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Highly Chemoselective Copper-Catalyzed Conjugate Reduction of Stereochemically Labile α,β-Unsaturated Amino Ketones

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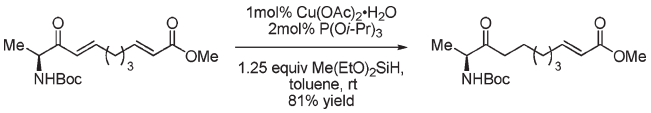
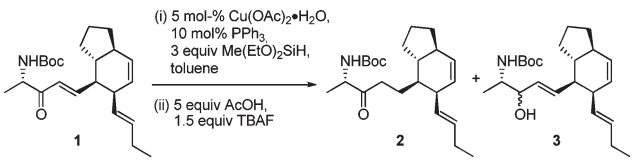


Highly chemoselective conjugate reduction of chiral α,β-unsaturated amino ketones has been developed by using triisopropyl phosphite ligated copper hydride complex. The highlights of the method are wide substrate compatibility and exceptional chemoselectivity.

Chemoselective reduction of variously conjugated and isolated C−C double bonds presents a significant challenge in organic chemistry even with the plethora of available methods since the report by Adkins on the use of nickel catalysts for reduction of mesityl oxide to methyl isobutyl ketone, among other substrates.[1] Several reagents are known for achiral conjugate reduction of unsaturated carbonyl compounds such as triethylsilane, using catalytic $(Ph_3P)_3RhCl$,[2] K-selectride,[3] hydrogen gas,[4] and trialkylammonium formates[5] in the presence of Pd/C, sodium dithionite,[6] Raney nickel,[7] and various silanes in the presence of catalytic amounts of rhodium(bisoxazolinylphenyl) complexes.[8] Stoichiometric $[CuH(PPh_3)]_6$ (Stryker's reagent)[9] and catalytic $[CuH(PPh_3)]_6$ in the presence of hydrogen gas[10] or silanes[11] can also be used for 1,4-reduction. None of the known methods exhibited the necessary selectivity and mildness in the context of our recent total synthesis of amaminol A,[12] where problems were encountered with selective reduction of an enone containing epimerizable stereocenters and other double bonds (Scheme 1). Among the many different methods tested, copper hydride based reductions turned out to be the most promising. As a result we used the modified conditions from Lee and Jun for preparing Stryker's reagent in situ using copper(II) acetate monohydrate, triphenylphosphine, and diethoxymethylsilane as the hydride source.[13] We decided to further investigate this new modified protocol for a wider range of substrates, containing additional electron-rich as well as electron-poor C−C double bonds. As a result we describe a highly chemoselective and mild nonepimerizing method for conjugate reduction of stereochemically labile α,β-unsaturated amino ketones using unprecedented (previously unused) phosphite ligated copper hydride, which turned out to be the key for high chemoselectivity.

SCHEME 1. Original Conditions As Used in Total Synthesis



We initially decided to investigate the effects of the phosphine and phosphite ligands on the reactivity and selectivity of the catalyst using the cyclohexanal derived aminoketone **4** as the model substrate. The ligand screening reactions were monitored with a gas chromatograph. The ratios of silylated intermediates **5**, **6**, and **7** corresponding to 1,4-reduction, 1,2-reduction, and fully reduced products were measured (Table 1). Isolated yields of hydrolyzed products were also measured.

Ligands with different numbers of coordination sites were tested. Monodentate ligands Ph_3P **L1**, $P(Oi\text{-}Pr)_3$ **L4**, and $P(OEt)_3$ **L5** showed comparable reaction times and high selectivity (Table 1). Triethyl phosphite **L5** showed some side reactions which lowered the yield. A reaction with DPPE monoxide **L2** was slower retaining high selectivity, whereas DPPP monoxide **L3** gave faster reaction but was slightly less selective toward 1,4-reduction. Bidentate ligands DPPE **L7**, DPPB **L8**, and the *o*-BDPPB ligand **L9** recently reported by

