Asymmetric 1,4-Reduction of Enones

CuH-Catalyzed Asymmetric Conjugate Reductions of Acyclic Enones**

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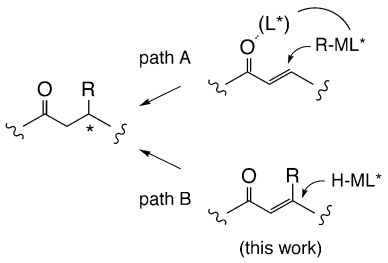
Strategies for controlling absolute stereochemistry at a site β to an electrophilic center, in particular a ketone, usually rely on organometallic-based Michael additions (Scheme 1, path A).[1] Processes that are catalytic in both the transition metal (M) and the associated nonracemic ligand (L*) are



Scheme 1. Control of stereochemistry β to a ketone.

most desirable, and outstanding progress continues to be made with several different Michael donors[1,2] and acceptors.[1,3] Acyclic enones have proven to be particularly challenging substrates in this regard, although breakthrough methodologies based on copper-catalyzed additions of organozinc reagents have recently been disclosed.[4] Far greater success, on the other hand, has been realized with unsaturated esters.[5] The alternative approach, wherein a nonracemic source of hydride is delivered to a preformed, unsymmetrical β,β-disubstituted enone (path B) would offer an attractive means of accomplishing the same net transformation, thereby doubling the number of potential routes to a selected target. To the best of our knowledge, there is no general procedure for effecting this type of reduction on acyclic unsaturated enones in both high yields and enantioselectivities.[6] In this report we disclose results from our preliminary studies which

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suggest that a solution to this long-standing problem may be in hand. We considered nonracemic biaryl ligands such as Roche's BIPHEP[7] and Takasago's SEGPHOS[8] (see Figure 1) for screening in the presence of CuH[9a,b] generated

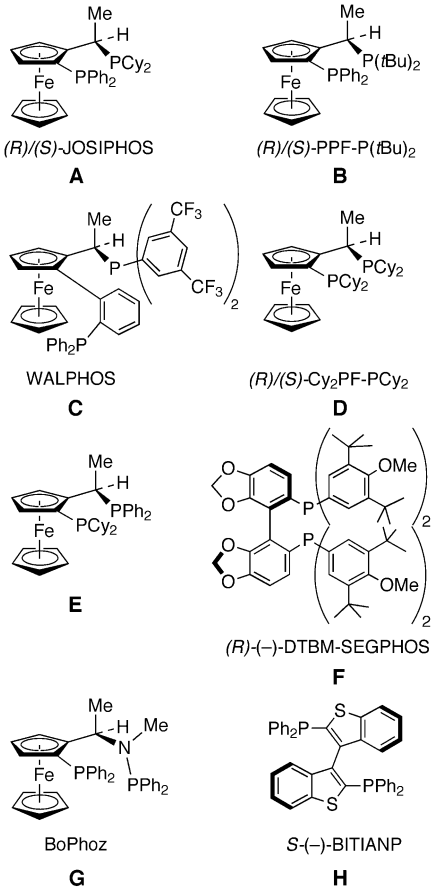
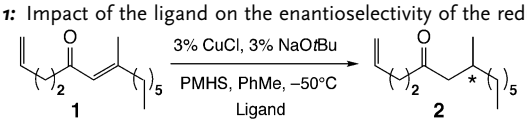


Figure 1. Ligands screened with cat. CuH/PMHS.

