Highly efficient conjugate reduction of α,β-unsaturated nitriles catalyzed by copper/xanthene-type bisphosphine complexes†

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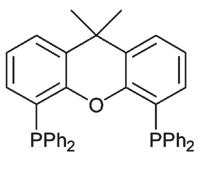
α,β-Unsaturated nitriles are chemoselectively reduced to the corresponding saturated nitriles in high yields using a copper-DPEphos or Xantphos complex as catalyst in the presence of polymethylhydrosiloxane (PMHS) as the stoichiometric reducing agent and *t*-butanol as additive.

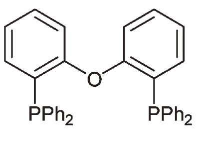
α,β-Unsaturated nitriles are versatile synthetic intermediates in organic synthesis[1] and the selective reduction of conjugated nitriles to their saturated counterparts has long been a synthetic interest. While various reduction methods of α,β-unsaturated nitriles have been developed by using a stoichiometric amount of metal[2] and metal hydrides,[3] only a few metal-catalyzed conjugate reductions were reported with a relatively nonreactive source of hydride entities such as silanes.[4] These reducing systems, however, have limitations, as the reduction is very slow, low-yielding, and often β,β-disubstituted-α,β-unsaturated nitriles cannot be reduced at all.

Despite recent advances of Cu–H catalyzed hydrosilylation methodologies,[5] an efficient conjugate reduction method of α,β-unsaturated nitriles catalyzed by Cu–H has not been reported. It was observed that unsaturated nitriles reacted more slowly than other related unsaturated functionalities in various metal-catalyzed reductions[4,6] and the linearity of the CN group prevented the formation of a stable enolate analogue.[4b] The CN functionality was also reported to inhibit the catalytic activity of Cu–H in other copper-catalyzed reductions.[5c,7]

Recently, we have shown that Cu–H for the asymmetric reduction of ketones could be generated from the combination of catalytic amounts of copper(II) acetate or copper(II) acetate monohydrate and (*S*)-BINAP in the presence of Ph_2SiH_2 or $PhSiH_3$.[8] We, therefore, decided to investigate the conjugate reduction of α,β-unsaturated nitriles with our catalytic system and report here that a complex of copper(II) acetate and Xantphos (**1**) or DPEphos (**2**) is quite effective for catalyzing the conjugate reduction of α,β-unsaturated nitriles in the presence of PMHS at ambient temperature.



Xantphos (**1**)

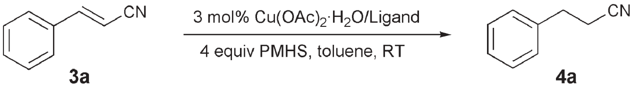


DPEphos (**2**)

In our initial investigations on the reduction of (*E*)-cinnamonitrile (**3a**) with PMHS, we employed the $Cu(OAc)_2 \cdot H_2O$/BINAP catalyst system, which was quite effective for the reduction of aromatic ketones. However, the reaction showed no appreciable conversion even after long reaction times. We screened a series of commercially available bisphosphine ligands and organosilanes with no success. We then turned our attention to the use of additives to promote reaction rates since many hydrosilylation reactions were reported to be accelerated by alcohol additives.[9] Addition of 4 equiv of *t*-BuOH to the reaction mixture led to an increased rate of reduction[10] and **3a** was quite efficiently reduced to its saturated analogue in high yield (Table 1, entry 5). Other achiral bisphosphine ligands were investigated and the results are summarized in Table 1. While bisphosphine ligands that have flexible backbones such as dppb, dppp are either inactive or moderately active (entries 3 and 4), bisphosphines based on rigid aromatic backbones proved quite efficient (entries 5–7). In particular, Xantphos (**1**)[11] was quite effective for the reduction of **3a** yielding the saturated counterpart **4a** in high yield (entries 7 and 8). DPEphos[11] showed comparable reactivity, but the isolated yield of **4a** was lower for this substrate.