(1) Covert, L. W.; Connor, R.; Adkins, H. *J. Am. Chem. Soc.* **1932**, *54*, 1651–1663.
(2) Ojima, I.; Kogure, T.; Nagai, Y. *Tetrahedron Lett.* **1972**, *13*, 5035–5038.
(3) Fortunato, J. M.; Ganem, B. *J. Org. Chem.* **1976**, *41*, 2194–2200.
(4) See e.g.: (a) Marker, R. E.; Rohrmann, E. *J. Am. Chem. Soc.* **1940**, *62*, 518–520. (b) Marker, R. E.; Tsukamoto, T.; Turner, D. L. *J. Am. Chem. Soc.* **1940**, *62*, 2525–2532.
(5) Cortese, N. A.; Heck, R. F. *J. Org. Chem.* **1978**, *43*, 3985–3987.
(6) Camps, F.; Coll, J.; Guitart, J. *Tetrahedron* **1986**, *16*, 4603–4609.
(7) Barrero, A. F.; Alvarez-Manzaneda, E. J.; Chanboun, R.; Meneses, R. *Synlett* **1999**, *10*, 1663–1666.
(8) Kanazawa, Y.; Nishiyama, H. *Synlett* **2006**, *19*, 3343–3345.
(9) (a) Mahoney, W. S.; Brestensky, D. M.; Stryker, J. M. *J. Am. Chem. Soc.* **1988**, *110*, 291–293. (b) Njardarson, J. T.; Gaul, C.; Shan, D.; Huang, X.-Y.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2004**, *126*, 1038–1040. (c) Kraft, P.; Eichenberger, W. *Eur. J. Org. Chem.* **2004**, 354–365.
(10) (a) Mahoney, W. S.; Stryker, J. M. *J. Am. Chem. Soc.* **1989**, *111*, 8818–8823. (b) Chen, J.-X.; Daeuble, J. F.; Brestensky, D. M.; Stryker, J. M. *Tetrahedron* **2000**, *56*, 2153–2166.
(11) For recent reviews on CuH-catalyzed reactions see: (a) Deutsch, C.; Krause, N.; Lipshutz, B. H. *Chem. Rev.* **2008**, *108*, 2916–2927. (b) Lipshutz, B. H. *Synlett* **2009**, 509–524. For other leading references, see: (c) Lipshutz, B. H.; Keith, J.; Papa, P.; Vivian, R. *Tetrahedron Lett.* **1998**, *39*, 4627–4630. (d) Lipshutz, B. H.; Crisman, W.; Noson, K.; Papa, P.; Sclafani, J. A.; Vivian, R. W.; Keith, J. M. *Tetrahedron* **2000**, *56*, 2779–2788. (e) Mori, A.; Fujita, A.; Kajiro, H.; Nishihara, Y.; Hiyama, T. *Tetrahedron* **1999**, *55*, 4573–4582. (f) Kim, D.; Park, B.-M.; Yun, J. *Chem. Commun.* **2005**, 1755–1757.
(12) Kumpulainen, E. T. T.; Koskinen, A. M. P.; Rissanen, K. *Org. Lett.* **2007**, *9*, 5043–5045.
(13) Lee, D.-W.; Yun, J. *Tetrahedron Lett.* **2005**, *46*, 2037–2039.

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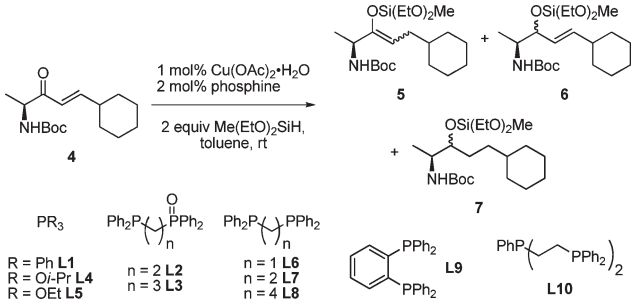
TABLE 1. Ligand Screening



