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Published on Web 10/11/2008

CuH-Catalyzed Enantioselective Intramolecular Reductive Aldol Reactions Generating Three New Contiguous Asymmetric Stereocenters

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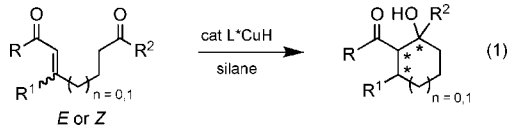
Asymmetric reductive aldol reactions provide powerful inroads to stereocontrolled centers of considerable value in synthesis.[1] Invariably, the β-site in an α,β-unsaturated carbonyl derivative either is unsubstituted or at most contains a single *E*- or *Z*-substituent. Hence, initial conjugate reduction, regardless of hydride source (e.g., pinacolborane),[1h] is of no stereochemical consequence. Rather, the in situ formed nonracemic enolate is the species that controls the subsequent aldol event, thereby giving rise to the anticipated two new centers of central chirality. We now describe the first hydrometallative intramolecular cycloreduction leading to three new contiguous stereocenters in a one-pot process, based on a nonracemically ligated (L*) catalytic source of CuH (eq 1).



(1)

Our approach derives from known conjugate reductions of β,β-disubstituted, α,β-unsaturated ketones[2] and related prochiral educts,[3] catalyzed by ligand-stabilized copper hydride. Facial discrimination in the initial 1,4-hydride addition generates an intermediate chiral (presumably copper) enolate that subsequently participates in an intramolecular aldol addition to ketones.[4a] Transmetalation of the resulting copper alkoxide with a particular stoichiometric silane as reductant regenerates ligated CuH.[4b]

Reactions of (*E*)-β,β-disubstituted enone **1** with CuH ligated by the Solvias[5] bis-phosphine (*S*,*R*)-PPF-P(*t*-Bu)$_2$ (**I**; Figure 1) in the presence of diethoxymethylsilane (DEMS)[6] gave a single diastereomer in high *ee*'s (Table 1). Yields of the newly formed six-membered ring cycloadduct **2** were somewhat depressed when reactions were conducted at concentrations above 0.25 M, presumably due to competition between silyl enol ether formation (i.e., transmetalation from the copper enolate)[7] and aldol cyclization (Table 1, entry 1). However, a good yield was obtained (91%) without loss of *ee* employing DEMS (1.5 equiv) with 0.5 mol % catalyst **I** in toluene (0.25 M) at 0 °C (entry 2). Further cooling to −10 °C raised the *ee* to 96% (entry 3). Reaction in the presence of phenylsilane ($PhSiH_3$) in toluene also gave a high *ee*, although the efficiency suffered (entry 4). Excess silane and ligand were required upon changing solvent from toluene to THF (entries 5, 6). Thus, further studies were conducted in toluene at −10 °C with DEMS as the source of mild hydride.

Representative reductive cyclizations of various β,β-disubstituted enones using 1 mol % catalyst are illustrated in Table 2. Both *E*- and *Z*-methyl enone pairs (entries 1 and 2; entries 3 and 4) gave enantiomeric products in good yields and *ee's*. The sense of stereoinduction was similar to that predicted based on previous studies with the related substrate/ligand combination,[2] despite any influence of the pendant carbonyl residue. X-ray data confirmed this trend (see Supporting Information, SI). Sterically more demanding groups located at both the β-position and adjacent to the enone carbonyl were tolerated (entry 5). Aryl enones (entries 6, 7) gave modest *ee*'s that were difficult to improve regardless of bis-phosphine ligand. On the other hand, the reaction involving the *E*-*n*-butyl enone (entry 9) that also initially afforded a lower *ee* with ligand **I** (64% *ee*) could be significantly improved by switching to Josiphos analogue **II**[8] (97% *ee*). The inverted sense of chirality (entry 9) follows from use of the (*R*,*S*)-enantiomer of this ligand. The five-membered ring precursor **3** gave rise to two isolable diastereomers, the *ee* for each was >90% (entry 10).

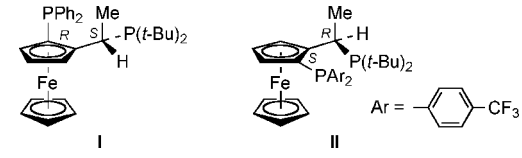
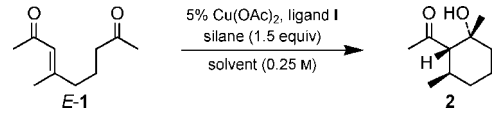


Figure 1. Josiphos ligands: **I** = (*S*,*R*)-PPF-P(*t*-Bu)$_2$; **II** = (*R*,*S*)-(4-CF_3Ph)$_2$PF-P(*t*-Bu)$_2$.