As shown in Table 2, a range of α,β-unsaturated nitriles prepared from the corresponding aldehydes or ketones were chemoselectively reduced smoothly at room temperature in high yields by a $Cu(OAc)_2$/Xantphos catalyst or $Cu(OAc)_2$/DPEphos catalyst, in the presence of PMHS and *t*-BuOH.[12] A wide range of aromatic and aliphatic substrates were reduced to the saturated nitrile products in good yields. Functional groups such as MeO, Cl, F, CN were tolerated (entries 2–4 and 9). A heterocyclic substrate, 3-(2-furanyl)-2-propenenitrile (**3e**), was also effectively

Table 1 Conjugate reduction of (*E*)-cinnamonitrile under various conditions



Entry	Ligand	Additive	Time/h	Yield/% [a]
1[b]	(*S*)-BINAP	—	no rxn	—
2	Xantphos	—	no rxn	—
3[c]	dppb	*t*-BuOH	no rxn	—
4[d]	dppp	*t*-BuOH	21	70
5	(*S*)-BINAP	*t*-BuOH	1.5	90
6	DPEphos	*t*-BuOH	<1	83
7	Xantphos	*t*-BuOH	<1	92
8[e]	Xantphos	*t*-BuOH	<1	96

[a] Isolated yields. [b] No reaction occurred with Ph_2SiH_2 and $PhSiH_3$ either. [c] dppb = 1,4-Bis(diphenylphosphino)butane. [d] dppp = 1,3-Bis(diphenylphosphino)propane. [e] $Cu(OAc)_2$ was used.

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† Electronic supplementary information (ESI) available: experimental procedures and spectroscopic data of all products (**4a–4j**). See http://www.rsc.org/suppdata/cc/b4/b418586b/

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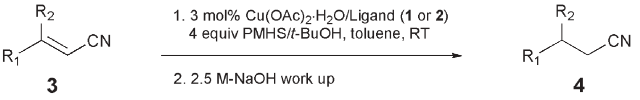
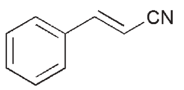
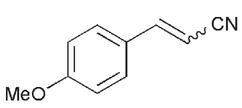
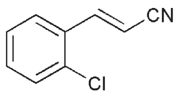
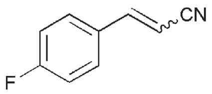
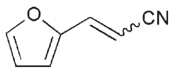
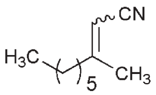
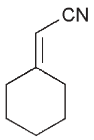
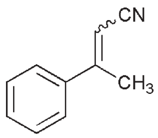
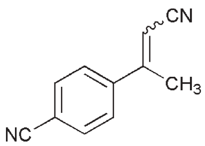
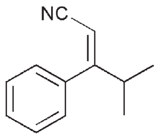
Table 2 Catalytic conjugate reduction of α,β-unsaturated nitriles



Entry	Substrate **3**	Ligand	Time/h	Yield/%[a]
1[b]	 **3a**	**1**	<1	92
2	 **3b**	**1**	1	89
3[b]	 **3c**	**1**	1	90
4	 **3d**	**1** **2**	1 1	92 87
5	 **3e**	**1**	1	85
6	 **3f**	**1**	7	80
7	 **3g**	**1**	3.5	87
8[c]	 **3h**	**2**	10	87
9[c]	 **3i**	**2**	9	84
10[b,c,d]	 **3j**	**2**	12	94

[a] Isolated yield. [b] Pure (*E*)-isomer was used. [c] $Cu(OAc)_2$ was used instead of $Cu(OAc)_2{\cdot}H_2O$. [d] Pure (*Z*)-isomer was used.

reduced in 85% isolated yield (entry 5). Conjugation of the double bond with an aromatic ring is not a requirement for reduction. Simple aliphatic substrates, **3f** derived from 2-octanone and **3g** from cyclohexanone afforded products in hours (entries 6 and 7).[13] Reduction of the sterically more hindered substrates (**3h–3j**) prepared from the corresponding aromatic ketones were conducted more efficiently by the Cu/DPEphos system than by the Cu/Xantphos system, leading reaction to completion in reasonable reaction times.

