. O.; Taylor, S. J.; Morken, J. P. *Org. Lett.* **2001**, *3*, 1829.
(17) Isayama, S.; Mukaiyama, T. *Chem. Lett.* **1989**, 2005.

(18) (a) Baik, T. G.; Luis, A. L.; Wang, L. C.; Krische, M. J. *J. Am. Chem. Soc.* **2001**, *123*, 5112. (b) Wang, L. C.; Jang, H. Y.; Baik, T. G.; Luis, A. L.; Lynch, V.; Krische, M. J. *J. Am. Chem. Soc.* **2002**, *124*, 9448. (c) Huddleston, R. R.; Krische, M. J. *Synlett* **2003**, 12.

(19) (a) Chiu, P.; Chen, B.; Cheng, K. F. *Tetrahedron Lett.* **1998**, *39*, 9299. (b) Chiu, P.; Szeto, C. P.; Geng, Z.; Cheng, K. F. *Tetrahedron Lett.* **2001**, *42*, 4091. (c) Chiu, P.; Szeto, C. P.; Geng, Z.; Cheng, K. F. *Org. Lett.* **2001**, *3*, 1901.

(20) Chiu, P.; Leung, S. K. *Chem. Commun.* **2004**, in press.