Entry	Ligand	Premix time[a]	Time	Ratio of **5**:**6**:**7**	Y (%)[b] keto:alcohol
1	**L1**	1 h	1.5 h	94:6:0	79:8
2	**L2**	1.5 h	4 h	96:4:0	65:5
3	**L3**	2 h	50 min	91:8:1	83:7
4	**L4**	4 h	55 min	96:4:0	95:3
5	**L5**	4 h	2 h	96:4:0	77:4
6	**L6**	1.5 h	9 h	92:6:2	82:9
7	**L7**	1 h	15 min	48:50:2	43:49
8	**L8**	2 h	3.5 h	54:46:0	43:36
9	**L9**	1 h	35 min	49:49:2	42:43
10	**L10**	1 h	18 h	10:81:9	9:71

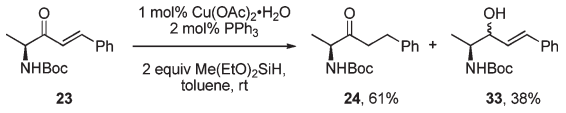
[a]Time needed for catalytically active species to be formed (copper salt fully dissolved and occurrence of color change). [b]Isolated yields after 1.5 equiv of TBAF/5 equiv of AcOH quench and silica gel chromatography for ketone **8** (from **5**) and diastereomeric alcohols (from **6** and **7**).

the Lipshutz group[14] showed unselective reactions giving roughly equal amounts of 1,2- and 1,4-reduction products. These results show that ligands with two carbons between phosphorus atoms provide the fastest reaction times (in accord with literature) but surprisingly lack any selectivity (entries 7 and 9). As an exception for bidentate ligands, the DPPM **L6** mediated reaction proceeded slowly, but with much higher selectivity. Interestingly a tridentate triphosphine ligand **L10** gave a reaction that was mainly selective toward 1,2-reduction. From these ligands P(O*i*-Pr)$_3$ **L4** turned out to be the most selective giving also the highest isolated yields. Although inexpensive and industrially available P(O*i*-Pr)$_3$ **L4** is known to produce stable copper hydride species,[15] it has not been used as a copper catalyst ligand in conjugate reductions to the best of our knowledge. It is also of importance to note that epimerization[16] of the potentially vulnerable stereogenic center at C2 was not observed during the conjugate reduction reaction.[17]

With the optimized conditions in hand we set out to determine the substrate scope for this reaction (Table 2). Since the use of 1.5 equiv of Me(EtO)$_2$SiH provided the same results and was more economical, with few exceptions we used this amount of hydride donor in further experiments.

Both sterically demanding (substrates **4** and **13**) and nondemanding (substrates **9** and **11**) enones derived from L-alanine were easily converted to ketones with good isolated yields. A similar enone **15** containing a benzyloxy group at the γ-position required longer reaction time (10 h) possibly due to nonbeneficial coordination to the catalyst. Sterically congested enones (subtrates **17** and **19**) derived from L-serine were also easily reduced to the corresponding ketones. An α,γ-diunsaturated ketone with an endocyclic and an exocyclic double bond produced only 1,4-reduction product **22**. Simple fully conjugated aromatic enone **23** gave rapid 1,4-reduction to ketone **24** (76%) with also some 19% of 1,2-reduction product **33**. For comparison, we executed reduction of **23** using in situ generated Stryker's reagent (Scheme 2). In this reaction we observed slightly poorer selectivity toward 1,4-reduction and only 61% of ketone **24** was recovered. Heteroaromatic compounds **25**, **27**, and **29** were found to be much more challenging substrates. These reactions required higher Me(EtO)$_2$SiH (3 equiv) amounts and elevated temperatures.

SCHEME 2. Comparison Experiment with Stryker's Reagent



The new conditions were tested also on complex advanced intermediates **1** and **31**. On nearly a gram scale **1** was smoothly reduced to the corresponding ketone in 86% yield. No epimerization of labile C-2 and C-6 stereocenters were observed. Finally as the ultimate test a substrate **31** containing both an enone and an α,β-unsaturated ester was selectively reduced to the monoreduced product **32** in 81% yield. This is a rare example of a catalytic system able to distinguish between two electronically similar double bonds and selectively reduce only one of them when careful control of hydride equivalents was used.[18] There is also a possibility of reductive Michael cyclization,[19] which we did not observe in this case.