Copper complexes of Xantphos or DPEphos are thermally more stable and more efficient for the hydrosilylation of nitriles than a Cu/BINAP complex. While the Cu/Xantphos-type ligands system reduces β,β-disubstituted-α,β-unsaturated nitriles effectively, the Cu/BINAP system results in slow conversion of the substrate and the reaction mixture eventually turns to a black color in hours (*ca.* 12 h), which is presumably resulted from decomposition of Cu–H at room temperature.[14]

It seems that in our reducing system employing a Cu(II) salt as the catalyst precursor, the active catalyst is Cu(I)–H, which is the same species normally generated from copper(I) chloride, sodium *t*-butoxide, and a reducing agent.[15] We postulate that 1,4-addition of the Cu–H to α,β-unsaturated nitriles takes place and the resulting organocopper species[16] reacts with *t*-BuOH to yield the protonated product rapidly and a copper alkoxide. The latter then regenerates the active catalyst Cu–H with PMHS.

In conclusion, we have developed an efficient method for the conjugate reduction of α,β-unsaturated nitriles based on Cu(I)–H generated in the presence of the xanthene-based ligands **1** and **2**. The active Cu(I)–H was generated from copper(II) acetate with an organosilane, and was thermally stable enough to carry out the reduction at ambient temperature. The use of *t*-BuOH as additive was a key to success and inexpensive polymeric hydrosilane PMHS could be used as the stoichiometric reducing agent. An asymmetric version of this reaction is actively under investigation in our group with chiral bisphosphine ligands based on a xanthene or ferrocenyl framework.

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12 General procedure for the conjugate reduction of α,β-unsaturated nitriles [using $Cu(OAc)_2 \cdot H_2O$ and Xantphos]: $Cu(OAc)_2 \cdot H_2O$ (3.0 mg, 0.015 mmol) and Xantphos (8.7 mg, 0.015 mmol) were placed in an oven-dried Schlenk tube and toluene (0.5 mL) was added under nitrogen. PMHS (0.12 mL, 2 mmol) was added to the reaction mixture and the reaction was stirred for 20–30 min at room temperature. α,β-Unsaturated nitrile substrate (0.5 mmol) was added by syringe, followed by *t*-BuOH (0.18 mL, 2 mmol). The reaction tube was washed with toluene (0.5 mL), sealed and stirred at room temperature until no starting material was detected by TLC or GC. The reaction mixture was quenched with water and transferred to a round-bottom flask with an aid of Et_2O (10 mL), and then NaOH (2.5 M, 1.2 mL) was added. The biphasic mixture was stirred vigorously for 0.5 h. The layers were separated and the aqueous layer was extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. The product was purified by Kugelrohr distillation or silica gel chromatography.

13 Acrylonitrile was also a good substrate for the reduction and its conversion could be followed by GC analysis (1.5 h, 100% conversion with 2 equiv. *t*-BuOH). However, the nitrile substrate derived from *t*-butyl methyl ketone (pinacolone) was not reduced under the reaction conditions, probably due to its steric effect.

14 For the thermal instability of CuH, see ref. 5*c*; in this report, reactions were conducted at low temperatures below 0 °C in order to prevent decomposition of the Cu–H, which resulted in the gradual formation of black particulates.

15 For the preparation of Styker's reagent, $[Ph_3PCuH]_6$, see: D. M. Brestensky, D. E. Huseland, C. McGettigan and J. M. Stryker, *Tetrahedron Lett.*, 1988, **29**, 3749. The same reagent can be prepared from the combination of copper(II) acetate, an organosilane, and PPh_3; *Tetrahedron Lett.*, in press.

16 Trapping of the organocopper species with chlorosilane was reported. See ref. 3*b*.