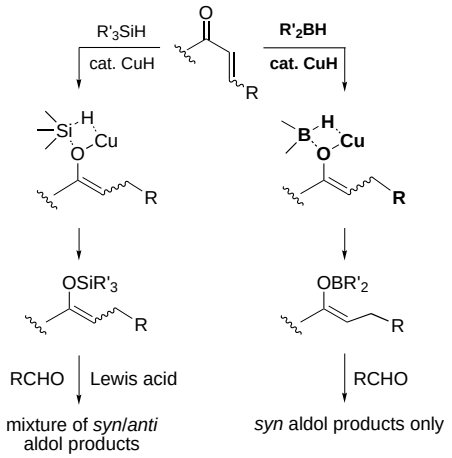
Copper-Catalyzed Reductive Alkylations of Enones: A Novel Transmetalation Protocol**

Bruce H. Lipshutz* and Patrick Papa

Previously,[1] we outlined an effective one-pot procedure for the 1,4-reduction/Mukaiyama aldol sequence which utilizes catalytic [(Ph$_3$P)CuH] (Stryker's reagent)[2] in the presence of a silane (e.g., polymethylhydrosiloxane).[3] Although the silylenol ethers derived in situ readily participated in Lewis acid mediated additions to various aldehydes at −78 °C, mixtures of diastereomers were invariably produced, in line with expectations based on literature precedents (Scheme 1).[4] The sequence leading to these intermediates



Scheme 1. Silanes versus boranes in transmetalations with copper enolates derived in situ.

presumably involves a transmetalation[5] between the initially formed copper enolate and silane.[6] It was reasoned that replacement of R$_3$SiH with a dialkyl borane (R$_2$BH) might likewise encourage the analogous ligand exchange, perhaps driven by the strength of the boron–oxygen bond, to afford the corresponding boron enolate. Although such a process is unknown, the thermodynamically favored *Z* orientation found in boron enolates derived from acyclic ketones might prevail, whereas cyclic enones would necessarily lead to the corresponding (*E*)-enolates. Should this unprecedented transmetalation occur cleanly and with good selectivity, in both situations subsequent aldol reactions in typical fashion would ultimately provide products in a regio- and stereocontrolled manner. Previous studies on 1,4-reduction[7] of enones (e.g., with Li/NH$_3$) indicate that limited control over enolate geometry and/or the derived aldol product[8] is to be expected from such an approach.[9] Alternatively, 1,4-hydroboration of acyclic conjugated enones provides a direct entry to (*Z*)-boron enolates,[10] although in practice most substitution patterns of the enone double bond are not amenable, especially in the important case of unsubstituted vinyl ketones (see below).[11] Herein we disclose new organometallic technology for site-specific boron enolate formation by using a transmetalation sequence.

The dialkyl borane selected to participate in the key transmetalation event, Et$_2$BH, could be easily generated by equilibration between commercial samples of Et$_3$B (in hexanes) and BH$_3$·THF.[12] An excess of the former is required to consume the majority of BH$_3$ present in solution, since borane appears to react over time adversely with Stryker's reagent. Once Et$_2$BH is formed, addition of an acyclic enone in toluene at 0 °C followed by a catalytic amount of [(Ph$_3$P)CuH] leads to clean conjugate reduction with concomitant (*Z*)-boron enolate formation (or the corresponding (*E*)-enolate with cyclic enones).[13] Evacuation of roughly half the solvent volume at 0 °C under vacuum and replacement with CH$_2$Cl$_2$ allows, upon cooling to −78 °C, the subsequent aldol reaction to smoothly take place, as expected.[14] Thus, introduction of an aldehyde to the intermediate (*Z*)-enolate leads to *syn*-aldol products[15a,b] in excellent overall yields. Cyclic enones, on the other hand, cleanly afford *anti*-aldol products.[15a,c] Table 1 provides a representative sampling of the enones examined to date. A number of examples are noteworthy in that they reflect cases which react nonproductively under hydroboration conditions.[10,11] For example, cyclohexenones **1** and **2**, which cannot hydroborate in a 1,4-sense,[11] readily participate to arrive at the corresponding (*E*)-boron enolates to ultimately yield the anticipated *anti* products (entries 1, 2). Vinyl ketone **3**, which is also a troublesome substrate toward 1,4-hydroboration,[11] is an ideal starting material toward a Cu^{I}-based conjugate addition in that it is sterically unencumbered at the β-site. Thus, an excellent sequence ensues and ultimately affords the *all-syn* diastereomer in high yield (entry 3). It should also be noted that unsubstituted vinyl ketones, albeit simple, are among the most synthetically valuable in that they provide an alternative inroad to the "methyl, hydroxy, methyl" array characteristic of the macrolide antibiotics.[16] On the basis of high-field NMR analyses, the limits of stereoselectivity are at least > 97:3, since neither of the diastereomeric products in each case could be detected. The coupling constant observed for the proton at C-3 in each aldol product (see Table 1) is in agreement with the expected literature values for simple aldol products unperturbed by proximate or remote stereocenters.[15]

