Copper Hydride Catalyzed Enantioselective Conjugate Reduction of Unsaturated Nitriles

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Abstract: \(\alpha,\beta\)-Unsaturated nitriles were reduced with high levels of enantioselectivity via copper hydride catalysis. In this procedure, bench-top stable copper(II) acetate and Josiphos ligand are used as the chiral catalyst and an inexpensive hydrosilane, polymethylhydrosiloxane (PMHS) is employed as the stoichiometric reducing agent. While the reactions are conducted at 0 °C in most cases, they also can be conducted at room temperature at enhanced rates with no significant drop in enantiomeric excess.

Key words: asymmetric catalysis, copper hydride, hydrosilanes, reduction, \(\alpha,\beta\)-unsaturated nitriles

Introduction

Enantiomerically enriched nitrile compounds with a \(\beta\)-stereocenter are valuable intermediates in organic synthesis\(^1\) and the nitrile group is a versatile functional group that can be transformed into other useful functionalities. The selective reduction of conjugated nitriles to their saturated counterparts has long been a synthetic problem.\(^2\) Recently, we have reported that the combination of copper(II) acetate and a chelating diphosphine is effective for the catalytic conjugate reduction of \(\alpha,\beta\)-unsaturated nitriles.\(^3\) The method reduces a range of \(\alpha,\beta\)-unsaturated nitriles including \(\beta,\beta\)-disubstituted substrates in good yields and displays good functional group tolerance.\(^3\) Based on these results, we have developed an enantioselective reduction of \(\alpha,\beta\)-unsaturated nitriles by employing copper(II) acetate as the precatalyst and Josiphos as the chiral ligand.\(^4\) This reaction provides \(\beta\)-chiral nitriles in good yields and with excellent enantioselectivities.

Scope and Limitations

The enantioselective reduction was optimized using \((E)\)-3-phenylbut-2-enenitrile (1a) as the starting material. The use of Josiphos\(^5\) as the chiral ligand was essential for a high level of enantiomeric excess (procedure 1, Scheme 1). \(C_2\)-Symmetric binaphthyl-based bisphosphine ligands, such as (S)-BINAP\(^6\) and (R)-\(p\)-Tol-BINAP,\(^7\) were not effective for the reduction, yielding the desired product 2a with only modest enantiomeric excess (65% ee). Other structurally related Josiphos-type ligands such as (R)-(S)-PPF-Pr-Bu\(^8\) and (R)-(S)-Cy\(_2\)PF-PCy\(_2\)\(^9\) were less enantioselective than Josiphos. While the reduction could...
be conducted either at 0 °C or at room temperature, the reaction proceeded at faster rates at room temperature with little change in enantiomeric excess (98% ee vs 97% ee). The inexpensive polymeric hydrosilane, polymethylhydrosiloxane (PMHS) was employed as the stoichiometric reducing agent for the reduction although monomeric diphenylsilane or phenylsilane could be used without affecting reactivity and enantioselectivity.

β,β-Disubstituted α,β-unsaturated nitriles (1a–f, 3) reacted to yield the corresponding saturated nitriles (2a–f, 4) in good yield and with excellent enantioselectivity (Table 1). Both the E- and Z-isomers of 1a and 1f were readily reduced to form the opposite enantiomers. Nitrile

Table 1

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Temp (°C)</th>
<th>Time (h)</th>
<th>Yield (%)</th>
<th>ee (%)</th>
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<td>5</td>
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<td>98 (R)</td>
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<tr>
<td>2</td>
<td></td>
<td>r.t.</td>
<td>1</td>
<td>91</td>
<td>97 (R)</td>
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<td>0</td>
<td>4.5</td>
<td>91</td>
<td>99</td>
</tr>
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<td>4d</td>
<td></td>
<td>0</td>
<td>23</td>
<td>92</td>
<td>97</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>r.t.</td>
<td>2</td>
<td>88</td>
<td>96</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>r.t.</td>
<td>1</td>
<td>92</td>
<td>94 (R)</td>
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<tr>
<td>7</td>
<td></td>
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<td>13</td>
<td>88</td>
<td>98</td>
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<tr>
<td>8</td>
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<td>2</td>
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<td>97</td>
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<tr>
<td>9d</td>
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<td>0</td>
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<td>8</td>
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<td>&gt;99</td>
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<tr>
<td>12e</td>
<td></td>
<td>r.t.</td>
<td>1</td>
<td>88</td>
<td>92</td>
</tr>
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</table>

