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Copper-Catalyzed Asymmetric Reduction of 3,3-Diarylacrylonitriles

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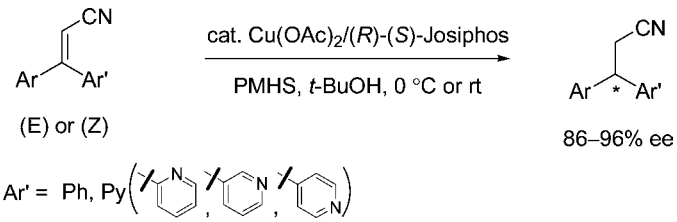
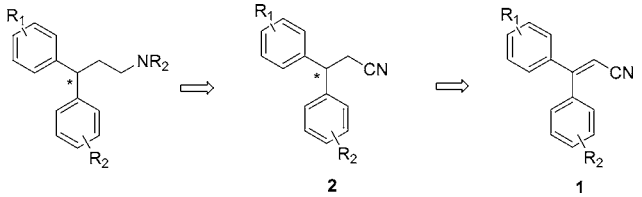
ABSTRACT



CuH-catalyzed enantioselective conjugate reduction of 3,3-diaryl-substituted acrylonitriles is described. A range of 3-aryl-3-pyridylacrylonitriles were reduced with high levels of enantioselectivity under optimal conditions employing a copper/Josiphos complex in the presence of polymethylhydrosiloxane (PMHS).

The 3,3-diarylpropylamine moiety is an important structural motif in many biologically active compounds and pharmaceutical agents (Scheme 1).[1] In view of the fact that the marketing of single enantiomers is becoming more popular,[2] the development of efficient enantioselective preparation methods of such building blocks is of great importance. A convenient route to 3,3-diarylpropylamines would be the enantioselective reduction of diaryl-substituted alkenyl substrates. However, β,β-diaryl-substituted alkenyl substrates have received little attention as the starting materials among a number of alkenyl substrates with various substitution patterns in asymmetric reductions.[3] This is presumably because low enantioselectivity is generally expected from the small steric difference between two aryl substituents and because steric congestion of the aryl groups influences activity of the catalysts. Only a few reports[4] appeared in the field of Rh- and Ru-catalyzed asymmetric hydrogenation that required an additional coordinating functionality to the metal of catalysts such as carbonyl,[4a] alcohol,[4b] and pyridyl[4c] for catalyst reactivity and enantioselectivity.

Scheme 1



Copper hydride (Cu-H) ligated by nonracemic ligands has been shown to be a powerful reagent for effecting asym-

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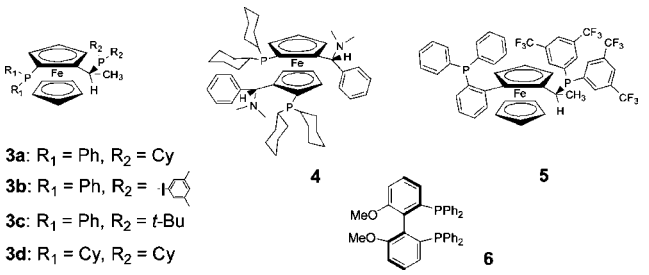
metric reductions of aryl ketones,[5] imines,[6] enones,[7] α,β-unsaturated esters,[8] nitroalkenes,[9] and α,β-unsaturated nitriles.[10] We envisioned that an asymmetric conjugate reduction of 3,3-diaryl-substituted acrylonitriles via copper hydride catalysis would be an unique and attractive route to 3,3-diarylpropionitriles and thus to 3,3-diarylpropylamines. Since the nitrile group prefers end-on coordination to a metal, most asymmetric hydrogenation catalysts are not generally competent. One report has been recently made on the enantioselective reduction of 3-aryl-3-pyridyl-α,β-unsaturated nitriles catalyzed by Ru−phosphine complexes.[4c] However, only substrates with a suitable secondary coordinating atom were reactive under high hydrogen pressure. In this reprot, we describe a copper-catalyzed enantioselective conjugate reduction of 3,3-diarylacrylonitriles that efficiently occurs with high levels of enantioselectivity. The substrate scope of this reaction includes 3,3-diaryl-substituted unsaturated substrates having no secondary coordinating functional groups and this is, to the best of our knowledge, the first example of the enantioselective reduction of such compounds.

