Reduction

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Highly Enantioselective Conjugate Reduction of β,β-Disubstituted α,β-Unsaturated Nitriles**

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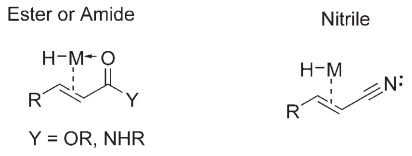
Optically active nitrile compounds with a β-stereocenter are versatile synthetic intermediates for a number of biologically active compounds.[1] The nitrile group is a very useful synthetic group that can be transformed into other useful functionalities, such as amine, aldehyde, and carboxylic acid groups; furthermore, the isolation of nitrile-containing natural products continues to increase.[2] Despite recent advances in metal-catalyzed conjugate reductions, the development of asymmetric reductions of conjugated nitriles still remains challenging because of their intrinsic low reactivity[3] and the linearity of the CN group. The two asymmetric examples that we are aware of are the Co-catalyzed conjugate reduction of α,β-unsaturated nitriles[4] and the Rh-catalyzed hydrogenation of α,β-unsaturated nitriles.[5] However, the enantioselectivities achieved by these catalyst systems were significantly lower than those for analogous esters and amides, presumably because of the steric and coordinating environment exerted by the linear nitrile group (Scheme 1).

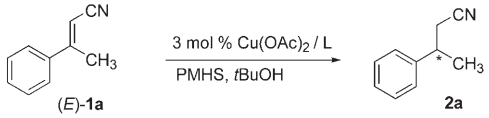


Scheme 1. Comparison of the coordinating environments of α,β-unsaturated esters, amides, and nitriles.

Copper hydride ligated by non-racemic ligands has been used for effecting the asymmetric hydrosilylation of aromatic ketones,[6] imines,[7] enones,[8] α,β-unsaturated esters,[9] and nitroalkenes[10] in the presence of excess hydrosilane. However, an enantioselective asymmetric conjugate reduction method of α,β-unsaturated nitriles catalyzed by copper hydride has not been reported yet. Herein, we report a highly enantioselective conjugation reduction of α,β-unsaturated nitriles employing a $Cu(OAc)_2$/josiphos catalyst.

Recently, we described the first use of air-stable Cu^{II} precursors $Cu(OAc)_2$ and $Cu(OAc)_2 \cdot H_2O$ for the reproducible generation of copper(I) hydride in copper-catalyzed reduction methodology.[6b,11] In contrast to previous reports of reductions catalyzed by copper hydride by others,[12] an inhibitory effect by the CN functional group on the activity of copper(I) hydride was not observed under our reduction conditions,[6b,13] in which a chelating bisphosphine ligand was used in combination with the copper precursors. On the basis of these results, we started to investigate asymmetric reductions of β-substituted cinnamonitrile (**1a**) using $Cu(OAc)_2$ as the catalytic precursor and a chiral bisphosphine ligand in the presence of polymethylhydrosiloxane (PMHS; Table 1). In initial experiments, C_2-symmetric binaphthyl-based bisphosphine ligands, such as (1,1'-binaphthalene)-2,2'-diylbis(diphenylphosphine)((*S*)-BINAP) and (*R*)-*p*-tol-BINAP, were investigated. The catalyst system prepared from $Cu(OAc)_2$/BINAP was not effective for the reduction of (*E*)-**1a**, as it lost its catalytic activity before the completion of the reaction (Table 1, entry 1). Although the reaction progressed smoothly to completion in 11 h with (*R*)-*p*-tol-BINAP, the saturated nitrile **2a** was produced with only moderate enantiomeric excess (65% *ee*; Table 1, entry 2). This level of enantioselectivity is considerably lower than that achieved for the reduction of analogous esters and enones with copper(I) hydride and the same ligand.[8a,9a] Moreover, when we applied this system to (*Z*)-**1a**, an almost racemic mixture of product (2% *ee*) was obtained (Table 1, entry 3).

Table 1: Asymmetric conjugate reduction of **1a**.[a]



(*E*)-**1a** **2a**

Entry	Substrate	Ligand	*t* [h]	*T* [°C]	Yield [%][b]	*ee* [%][c]
1	(*E*)-**1a**	(*S*)-BINAP	>24[d]	RT	25	65 (*S*)
2	(*E*)-**1a**	(*R*)-*p*-tol-BINAP	11	RT	92	65 (*R*)
3	(*Z*)-**1a**	(*R*)-*p*-tol-BINAP	11	RT	65	2 (*S*)
4	(*E*)-**1a**	(*S,R*)-**3**	**5**	**0**	**92**	**97** (*S*)
5	(*E*)-**1a**	(*R,S*)-**4**	24	0	90	65 (*R*)
6	(*E*)-**1a**	(*R,S*)-**5**	4.5	0	81	96 (*R*)
7[e]	(*E*)-**1a**	(*R,S*)-**5**	12.5	RT	80	95 (*R*)
8[f]	(*Z*)-**1a**	(*R,S*)-**3**	**4.5**	**0**	**91**	**99** (*S*)
9	(*Z*)-**1a**	(*R,S*)-**5**	4.5	RT	87	89 (*S*)

[a] Reaction conditions: $Cu(OAc)_2$ (3 mol%), ligand (3 mol%), PMHS (4 equiv), and *t*BuOH (4 equiv) were used unless otherwise noted. [b] Yield of the isolated product. [c] Determined by chiral HPLC. [d] Incomplete conversion. [e] Catalyst = 1.5 mol%. [f] Ligand = (*R,S*)-josiphos.