In summary, we have developed a highly chemoselective nonracemizing conjugate reduction of easily epimerizable unsaturated α-aminoketones using triisopropyl phosphite ligated copper hydride as the catalyst. The method shows very good substrate compatibility: substrates containing free N−H groups (acyclic and heterocyclic) as well as basic pyridine groups can be reduced. Furthermore, we have shown that the method is selective enough to reduce only an enone in the presence of multiple less and more electron-rich olefins and even an enoate. Therefore our method complements the recent Lipshutz method, which can be used when high efficiency and low catalyst loading is required, whereas our method may find use in cases where high chemoselectivity and mildness is required in reducing complex and sensitive substrates.

Experimental Section

Typical Conditions for Conjugate Reduction Reaction. A flame-dried round-bottomed flask was charged with Cu(OAc)$_2\cdot$H$_2$O

(14) Baker, A. B.; Boskovic, Z. V.; Lipshutz, B. H. *Org. Lett.* **2008**, *10*, 289–292.

(15) It is known that (*i*-PrO)$_3$P forms crystalline complexes with copper hydride of type (*i*-PrO)$_3$PCuH, [(*i*-PrO)$_3$P]$_2$CuH, and [(*i*-PrO)$_3$P]$_2$(CuH)$_3$. (a) Malykhina, I. G.; Kazankova, M. A.; Lutsenko, I. F. *Zh. Obshch. Khim.* **1971**, *41*, 2103–2104. (b) Lutsenko, I. F.; Kazankova, M. A.; Malykhina, I. G. *Zh. Obshch. Khim.* **1967**, *37*, 2364–2365.

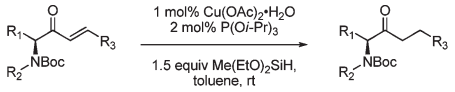
(16) Epimerization of an α-stereocenter of a ketone has been observed during copper hydride catalysis due to strongly basic copper alkoxides. See ref 10b for details.

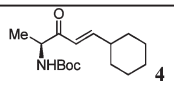
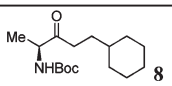
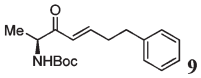
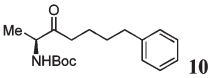
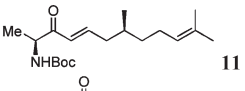
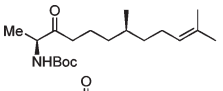
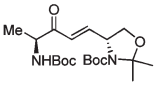
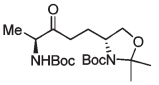
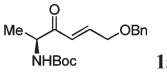
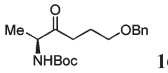
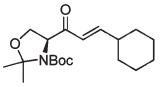
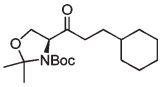
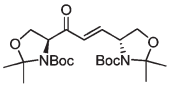
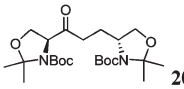
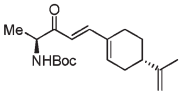
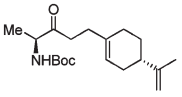
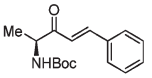
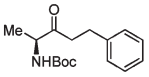
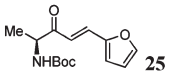
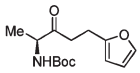
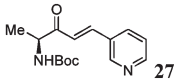
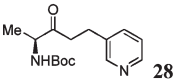
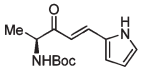
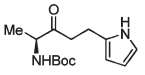
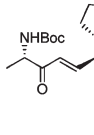
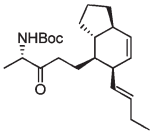
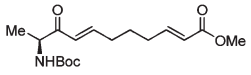
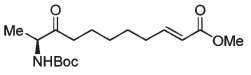
(17) See the Support Information for details.

(18) (a) Eiter, K. *Liebigs Ann. Chem.* **1962**, *658*, 91–99. (b) Lee, H.-Y.; An, M. *Tetrahedron Lett.* **2003**, *44*, 2775–2778. (c) Yang, J. W.; Hechavarria, F.; List, B. *J. Am. Chem. Soc.* **2005**, *127*, 15036–15037.