We prepared (*E*)-3-phenyl-3-(pyridin-2-yl)acrylonitrile (**1a**) as the starting material. The aryl(pyridyl)propionitriles resulting from this type of substrate constitute a characteristic feature of H_1 antihistaminic agents, pheniramines,[11] and the potent histamine H_2 agonist, arpromidine and its analogues (Figure 1).[12] In initial studies on the reduction of (*E*)-**1a** with 3 mol % of $Cu(OAc)_2$ in the presence of excess PMHS, we screened various chiral ligands (Table 1). To our delight, with Josiphos-type ligands (**3a**−**d**),[13] the reaction proceeded



smoothly to yield the desired product (entries 1−4). In particular, the Josiphos ligand (**3a**) afforded the reduced

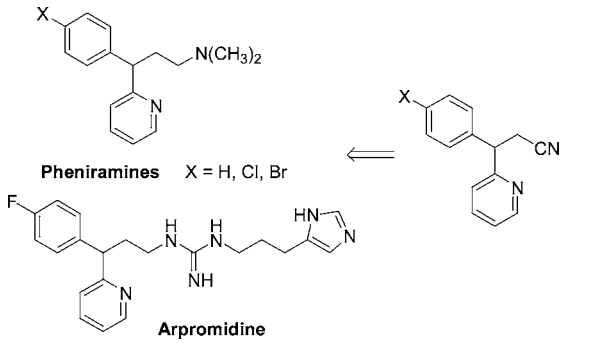
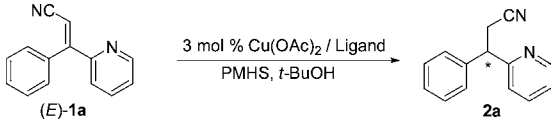


Figure 1. Structures of pheniramines and arpromidine.

product **2a** of very high ee (96% ee; Table 1, entry 1). Reductions with Mandyphos ((*R*)-(*S*)-**4**; entry 5) and Walphos-type ligand ((*R*)-(*S*)-**5**; entry 6) were very slow,

Table 1. Asymmetric Conjugate Reduction of (*E*)-**1a** with Various Ligands



entry	ligand	temp (°C)	concn (M)	time (h)	yield (%)	ee (%)[a]
1	**3a** (Josiphos)	**0**	**0.5**	**17**	**90**	**96**
2	**3b**	0	0.5	12	70	86
3	**3c**	0	0.5	24	70	65
4	**3d**	0	0.5	24	78	53
5	**4**	0	0.5	60	66	18
6	**5**	0	0.5	60	87	94
7	**6**	0	0.5	24	70	37
8[b]	**3a**	**rt**	**0.5**	**4**	**86**	**92**
9	**3a**	0	1	17	91	95

[a] Determined by chiral HPLC. [b] rt = ~ 22 °C.

although the latter ligand gave good enantioselectivity. The C_2-symmetric (*R*)-Ph-MeOBiphep ligand (**6**; entry 7) showed poor enantioselectivity. We chose Josiphos as the chiral ligand for further investigation. Increasing reaction temperature to room temperature resulted in a small drop in ee (entry 8) with an increase of reaction rate, and conducting the reduction of **1a** at a higher substrate concentration had no significant effect on the enantioselectivity (entry 9).

Next, we examined the asymmetric reductions of several substrates by employing a catalytic amount of $Cu(OAc)_2$ and **3a** in toluene in the presence of PMHS and *t*-BuOH (Table 2). In general, most of the reactions proceeded to completion within 1−4 h at room temperature to furnish diaryl products in good ee and yields. Both (*E*)- and (*Z*)-isomers (**1d**, **1e**, and **1g**) were reduced smoothly, affording the product in the opposite configuration.[14]

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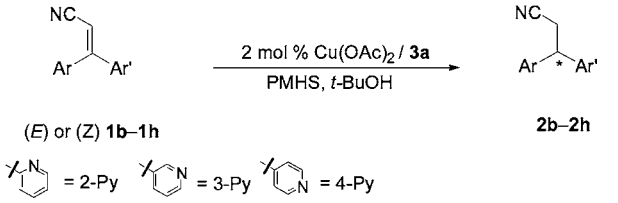
Table 2. Enantioselective Reduction of 3,3-Diarylacrylonitriles[a]