in situ,[9c] along with stoichiometric polymethylhydrosiloxane (PMHS)[10] based on their exceptional influence on aryl ketones undergoing asymmetric hydrosilylation.[11] Also taken into account were the significant improvements in asymmetric 1,4-reductions of hindered β,β-disubstituted cyclic enones found when the latter reagent combination (i.e., cat. CuH·DTBM-SEGPHOS/PMHS) was used.[9c,12] As indicated in Table 1, however, neither the SEGPHOS-based system (ligand **F** in Figure 1, entry 1 in Table 1) nor any of several other ligands of recent vintage[13] afforded useful levels of enantioselectivity in reactions with acyclic enone **1**. On the other hand, use of JOSIPHOS[14] (ligand **A**, Figure 1), as supplied within the Solvias "kit", led to an excellent reaction both in terms of educt consumption (100%) and enantioselectivity (91% *ee* at −50°C, 92% *ee* at −78°C) giving keto product **2** after hydrolytic workup of the presumed polymeric silyl enol ether. Remarkably, the mono-(di-*tert*-butyl)phosphane analogue of JOSIPHOS (ligand *ent*-**B**) was even more effective at the same temperature (93% *ee*), while at −78°C ketone **2** was isolated in good yield (94%) and with an even higher enantioselectivity (97% *ee*).

Table 1: Impact of the ligand on the enantioselectivity of the reduction.

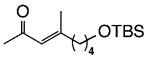
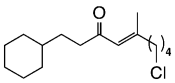
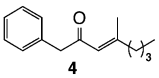
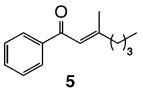
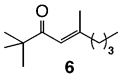
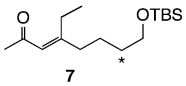


Ligand[a]	Conv. [%]	*ee* [%][b]	Yield [%][c]	*R*/*S*[d]
F	100	35	–	*S*
G	100	0	–	–
H	95	23	–	*R*
Phanephos[e]	20	23	–	*S*
A	100	91[f]	95	*S*
ent-**B**	100	97[g]	94	*R*

[a] Cf. Figure 1. [b] By capillary GC. [c] Yield of isolated product. [d] Stereochemistry of product ketone. [e] Cf. ref [16]. [f] 92% *ee* at −78°C. [g] Reaction conducted at −78°C.

Table 2 gives a survey of reactions run in toluene at −78°C with additional substrates and mainly PPF-P(*t*Bu)$_2$ (**B** or *ent*-**B**, Figure 1) as the ligand of choice on copper. With **3** as a representative enone, the 1,4-adduct was obtained in 98% *ee* (entry 2). Conducting the same experiment at 0°C decreased the level of induction, although an *ee* of 90% was still observed (entry 4). Curiously, while the switch from cyclohexyl groups on phosphorus in JOSIPHOS (**A**) to *tert*-butyl residues in **B** enhances the level of stereodifferentiation, replacing the phenyl residues on phosphorus for cyclohexyl groups (as in ligands **D** and **E**, entries 5 and 6) significantly lowers the enantioselectivity of the reaction. In the sequence

Table 2: Asymmetric 1,4-hydrosilylations of acyclic enones.[a]

Entry	Substrate (enone)[b]	Ligand	Yield [%][c]	*ee* [%][d]	*R*/*S*
1		**A**	94	94	*S*
2		**B**	96	98	*S*
3		*ent*-**B**	96	98	*R*
4	**3**	**B**	95	90[e]	*S*
5		**D**	95	55	–[f]
6		**E**	97	35	–[f]
7		*ent*-**B**	93	99	*R*
8		**A**	91	91	*S*
9	 **4**	**B**	88	90	*S*
10		**B**	96	87	*R*
11	**5**	**C**	91	91	*S*
12	 **6**	**C**	93	95[g]	*R*
13		*ent*-**B**	95	96	*R*
14	**7**	**C**	95	97	*R*

[a] Conditions: 2% CuCl, 2% NaO*t*Bu, 1% ligand, PMHS, 1.0 M in toluene, −78°C, 6–9 h. [b] TBS = *tert*-butyldimethylsilyl. [c] Yield of keto product isolated and purified by chromatography. [d] By capillary GC. [e] Reaction conducted at 0°C. [f] Not determined. [g] Reaction time 60 h.