Dihydrocarvone (**4**) is representative of a site-specific generation of a boron enolate which might be otherwise difficult to form regiospecifically from the corresponding saturated (cyclohexanone) analogue (Scheme 2).[17] Application of the three-step/one-pot sequence affords mainly *anti* product **5**[18] that bears an α-quaternary center of defined stereochemistry[19] resulting from favored axial alkylation.[20]

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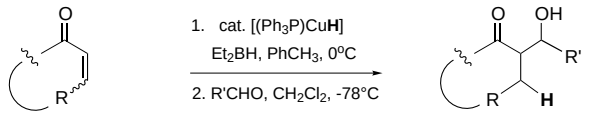
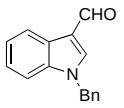
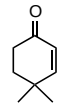
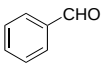
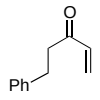
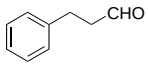
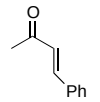
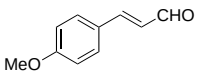
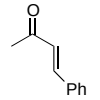
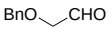
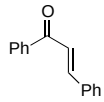
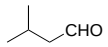
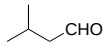
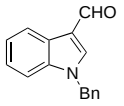
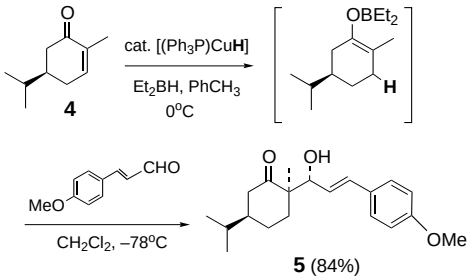
Table 1. Representative conjugate reduction/transmetalation/aldol reactions.



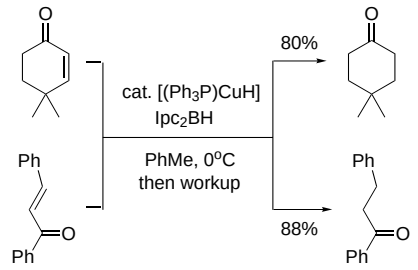
Entry	Enone	Aldehyde	Yield [%][c]
1	 **1**		85
2	 **2**		80
3	 **3**		86
4			90
5			83
6			95
7			85
8			86

[a] J_{syn}: entry 3, 4.6 Hz; entry 4, 5.4 Hz; entry 5, 6.3 Hz; entry 6, 4.0 Hz; entry 7, 3.7 Hz; entry 8, 7.0 Hz. [b] J_{anti}: entry 1, 9.2 Hz; entry 2, 8.6 Hz. [c] Yield of isolated product, that is, chromatographically purified material. All aldol products were fully characterized by IR, NMR, MS, and HRMS data.



Scheme 2. 1,4-Reduction/transmetalation/aldol reaction of dihydrocarvone.

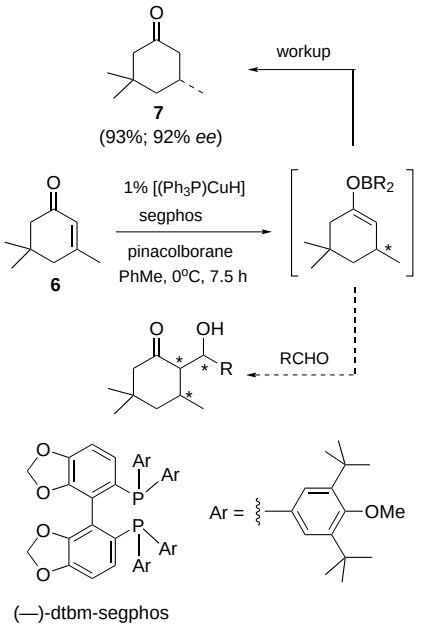
In anticipation of controlling the absolute stereochemical outcome from a related 1,4-reduction/transmetalation/aldol sequence, nonracemic Ipc_2BH[21] was investigated as the stoichiometric source of hydride in place of Et_2BH (Scheme 3). From both an acyclic and cyclic example, the products of 1,4-reduction/proton quenching were obtained in good yields which strongly implicates a nonracemic boron enolate intermediate in each reaction.