entry	substrate	Ar	Ar′	temp (°C)[b]	time (h)	yield (%)[c]	ee (%)[d]
1	(*E*)-**1b**:	3,4-F_2-Ph	2-Py	0	18	87	84 (*S*)
2	(*E*)-**1b**			**rt**	2	95	**91** (*S*)
3	(*E*)-**1b**			40	1	90	84 (*S*)
4	(*E*)-**1c**:	4-Cl-Ph	2-Py	0	30	91	79
5	(*E*)-**1c**			**rt**	2	89	**93**
6	(*E*)-**1c**			40	1	92	89
7	(*E*)-**1c**			60	45 min	87	85
8	(*E*)-**1d**	4-MeO-Ph	2-Py	rt	3	93	95
9	(*Z*)-**1d**	2-Py	4-MeO-Ph	rt	4	97	62
10	(*E*)-**1e**:	*o*-tolyl	2-Py	rt	1	83	86
11	(*Z*)-**1e**	2-Py	*o*-tolyl	0	9	86	95
12	(*Z*)-**1e**			rt	1	85	87
13	(*E*)-**1f**	Ph	3-Py	rt	4	92	96
14	(*E*)-**1g**	Ph	4-Py	rt	1	86	90
15	(*Z*)-**1g**	4-Py	Ph	rt	1	87	92
16	(*E*)-**1h**	Ph	*p*-tolyl	rt	1	94	94

[a] Reaction conditions: $Cu(OAc)_2$ (2 mol %), (*R*)-(*S*)-Josiphos (**3a**) (2 mol %), PMHS (4 equiv), and *t*-BuOH (4 equiv) were used unless otherwise noted. [Substrate] = 0.5 M. [b] rt = ~22 °C. [c] Yield of the isolated product. [d] Determined by chiral HPLC.

Intriguingly, the ee values of the nitrile substrates (**1b**, **1c**) bearing halogen substituents at the para and meta position of the phenyl ring were highly sensitive to reaction temperature. With these substrates, higher levels of enantioselectivities were observed when the reactions were carried out at room temperature rather than at 0 °C (entries 1−3 and 4−7). This trend is in contrast to the observed results with (*E*)-**1a** (entries 1 and 8, Table 1) and (*Z*)-**1e** (entries 11 and 12, Table 2), in cases where cooling the reaction increased the selectivity. To examine further a temperature effect on the enantioselectivity, we carried out reductions of the two substrates **1b** and **1c** at higher temperatures. Increasing the reaction temperature had a negative effect on enantioselectivity in both cases, providing **1b** in 84% ee at 40 °C (entry 3), and **2c** in 89% ee at 40 °C (etnry 6) and in 85% ee at 60 °C (entry 7). The results show the existence of the inversion temperature (T_{inv})[15] for both **1b** and **1c** around room temperature.[16]

To see whether the 2-pyridyl group is a requisite for the reactivity and good enantioselectivity of the reduction, we prepared substrates **1f** and **1g** that possess the 3-pyridyl and 4-pyridyl group, respectively. The compounds were reduced with high levels of enantioselectivities as well (90−96% ee; entries 13−15), showing that the position of the N-atom of the pyridyl substituent is not crucial to high enantioselectivity. These results also indicate that an additional coordination site is not a requirement for reaction conversion in the copper hydride catalysis. Given the similar sterics of the phenyl and 3-/4-pyridyl substituent around the C=C bond, this level of enantioselectivity was rather unexpected. Encouraged by these results, we carried out the conjugate reduction of (*E*)-3-phenyl-3-*p*-tolylacrylonitrile (**1h**). The desired product was obtained in 94% ee in high yield again (entry 16).

In summary, we have developed a copper-catalyzed asymmetric reduction of 3,3-diarylacrylonitriles that provides ready access to optically active 3,3-diarylpropionitriles and thus to 3,3-diarylpropylamines. A range of 3-aryl-3-pyridylacrylonitriles were reduced with high degrees of enantioselectivity over 90% ee under optimal conditions employing a copper/Josiphos complex in the presence of hydrosilane. Some of the reduction examples showed an interesting inverse temperature dependence of the enantioselectivity. Current efforts are focused on exploring the scope of this method and the temperature dependence of enantioselectivity in more detail.

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

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(14) Judged by comparison of the retention time of each enantiomer on HPLC.

(15) T_{inv} is the temperature at which two distinct linear regions intercept in the Eyring graph: (a) Eyring, H. *J. Chem. Phy.* **1935**, *3*, 107. For other recent examples of inverse temperature dependence in asymmetric catalysis, see: (b) Fontes, M.; Verdaguer, X.; Solà, L.; Pericàs, M. A.; Riera, A. *J. Org. Chem.* **2004**, *69*, 2532. (c) Reboule, I.; Gil, R.; Collin, J. *Tetrahedron*: *Asymmetry* **2005**, *16*, 3881. (d) Haag, D.; Runsink, J.; Scharf, H.-D. *Organometallics* **1998**, *17*, 398. (e) Muzart, J.; Hénin, F.; Aboulhoda, S. J. *Tetrahedron*: *Asymmetry* **1997**, *8*, 381.

(16) See the Supporting Information for the Eyring diagram for the reduction of (*E*)-**1c**, although more detailed studies are needed to obtain the exact T_{inv} for **1b** and **1c**.