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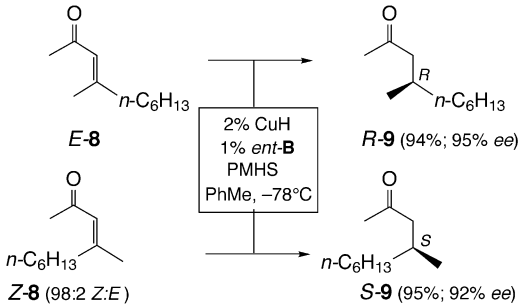
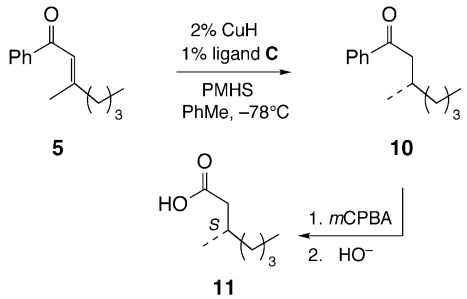
of substrates with alkyl, then benzylic (**4**, entry 9), and aryl (**5**, entry 10) substituents, the enantioselecitivities dropped from >95 to $\leq 90\%$ *ee*, suggesting an influential stereoelectronic effect or perhaps arene–arene or arene–metal coordination. Switching to WALPHOS (ligand **C**, Figure 1) in the case of the phenyl enone **5** (entry 11) raised the enantioselectivity of the reaction back to the $>90\%$ *ee* level. Further evidence that steric factors do not seem to play a major role in determining the enantioselectivity comes from conjugate reduction of *tert*-butyl enone **6** (entry 12) which, although slow, was both efficient and highly enantioselective. Indeed, in a direct comparison in reactions with the alkyl enone **7**, it was ligand **C** that appeared to be slightly more effective (entries 13 and 14). The high level of facial discrimination exemplified with educt **7**, where the reagent must recognize differences in olefin substitution three carbons removed from the β-site (cf. starred carbon in **7**) is especially noteworthy.

The tentative assignment of stereochemistry for all non-aromatic keto products is based on comparison of the optical rotation of product ketone **9** with that in the literature.[15] Thus, ligand *ent*-**B**, in the case of educt *E*-**8**, leads to product **9** with *R* stereochemistry (Scheme 2). Inverting the geometry of the enone as in *Z*-**8**, under otherwise identical reaction conditions, inverts the stereochemical outcome to give *S*-**9**, as expected. Employing ligand **B** in the reaction of enone *E*-**8**, likewise gives rise to enantiomeric keto product *S*-**9** (Scheme 3). Thus, on the basis of either ligand stereochemistry or geometry of the enone double bond, the newly formed stereocenter β to the product ketone is readily controlled. Interestingly, in reactions with aryl ketones the induction proceeds in the opposite sense, as indicated by the processing of product ketone **10** obtained from enone **5** (cf. Table 2, entries 10 and 11). Thus, treatment of **10** with *meta*-chloroperbenzoic acid (*m*CPBA) followed by aqueous base and an acidic workup led to the known[17] carboxylic acid **11** (Scheme 4).



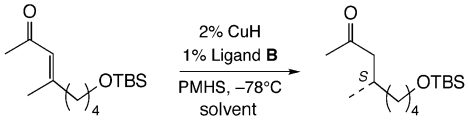
Scheme 2. Effect of substrate geometry on the stereochemistry of the conjugate reduction.

The impact of solvent on reaction rate and enantioselectivity was also determined with substrate enone **3** (Table 3), since these reductions (cf. Table 1 and Table 2) were routinely run in toluene (1.0 M). THF appears to cause a slight decrease in stereoinduction, while reactions run in CH_2Cl_2 are substantially less selective. The best solvent appears to be Et_2O, which led to a stereospecific conjugate reduction within our limits of detection. No significant effect on reaction rate was noted, as all the reactions required between four and six hours to reach completion. Substrate-to-ligand (S/L) ratios of 100:1 were typically used in the above reactions, mainly on the basis of convenience. However, the amount of ligand could be substantially reduced. As illustrated in Scheme 5, complete reduction of 1.64 grams of enone **3** could be achieved in high yield and with excellent optical purity even when only two milligrams of ligand **B** were used (i.e., S/L = 1650:1). The actual limits for the S/L ratio, however, have yet to be ascertained.