Scheme 3. CuH-catalyzed 1,4-reductions/transmetalations with nonracemic Ipc_2BH (Ipc = isopinocampheyl).

Lastly, whereas conjugate reductions of highly hindered β,β-disubstituted enones with [(Ph$_3$P)CuH] remain problematic,[2a, 22] we have found that with proper choices of ligand, such reductions can be realized. Thus, by adding 0.5 mol %[23] of the di-*tert*-butylmethoxy (DTBM) analogue of Takasago's new segphos series of biaryl ligands[24] to Stryker's reagent in the presence of a borane (e.g., pinacolborane), ligand-accelerated catalysis leading to 1,4-reduction of isophorone **6** is complete at 0 °C (Scheme 4).[25] The keto product (*R*)-**7**[22] was isolated in high yield and with an *ee* of 92 %. This finding suggests that in the presence of the appropriate dialkyl borane,[26] a subsequent aldol reaction could allow control of three contiguous asymmetric centers.

In summary, a 1,4-reduction/transmetalation protocol has been uncovered which is catalytic in transition metal and provides a novel entry to essentially isomerically pure boron enolates of unsymmetrical ketones. The methodology is of



Scheme 4. Asymmetric 1,4-reduction of isophorone by using CuH chelated by (−)-dtbm-segphos (0.5 mol %).

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broad scope; it relies on an efficient ligand exchange process between a dialkyl borane and an in situ generated copper enolate. Thus, a unique route to boron enolates which avoids base-induced enolization/electrophilic trapping with a sensitive and expensive dialkyl boron halide or triflate is now in hand. Ongoing studies involving nonracemic boron (and titanium) enolate formation/aldol couplings, and new 1,4- (and 1,2-) additions of nonracemic ligand-modified CuH, will be reported in due course.

Experimental Section

1,4-Reduction/transmetalation/aldol reactions; representative procedure: An oven-dried round-bottomed flask equipped with a stir bar and two septa was cooled under an argon atmosphere. The reaction flask was cooled to 0 °C, charged with Et_3B (1.0 M in hexane, 8.0 equiv), followed by slow addition of BH_3 (1.0 M in THF, 0.5 equiv) and the mixture allowed to stir for 30 min. The reaction mixture was warmed to RT, stirred for an additional 15 min, then cooled back down to 0 °C. The enone (1.0 equiv) was slowly added through a syringe or, in the case of a solid, dissolved in toluene (1.0 mL) and transferred through a cannula. [$(Ph_3P)CuH$] (0.05 equiv) was dissolved in toluene (3.0 mL) and then transferred to the reaction mixture through a cannula and allowed to stir at 0 °C until the enone had been consumed to form the intermediate boron enolate (usual times for reaction completion range from 10 min to 2 h). After the conjugate reduction was complete approximately half of the solvent was removed under vacuum and CH_2Cl_2 (6.0 mL) was added through a syringe. The reaction was cooled to −78 °C followed by addition of the aldehyde (1.5 equiv, neat or as a solution in CH_2Cl_2). Upon consumption of the boron enolate and formation of the aldol product (ca. 15 min) the reaction was warmed to 0 °C and slowly quenched with pH 7 phosphate buffer (2.0 mL), followed by 30 % H_2O_2 (2.0 mL) and allowed to stir for 2 h. The quenched reaction mixture was then subjected to an aqueous extractive workup (2×10 mL H_2O, 4×10 mL Et_2O). The combined organic layers were then washed with brine (1×20 mL), dried with anhydrous Na_2SO_4, and the solvent removed in vacuo. The residue was purified by column chromatography on silica gel with triethylamine (1–2 %) as a doping agent which prevents elimination and retro-aldol side reactions. Under these conditions, no retro-aldol side reaction was observed.

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[1] B. H. Lipshutz, W. Chrisman, K. Noson, P. W. Papa, J. A. Sclafani, R. W. Vivian, J. Keith, *Tetrahedron* **2000**, *56*, 2779.

[2] a) W. S. Mahoney, D. M. Brestensky, J. M. Stryker, *J. Am. Chem. Soc.* **1988**, *110*, 291; b) W. S. Mahoney, J. M. Stryker, *J. Am. Chem. Soc.* **1989**, *111*, 8818; D. M. Brestensky, J. M. Stryker, *Tetrahedron Lett.* **1989**, *30*, 5677.

[3] N. J. Lawrence, M. D. D. Drew, S. M. Bushell *J. Chem. Soc. Perkin Trans.* **1999**, *1*, 3381.

[4] T. Mukaiyama, K. Banno, K. Narasaka, *J. Am. Chem. Soc.* **1974**, *96*, 7503.