a Reaction conditions: Cu(OAc)₂ (3 mol%), (R)-(S)-Josiphos·EtOH (3 mol %), PMHS (4 equiv), t-BuOH (4 equiv) in toluene.
b Yield of isolated product.
c Determined by chiral HPLC.
d (S)-(R)-Josiphos was used as ligand.
e 2 mol% each of Cu(OAc)₂ and (R)-(S)-PPF-P(t-Bu)₂ ligand were used.
substrates (1d, 1e) that possess bulkier alkyl substituents (Et, i-Pr) than methyl were also suitable substrates for the reaction (entries 7–9). The substrate 3 with a 2-pyridyl substituent at the β-position was reduced with high enantioselectivity (92% ee) by employing (R)-(S)-PPF-P(t-Bu)₃ as the chiral ligand (entry 12).

In summary, the enantioselective reduction of α,β-unsaturated nitriles is conducted by using a copper(II) acetate/Josiphos complex under hydrosilylation conditions. The resulting β-chiral nitriles are valuable building blocks in organic synthesis.

Procedures

Herein, we describe two typical procedures for the enantioselective reduction of α,β-unsaturated nitriles depicted in Scheme 1 and Table 1. Both procedures describe reactions conducted at room temperature and Procedure 2 uses the ligand PPF-P(t-Bu)₃ instead of Josiphos for the reduction of (E)-3. Except for these two facts, the procedures described here are almost the same as the one previously reported.⁴

Cu(OAc)₂, hydrosilanes, and other commercial substrates were purchased and used as received and toluene was distilled under N₂ from Na/Benzophenone ketyl. NMR spectra were obtained on Varian Mercury 400 systems with TMS as internal standard. ¹H NMR spectra used CDCl₃ as internal standard (δ 7.27). IR spectra were obtained on a Nicolet 205 FT-IR instrument. HPLC analysis was performed on a Younglin Acme 9000 series. Low resolution MS were recorded using a Varian 4000 GC/MS. Flash chromatography was performed on silica gel from Merck (70–230 mesh).

Procedure 1

(R)-3-Phenylbutanenitrile (2a)⁶

Typical Procedure
Cu(OAc)₂ (2.72 mg, 0.015 mmol) and (R)-(S)-Josiphos·EtOH (9.60 mg, 0.015 mmol) were placed in an oven-dried Schlenk tube. The tube was evacuated and backfilled with N₂ and then capped with a rubber septum. PMHS (0.12 mL, 2.0 mmol) and toluene (0.5 mL) were added via syringe and the mixture was stirred at r.t. for 15 min. The unsaturated nitrile (E)-1a (72 mg, 0.50 mmol) was added, followed by t-BuOH (0.19 mL, 2.0 mmol). The reaction tube was washed with toluene (0.5 mL), sealed with a Teflon screwcap, and stirred until the starting material was completely consumed as judged by TLC. The mixture was quenched with H₂O and transferred to a round-bottomed flask with the aid of Et₂O (10 mL), and 2.5 M NaOH (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 Et₂O (3 × 20 mL) and concentrated. The combined organic layers were washed with water, dried (MgSO₄), and concentrated. The crude product was purified by column chromatography (hexanes–EtOAc, 1:1) to give 2a (66.0 mg, 91%); 97% ee, chiral HPLC (OD-H column, i-ProH–hexane 10:90, 0.5 mL/min; t₁₈ = 18.0 min (major isomer) and 18.2 min (minor isomer).

Acknowledgment

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References


(6) BINAP = 2,2’-bis(diphenylphosphino)-1,1’-binaphthalene.

(7) p-Tol-BINAP = 2,2’-bis(di-4-tolylphosphino)-1,1’-binaphthalene.


(9) (R)-(S)-Cy₂PF-PC₁₆ = dicyclohexyl{(R)-(S)-2-(dicyclohexylphosphino)ferrocenyl]ethyl}phosphine.