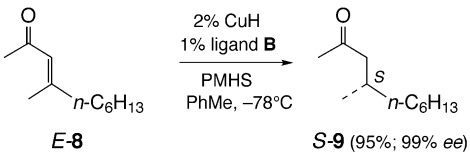
Scheme 4. Conversion of product **10** to the known carboxylic acid **11**.

Table 3: Impact of solvent on the enantioselecitivity of the reduction.



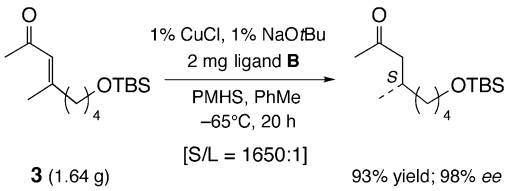
Solvent	*ee* [%][a]	Yield [%][b]
THF	91	94
PhMe	98	95
Et_2O	>99	96
CH_2CH_2	80	95

[a] By capillary GC. [b] Yield of isolated product.



Scheme 3. Effect of the ligand on the stereochemistry of the conjugate reduction.

In summary, a powerful new reaction has been developed in which, for the first time, asymmetric 1,4-reductions of



Scheme 5. Increasing the substrate/ligand ratio.

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prochiral enones provides access to compounds with highly stereodefined centers β to acyclic ketones. Reliance on catalytic quantities of a base metal in the form of CuH, along with readily available nonracemic ferrocenyl ligands and inexpensive PMHS as the stoichiometric source of hydride, all combine to offer an exceedingly mild and straighforward procedure.[18] New technologies utilizing this initial CuH-based 1,4-reduction/transmetalation protocol but which rely on boranes[19] (in place of silanes), thereby providing entries to subsequent aldol reactions, α-arylations, etc., will be reported in due course.