[5] P. Wipf, *Synthesis* **1993**, 537.

[6] a) K. Miura, H. Sato, K. Tamaki, H. Ito, A. Hosomi, *Tetrahedron Lett.* **1997**, *38*, 8887; b) H. Ito, T. Ishizuka, K. Arimoto, K. Miura, A. Hosomi, *Tetrahedron Lett.* **1997**, *38*, 888.

[7] H. O. House, *Modern Synthetic Reactions*, 2nd ed., Benjamin/Cummings, Menlo Park, CA, **1972**, 145.

[8] a) P. Arya, H. Qin, *Tetrahedron* **2000**, *56*, 917; C. J. Cowden, I. Paterson, *Org. React.* **1997**, *51*, 1; b) I. Paterson, C. J. Cowden, D. Wallace, *Modern Carbonyl Chemistry*, Wiley-VCH, Weinheim, **2000**, 249.

[9] a) S. Masamune, T. Sato, B. M. Kim, T. A. Wollmann, *J. Am. Chem. Soc.* **1986**, *108*, 8279; b) S. Masamune, J. W. Ellingboe, W. Choy, *J. Am. Chem. Soc.* **1982**, *104*, 5526.

[10] D. A. Evans, G. C. Fu, *J. Org. Chem.* **1990**, *55*, 5678.

[11] G. P. Boldrini, M. Bortolotti, F. Mancini, E. Tagliavini, C. Trombini, A. Umani-Ronchi, *J. Org. Chem.* **1991**, *56*, 5820.

[12] P. Knochel, P. Bhanu, S. Appana, H. Eick, *J. Organomet. Chem.* **1998**, *562*, 133.

[13] Irradiation at the frequency of the resonance of the vinyl proton of the boron enolate derived from 4-hexen-3-one showed two interactions which can only exist for the *Z* geometry.

[14] a) D. A. Evans, E. Vogel, J. V. Nelson, *J. Am. Chem. Soc.* **1979**, *101*, 6120; b) D. A. Evans, V. J. Nelson, E. Vogel, *J. Am. Chem. Soc.* **1981**, *103*, 3099; c) D. A. Evans, T. R. Taber, *Tetrahedron Lett.* **1980**, *21*, 4675; d) S. Masamune, W. Choy, F. Kerdesky, *J. Am. Chem. Soc.* **1981**, *103*, 1566.

[15] a) Aldol products uncomplicated by additional stereocenters in either coupling partner can be readily assigned on the basis of coupling constants between protons at the C-2 and C-3 sites; see D. A. Evans, J. Bartoli, T. L. Shih, *J. Am. Chem. Soc.* **1981**, *103*, 2127; L. M. Jackman, S. Sternhell, *Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry*, 2nd ed., Pergamon Press, Oxford, UK, **1969**; b) typically, *syn* products show $J = 3$–6 Hz; c) isomers bearing an *anti* relationship tend to show $J = 5$–9 Hz.

[16] *Recent Progress in the Chemical Synthesis of Antibiotics* (Eds.: G. Lukacs, M. Ohno), Springer, Berlin, **1990**; R. D. Norcross, I. Paterson, *Chem. Rev.* **1995**, *95*, 2041.

[17] I. Paterson, M. Goodman, M. A. Lister, R. C. Schumann, C. K. McClure, R. D. Norcross, *Tetrahedron* **1990**, *46*, 4663.

[18] Determined by NMR analysis of crude material to be a 9:1 mixture of *anti* products.

[19] Confirmed via X-ray analysis.

[20] J. D. Morrison, *Asymmetric Synthesis*, Academic Press, London, UK, **1984**.

[21] H. C. Brown, N. N. Joshi, *J. Org. Chem.* **1988**, *53*, 4059.

[22] Y. Moritani, D. H. Appella, V. Jurkauskas, S. L. Buchwald, *J. Am. Chem. Soc.* **2000**, *122*, 6797.

[23] This corresponds to a substrate:ligand (S/L) ratio of 2000:1; see ref. [22a].

[24] T. Saito, T. Yokozawa, T. Ishizaki, T. Moroi, T. Miura, N. Sayo, H. Kumobayashi, *Adv. Synth. Catal.* **2001**, *343*, 264.

[25] By contrast, use of biphemp[22a] in place of dtbm-segphos under otherwise identical conditions on isophorone afforded ca. 10–20 % (by TLC analysis) of the product of 1,4-reduction.

[26] a) R. W. Hoffmann, K. Ditrich, *Tetrahedron Lett.* **1984**, *25*, 1781; b) C. Gennari, L. Colombo, C. Scolastico, R. Todeschini, *Tetrahedron* **1984**, *40*, 4051.

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