(19) (a) Baik, T.-G.; Luis, A. L.; Wang, L.-C.; Krische, M. J. *J. Am. Chem. Soc.* **2001**, *123*, 5112–5113. (b) Wang, L.-C.; Jang, H.-Y.; Roh, Y.; Lynch, V.; Schultz, A. J.; Wang, X.; Krische, M. J. *J. Am. Chem. Soc.* **2002**, *124*, 9448–9453. (c) Miura, K.; Yamada, Y.; Tomita, M.; Hosomi, A. *Synlett* **2004**, 1985–1989. (d) Lee, H.; Jang, M.-S.; Hong, J.-T.; Jang, H.-Y. *Tetrahedron Lett.* **2008**, *49*, 5785–5788.

TABLE 2. Reduction of Different α-Chiral Enones[a]



Entry	Substrate	Product	Time (h)	Yield (%)[b]
1	 **4**	 **8**	1	90
2	 **9**	 **10**	1	87
3	 **11**	 **12**	0.5	90
4	 **13**	 **14**	1	87
5	 **15**	 **16**	10	75
6	 **17**	 **18**	1	96
7	 **19**	 **20**	0.7	77[c]
8	 **21**	 **22**	20	72
9	 **23**	 **24**	1	76
10	 **25**	 **26**	24	81[d]
11	 **27**	 **28**	24	67[e]
12	 **29**	 **30**	48	42[f]
13	 **1**	 **2**	3	86[g]
14	 **31**	 **32**	20	81[h]

[a]Typical conditions: 1 mol % of $Cu(OAc)_2 \cdot H_2O$, 2 mol % of $P(Oi\text{-}Pr)_3$, 1,5 equiv of $Me(EtO)_2SiH$, toluene, rt. [b]Isolated yields after 1.5 equiv of TBAF/5 equiv of AcOH quench and silica gel chromatography. [c]HF/pyridine was used for workup. [d]3 equiv of $Me(EtO)_2SiH$ was used. [e]3 equiv of $Me(EtO)_2SiH$ was used at 40 °C. [f]3 equiv of $Me(EtO)_2SiH$ was used at 70 °C. [g]0.83 g (2.2 mmol) of **1** was used. [h]1.25 equiv of $Me(EtO)_2SiH$ was used.

(1.4 mg, 7.1 μmol) and evacuated under vacuum and refilled with argon. Then 2 mL of dry toluene was added followed by triisopropyl phosphite (3.3 μL, 14.2 μmol) and $Me(EtO)_2$-SiH (0.17 mL, 1.07 mmol). The mixture was stirred at room temperature under positive pressure of argon for 3−4 h until the color changed from blue through light green to light brown. Then 0.20 g (0.71 mmol) of substrate **3** was cannulated into the reaction mixture as a solution in toluene (2 mL). After 1 h of reaction time acetic acid (0.20 mL, 3.55 mmol) was added. After 5 min 1 M TBAF (1.09 mL, 1.09 mmol) in THF was added to quench the reaction. The mixture was stirred for 15 min and evaporated to dryness. The residue was purified by silica gel chromatography (10% EtOAc/hexanes) furnishing 0.18 g (90%) of reduction product **8**. R_f 0.62 (33% EtOAc/hexanes); IR (thin film, cm^{-1}) 3354, 2978, 2925, 2852, 1710, 1508, 1498, 1450, 1367, 1248, 1171; ^1H NMR (400 MHz, $CDCl_3$) δ 5.34 (d, J = 6.4 Hz, 1H), 4.20 (dq, J = 6.9, 6.7 Hz, 1H), 2.32−2.47 (m, 2H), 1.48−1.58 (m, 5H), 1.34−1.40 (m, 2H), 1.32 (s, 9H), 1.20 (d, J = 7.2 Hz, 3H), 1.00−1.16 (m, 4H), 0.73−0.81 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.8, 155.0,

79.3, 54.8, 37.1, 36.5, 32.9, 32.9, 30.7, 28.2, 26.3, 26.0, 17.7; HRMS (ESI) calcd for [M + Na] $C_{16}H_{29}NO_3Na$ 306.2045, found 306.2040.

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Supporting Information Available: Experimental details and characterization data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.