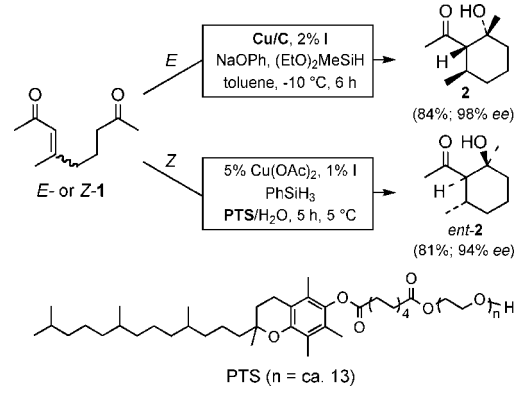
Table 1. Optimization: Enantioselective Reductive Aldol Cyclizations[a]



entry	**1** (%)	silane	solvent	temp (°C)	time (h)	yield (%)[b]	*ee* (%)[c]
1[d]	1	DEMS	toluene	0	6	81	93
2	1	DEMS	toluene	0	6	91	93
3	**0.5**	**DEMS**	**toluene**	**−10**	**12**	**87**	**96**
4[e]	1	$PhSiH_3$	toluene	0	6	65	97
5	1	DEMS	THF	−10	12	35	96
6	2	DEMS[f]	THF	−10	8	85	96

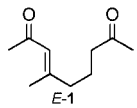
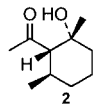
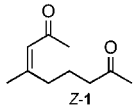
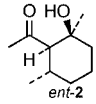
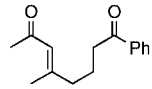
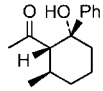
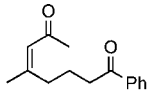
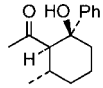
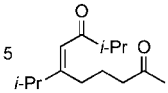
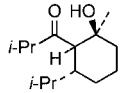
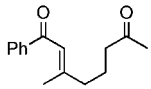
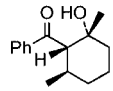
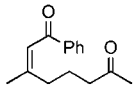
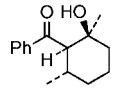
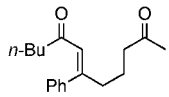
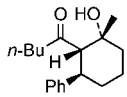
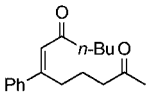
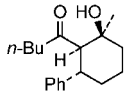
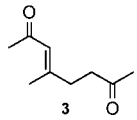
[a] All reactions were quenched with NH_4F-MeOH. [b] Isolated yields. [c] Determined by chiral HPLC analysis (see Supporting Information). [d] 0.5 M in toluene. [e] 1.0 M in toluene. [f] 5 equiv.

Scheme 1. Heterogeneous and Aqueous Asymmetric Reductive Aldol Reactions



10.1021/ja8045475 CCC: $40.75

Table 2. Asymmetric Cycloreductions Using Catalytic CuH[a]

entry	substrate	product	yield(%)	*ee*(%)
1	 *E*-**1**	 **2**	91	96
2	 *Z*-**1**	 *ent*-**2**	88	96
3			77	97
4			75	97
5			66	84
6			98	85[b]
7			98	75
8			83	77
9			92 94[c]	64 -97[c]
10	 **3**		75[d]	97,92

[a] Conditions: 3−5% $Cu(OAc)_2 \cdot H_2O$, 1% (*S*,*R*)-PPF-P(*t*-Bu)$_2$ (**I**), 1.5 equiv of DEMS, toluene, 12 h, −10 °C. [b] At −20 °C. [c] 1% (*R*,*S*)-(4-CF_3Ph)$_2$PF-P(*t*-Bu)$_2$ (**II**). [d] Combined isolated yield for diastereomers (dr = 59:41).

Copper-catalyzed cycloreduction of keto enone *E*-**1** was also quite successful under the same low temperature conditions using heterogeneous Cu/C[9] (Scheme 1; *E*-isomer). Best results were obtained at −10 °C in the presence of NaOPh (10−20 mol %) and ca. 4 equiv of DEMS in toluene to afford **2** (84% yield, 98% *ee*). Raising the temperature to ambient, surprisingly, did not significantly erode enantioselectivity (97% *ee* at 0 °C; 96% *ee* at rt). An asymmetric reductive aldol could also be run entirely in water notwithstanding the water-insoluble nature of educt *Z*-**1**. Thus, in the presence of nanomicelle-forming PTS[10] (a nonionic, vitamin E based surfactant; 2% by weight), 1,4-reduction/cyclization in the presence of excess $PhSiH_3$ at 5 °C led to adduct *ent*-**2** in comparable yield and *ee* (cf. Table 2, entry 2, using toluene at −10 °C).

In summary, we have described the first asymmetric conjugate reduction/intramolecular aldol reactions of acyclic β,β-disubstituted keto enones, catalyzed by nonracemic bis-phosphine-ligated copper hydride. Yields, *de*'s, and *ee*'s for six-membered rings containing three newly fashioned contiguous asymmetric centers, in particular, are uniformly high. This sequence can also be carried out both heterogeneously with Cu/C and in pure water as solvent in the presence of the commercially available amphiphile PTS.[11]

Acknowledgment. Financial support provided by the NSF (CHE 05-50232) and Zymes, LLC is warmly acknowledged. We also sincerely thank Solvias for a generous supply of the ligands used in this study.

Supporting Information Available: Experimental details, spectroscopic data for all products, and X-ray data (Table 2, entries 1 and 4). This material is available free of charge via the Internet at http://pubs.acs.org.

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JA8045475