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[1] N. Krause, A. Hoffmann-Roder, *Synthesis* **2001**, 171.
[2] a) B. L. Feringa, R. Naasz, R. Imbos, L. A. Arnold in *Modern Organocopper Chemistry* (Ed.: N. Krause), Wiley-VCH, Weinheim, **2002**; b) K. Yoshida, M. Ogasawara, T. Hayashi, *J. Org. Chem.* **2003** *68*, 1901; c) Y. Iguchi, R. Itooka, N. Miyaura, *Synthesis* **2003**, 1040; d) K. Yoshida, M. Ogasawara, T. Hayashi, *J. Am. Chem. Soc.* **2002**, *124*, 10984; e) R. Amengual, R. Michelet, J.-P. Genet, *Synlett* **2002**, 1791; f) M. Pucheault, S. Darses, J.-P. Genet, *Eur. J. Org. Chem.* **2002**, 3552; g) M. Kuriyama, K. Nagai, K. Yamada, Y. Miwa, T. Taga, K. Tomioka, *J. Am. Chem. Soc.* **2002**, *124*, 8932; h) S. Sakuma, N. Miyaura, *J. Org. Chem.* **2001**, *66*, 8944; i) S. M. W. Bennett, S. M. Brown, A. Cunningham, M. R. Dennis, J. P. Muxworthy, M. A. Oakley, S. Woodward, *Tetrahedron* **2000**, *56*, 2847.
[3] M. Shibasaki, H. Sasai, T. Arai, *Angew. Chem.* **1997**, *109*, 1290; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1236.
[4] a) H. Mizutani, S. J. Degrado, A. H. Hoveyda, *J. Am. Chem. Soc.* **2002**, *124*, 779; b) S. J. Degrado, H. Mizutani, A. H. Hoveyda, *J. Am. Chem. Soc.* **2002**, *124*, 13362; c) J.-G. Boiteau, R. Imbos, A. J. Minnaard, B. L. Feringa, *Org. Lett.* **2003**, *5*, 681; d) I. H. Escher, A. Pfaltz, *Tetrahedron* **2000**, *56*, 2879; e) A. Alexakis, C. Benhaim, S. Rosset, M. Humam, *J. Am. Chem. Soc.* **2002**, *124*, 5262; f) A. Alexakis, C. L. Winn, F. Guillen, J. Pytkowicz, S. Roland, P. Mangeney, *Adv. Synth. Catal.*. **2003**, *345*, 345; g) A. Alexakis, C. Benhaim, *Eur. J. Org. Chem.* **2002**, 3221.
[5] D. H. Appella, Y. Moritani, R. Shintani, E. M. Ferreira, S. L. Buchwald, *J. Am. Chem. Soc.* **1999**, *121*, 9473.
[6] Due to the lack of any suitable means of effecting such asymmetric conjugate reductions, this strategy is usually not even considered an option for the control of stereochemistry at a site β to a ketone.[1] For early hydrogenation studies on enones using nonracemic ruthenium and cobalt complexes, see V. Massonneau, P. Le Maux, G. Simonneaux, *J. Organomet. Chem.* **1987**, *327*, 269; P. Le Maux, V. Massonneau, G. Simonneaux, *J. Organomet. Chem.* **1985**, *284*, 101.
[7] a) R. Schmid, E. A. Broger, M. Cereghetti, Y. Crameri, J. Foricher, M. Lalonde, R. K. Muller, M. Scalone, G. Schoettel, U. Zutter, *Pure. Appl. Chem.* **1996**, *68*, 131; b) R. Schmid, J. Foricher, M. Cereghetti, P. Schonholzer, *Helv. Chim. Acta* **1991**, *74*, 370.
[8] T. Saito, T. Yokozawa, T. Ishizaki, T. Moroi, N. Sayo, T. Miura, H. Kumobayashi, *Adv. Synth. Catal.* **2001**, *343*, 264.
[9] a) J.-X. Chen, J. F. Daeuble, D. M. Brestensky, J. M. Stryker, *Tetrahedron* **2000**, *56*, 2153; b) W. S. Mahoney, J. M. Stryker, *J. Am. Chem. Soc.* **1989**, *111*, 8818. c) For in situ generation of CuH, see ref. [5] and Y. Moritani, D. H. Appella, V. Jureakauseas, S. L. Buchwald, *J. Am. Chem. Soc.* **2000**, *122*, 6797.
[10] N. J. Lawrence, M. D. Drew, S. M. Bushell, *J. Chem. Soc. Perkin Trans. 1* **1999**, 3381. Although four equivalents of hydride were used in these experiments, we have since found that only two equivalents are actually needed.