We continued our investigation with screening of the commercially available josiphos family of ligands **3**–**5**, which were found to be effective in a number of asymmetric reactions (Scheme 2).[14] Gratifyingly, the use of josiphos ligand **3** dramatically enhanced the enantioselectivity of the reduction of (*E*)-**1a**, thus providing **2a** in 97% *ee* (Table 1, entry 4). Ligand **4** proved to be inferior to the other

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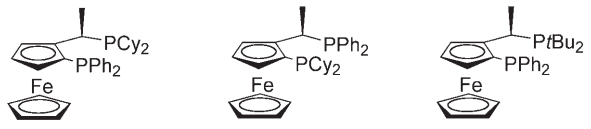
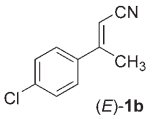
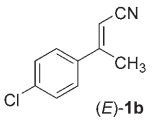
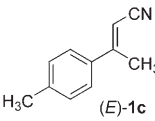
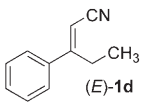
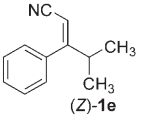
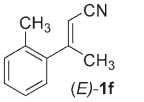
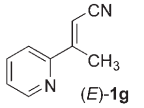


Scheme 2. Chiral ferrocenyl-based bisphosphines.

structurally related bisphosphine ligands in terms of reactivity and enantioselectivity (Table 1, entry 5). Ligand **5**, which possesses *tert*-butyl groups instead of the cyclohexyl groups of the original josiphos ligand **3**, displayed a similar reactivity but yielded the product **2a** with a lower enantiomeric excess (Table 1, entry 6). It is of note that ligand **3** was also highly effective for the reduction of (*Z*)-**1a**, thus affording **2a** in 91% yield and with 99% *ee* (Table 1, entry 8). The reduction of the *E* and *Z* isomers resulted in the formation of opposite enantiomers.

With an established, optimal protocol using ligand **3**, the conjugate reduction of different β-aryl-substituted α,β-unsaturated nitriles was examined, and the results are summarized in Table 2. In general, the reduction of the substrates occurred smoothly at 0°C to give the corresponding chiral saturated nitriles in good yields and with high enantioselectivities. The reduction of Cl- and CH_3-substituted aromatic unsaturated nitriles provides the respective saturated nitrile products in good yield and with high enantiomeric excess (Table 2, entries 1–3). Bulky alkyl substituents (Et, *i*Pr) at the β-position of the nitrile did not affect the efficiency of the process, thus affording reduced products **2d** and **2e** in 98 and 99% *ee*, respectively (Table 2, entries 4 and 5). The substrate **1f** with the phenyl ring substituted at the *ortho* position was reduced with high enantioselectivity as well (Table 2, entry 6). However, the level of enantioselectivity (65% *ee*) obtained with a heteroaromatic pyridyl substrate **1g** was significantly lower than that of the analogous phenyl derivative (Table 2, entry 7). It is presumed that the steric change at the *ortho* position of the aromatic counterpart is the main reason for the lower enantiomeric excess.

Table 2: Enantioselective conjugate reduction of α,β-unsaturated nitriles.[a]

Entry	Substrate	Ligand	*t* [h]	Yield [%][b]	*ee* [%][c]
1	 (*E*)-**1b**	(*S*,*R*)-**3**	23	92	97
2	 (*E*)-**1b**	(*R*,*S*)-**5**	23	98	94
3	 (*E*)-**1c**	(*S*,*R*)-**3**	21	91	95 (*S*)
4	 (*E*)-**1d**	(*S*,*R*)-**3**	12	88	98
5	 (*Z*)-**1e**	(*S*,*R*)-**3**	10	81	99
6	 (*E*)-**1f**	(*R*,*S*)-**3**	10	92	98
7	 (*E*)-**1g**	(*S*,*R*)-**3**	8.5	96	65

[a] Reaction conditions: $Cu(OAc)_2$ (3 mol%), ligand (3 mol%), PMHS (4 equiv), and *t*BuOH (4 equiv) in toluene at 0°C. [b] Yield of the isolated product. [c] Determined by chiral HPLC.

Currently, we presume that a bisphosphine-ligated copper(I) hydride species is the active catalytic species and that silanes[15] effect the generation of copper(I) hydride from the Cu^{II} precursor. The active copper hydride species reacts with a α,β-unsaturated nitrile to form a new organocopper species, and the intermediate undergoes rapid deprotonation by *t*BuOH to yield the chiral protonated product and a copper alkoxide. The latter then regenerates the active copper hydride catalyst with PMHS.

In summary, we have shown that a highly enantioselective reduction of α,β-unsaturated nitriles can be conducted by using a $Cu(OAc)_2$/josiphos complex as the catalyst under hydrosilylation conditions. This reaction provides access to valuable β-aryl-substituted chiral nitriles in good yields and with excellent enantioselectivities by employing a bench-top stable catalytic precursor and a readily available, commercial bisphosphine ligand. Studies are underway to establish the full scope of this methodology.

Experimental Section

General procedure for the conjugate reduction of α,β-unsaturated nitriles: $Cu(OAc)_2$ (2.72 mg, 0.015 mmol) and ligand (0.015 mmol) were placed in an oven-dried Schlenk tube, and PMHS (0.12 mL, 2 mmol) and toluene (0.5 mL) were added under nitrogen. The reaction mixture was stirred for 5 min at 0°C and then α,β-unsaturated nitrile (0.5 mmol) was added, followed by *t*BuOH (0.19 mL, 2.0 mmol). The reaction tube was washed with toluene (0.5 mL) and sealed, and the reaction mixture was stirred until no starting material was detected by TLC analysis. The reaction mixture was quenched with water and transferred into a round-bottom flask with the 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 chromatography on silica gel or Kugelrohr distillation.

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[15] Silanes, such as $PhSiH_3$, Ph_2SiH_2, and PMHS, were effective for the activation of the copper precursor, although alkyl silanes were less effective.