[11] a) B. H. Lipshutz, K. Noson, W. Chrisman, A. Lower, *J. Am. Chem. Soc.* **2003**, *125*, 8779; b) B. H. Lipshutz, K. Noson, W. Chrisman, *J. Am. Chem. Soc.* **2001**, *123*, 12917.
[12] Y. Moritani, D. H. Appella, V. Jurkauskas, S. L. Buchwald, *J. Am. Chem. Soc.* **2000**, *122*, 6797. See also, B. H. Lipshutz, J. M. Servesko, P. Papa, T. Petersen, A. Lover, in preparation.
[13] a) *S*-(−)-BITIANP: T. Benincori, E. Brenna, F. Sannicolo, L. Trimarco, P. Antognazza, E. Cesarotti, F. Demartin, T. Pilati, *J. Org. Chem.* **1996**, *61*, 6244; b) *R,S*-(−)-BoPhoz: N. W. Boaz, S. D. Debenham, E. B. Mackenzie, S. E. Large, *Org. Lett.* **2002**, *4*, 2421; c) TaniaPhos: T. Ireland, K. Tappe, G. Grossheimann, P. Knochel, *Chem. Eur. J.* **2002**, *8*, 843 (only 2% conversion after 7 h).
[14] a) A. Togni, C. Breutel, A. Schnyder, F. Spindler, H. Landert, A. Tijani, *J. Am. Chem. Soc.* **1994**, *116*, 4062; b) H.-U. Blaser, W. Brieden, B. Pugin, F. Spindler, M. Studer, A. Togni, *Top. Catal.* **2002**, *19*, 3.
[15] Product *S*-**9** gave a negative rotation ($[\alpha]_{546}^{20} = -6.0$ ($c = 1.8$, $CHCl_3$), whereas *R*-**9** gave an equal and opposite (positive) rotation, as expected for these known compounds; cf. G. Bram, D. Caberet, N. Maigrot, J.-P. Mazaleyrat, Z. Welvart, *J. Chem. Res. Synop.* **1979**, 196; D. Caberet, N. Maigrot, Z. Welvart, *Tetrahedron Lett.* **1981**, *22*, 5279.
[16] P. J. Pye, K. Rossen, R. A. Reamer, N. N. Tsou, R. P. Volante, P. J. Reider, *J. Am. Chem. Soc.* **1997**, *119*, 6207.
[17] S. Norsikian, I. Marek, S. Klein, J. F. Poisson, J. F. Normant, *Chem. Eur. J.* **1999**, *5*, 2055.
[18] Represenative procedure (Table 3, entry 2): To a 5-mL round-bottom flask flame-dried and purged with argon was added $CuH{\cdot}PPh_3$ (2 mg, 0.006 mmol) and ligand *ent*-**B** (5.42 mg, 0.003 mmol). Toluene (0.3 mL) was added and the solution cooled to −78 °C. PMHS (78 μL, 1.21 mmol) was introduced dropwise by syringe and then the enone was added (neat; 82 mg, 0.304 mmol). The reaction mixture was stirred for 6 h at −78 °C until the reaction was complete by TLC (2% Et_2O:ligroin). It was then quenched at −78 °C with 3 M NaOH, warmed to room temperature, diluted with Et_2O/H_2O, and stirred for 2 h. The aqueous layer was extracted twice with Et_2O, and the combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated by rotary evaporation. The residue was purified by flash chromatography (2% Et_2O:ligroin) to afford the product ketone (78 mg, 95%) as a clear oil. The product ($R_f = 0.27$, 10% Et_2O/ligroin) was analyzed by chiral GC (BDM 110) which indicated an *ee* of 98%. IR (neat): $\tilde{\nu} =$ 2929, 1718, 1255, 1097, 835, 774 cm^{-1}; ^1H NMR (400 MHz, C_6D_6): $\delta = 0.08$ (s, 6H), 0.82 (d, $J = 6.4$ Hz, 3H), 1.00 (s, 9H), 1.14–1.24 (m, 2H), 1.24–1.37 (m, 2H), 1.43 (m, 2H), 1.66 (s, 3H), 1.80 (dd, $J = 17.5$, 6.8 Hz, 1H), 1.95 (m, 1H), 1.98 (dd, $J = 17.5$, 5.7 Hz, 1H), 3.54 ppm (t, $J = 6.1$ Hz, 2H); EIMS: *m*/*z* (%): 215 (40) [M^+−Bu], 171 (64), 115 (29), 75 (100); HR-EIMS calcd for $C_{15}H_{32}O_2Si{\cdot}C_4H_9$: 215.1467; found 215.1470. Additional data for all new compounds can be found in the Supporting Information.
[19] B. H. Lipshutz, P. Papa, *Angew. Chem.* **2002**, *114*, 4762; *Angew. Chem. Int. Ed.* **2002**, *41*, 4580.

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