Chiral ferrocenyl phosphine-phosphoramidite ligands for Cu-catalyzed asymmetric conjugate reduction of \(\alpha,\beta\)-unsaturated esters

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Abstract

Unsymmetrical hybrid chiral ferrocenyl phosphine-phosphoramidite ligands have been applied for the first time in the Cu-catalyzed asymmetric 1,4-reduction of \(\beta\)-aryl substituted \(\alpha,\beta\)-unsaturated esters. The results show that the ligand bearing (\(S_a\))-central, (\(R_p\))-planar, and (\(R_a\))-axial chiralities gave the best performance. The present catalytic system proved to be highly substrate-dependent, catalyzing the conjugate reduction of \(\alpha,\beta\)-unsaturated esters in moderate to excellent enantioselectivities.

1. Introduction

The catalytic asymmetric 1,4-reduction of \(\alpha,\beta\)-unsaturated compounds is an important method for the construction of tertiary stereogenic centers in organic synthesis. In the past decades, significant progress has been made in the development of efficient and economic protocols for achieving this transformation with substantial emphasis on the use of transition metal catalysts, of which copper hydride complexes ligated by non-racemic ligands have arguably demonstrated the greatest synthetic utility.\(^1\) In 1999, Buchwald et al. reported for the first time that a catalyst formed from p-tol-BINAP, CuCl, and NaO-t-Bu could affect the asymmetric conjugate reduction of \(\alpha,\beta\)-unsaturated esters in the presence of 4 equiv of polymethylhydrosiloxane (PMHS) relative to the substrate.\(^2\) Since then, a series of \(\alpha,\beta\)-unsaturated compounds (i.e., enones, \(^3\) \(\alpha,\beta\)-unsaturated esters, \(^2,4\) \(\alpha,\beta\)-unsaturated phosphonates, \(^5\) \(\alpha,\beta\)-unsaturated lactones and lactams, \(^6\) \(\alpha,\beta\)-unsaturated sulfones, \(^7\) \(\alpha,\beta\)-unsaturated nitrile, \(^8\) nitroalkenes, and \(^9\) 2-alkenylheteroarenes)\(^10\) has been subjected to the 1,4-reduction with the Cu/diphosphine catalytic system, giving the reduction products with excellent enantioselectivities. Despite these achievements, chiral ligands employed in the Cu-catalyzed asymmetric 1,4-reduction remain very limited, and only a few diphosphine ligand types, such as BINAP, BIPHEP, SEGPHOS, JosiPhos, and Taniaphos, have been found to be efficient for this important transformation. The search for new chiral ligands for the Cu-catalyzed asymmetric 1,4-reduction is, therefore, of great interest.

Recently, we and some other groups developed a series of unsymmetrical hybrid chiral phosphine-phosphoramidite ligands.\(^11\) These ligands have the advantages of easy accessibility, modularity, and stability toward air and moisture, which make them highly practical for both academic and industrial applications. Indeed, these ligands have been found to display wide utility in asymmetric catalysis, and give excellent results in Rh-catalyzed asymmetric hydroformylations,\(^13\) Pd-catalyzed asymmetric allylic alkylation,\(^14\) Cu-catalyzed asymmetric conjugate additions of diethylzinc to enones\(^15\) and Ag-catalyzed [3+2] cycloadditions of azomethine ylides with dimethyl maleate.\(^16\) To the best of our knowledge, however, there is no reported example of an asymmetric conjugate reduction with a phosphine-phosphoramidite ligand. Herein, we report our investigation on the use of a Cu/ferrocenyl phosphine-phosphoramidite catalytic system in the asymmetric 1,4-reduction of \(\alpha,\beta\)-unsaturated esters, in which up to 99% ee was obtained although this reduction was found to be highly substrate-dependent.

2. Results and discussion

As we have reported, these chiral ferrocene-based phosphine-phosphoramidite ligands (PPFAPhos) can be easily prepared from Ugi’s amine through a modular procedure.\(^12c\) With these ligands in hand (Fig. 1), we then examined their efficiency in the Cu-catalyzed asymmetric conjugate reduction of \(\alpha,\beta\)-unsaturated esters. Ethyl (\(E\))-3-phenylbut-2-enoate \(2a\) was selected as a model substrate for the screening process, and the results are summarized in Table 1. Initially, we examined a range of chiral ferrocenyl phosphine-phosphoramidite ligands for effecting the conjugate reduction of (\(E\))-3-phenylbut-2-enoate \(2a\) with polymethylhydrosiloxane (PMHS) under catalytic conditions: Cu(OAc)\(_2\)-H\(_2\)O (5 mol %), ligand (6 mol %), and t-BuOH (4 equiv) in THF for 24 h. At first we tested (\(S_a,R_p,S_a\))-PPFAPhos, which was found to possess the matched chiralities and display the best performance in the

\[ \text{Cu(OAc)}_2\cdot\text{H}_2\text{O} \quad \text{ligand} \quad \text{t-BuOH} \quad \text{THF} \]

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Rh−catalyzed asymmetric hydrogenation of various functionalized olefins.16 However, only low enantioselectivity was achieved although full conversions were observed (entry 1). Since the absolute configuration of a chiral ligand normally affects the catalytic activity and enantioselectivity, we then investigated the efficiency of the diastereomeric ligands 1b−d of (S,R,R,S)-1a in this transformation. In most cases, the reduction proceeded very slowly, giving only low enantioselectivity (entries 3 and 4). However, ligand 1b, which holds (S,R,R,R)-central, (R,S)-planar, and (R,R)-axial chiralities, gave an ee-value of 79% and full conversion (entry 2). The introduction of a stereogenic P-donor atom into (S,R,R,R)-1b resulted in significantly decreased conversion and enantioselectivity (entry 5). An optimization study with (S,R,R,R)-1b revealed that copper salts, such as CuCl and CuF(PPh3)3, 2MeOH, gave similar results (entries 6 and 7), but CuF(PPh3)3, 2MeOH was slightly superior to CuCl with respect to the selectivity (entry 7). Silanes significantly affected the reactivity and enantioselectivity, and the best results were achieved with PMHS (entries 7−11). It is noteworthy that PhSiH2 resulted in significantly decreased conversion and enantioselectivity, which is different from most other hydrosilylation reactions reported so far.6,17 For further reaction optimization, the solvent effect was also investigated (entries 12−14). The best result was obtained with a THF as solvent (entry 7).

With the optimal catalyst combination and reaction conditions in hand, the scope of the reduction of a series of β-aryl substituted α,β-unsaturated esters was then investigated, and the results are summarized in Table 2. The results disclosed that the ester functional group had an important influence on the reactivity and enantioselectivity. Thus, a modest change from an ethyl ester 2a to a methyl ester 2b led to greatly decreased enantioselectivities.
Table 2
Cu-catalyzed asymmetric 1,4-reduction of β-aryl substituted α,β-unsaturated esters 2 with (S,R,R)-PFFPAPlus 1b

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate (R1, R2)</th>
<th>Conversion (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2a (Ph, Me, Et)</td>
<td>100 (95)</td>
<td>82 (5)</td>
</tr>
<tr>
<td>2</td>
<td>2b (Ph, Me, Me)</td>
<td>100</td>
<td>44 (5)</td>
</tr>
<tr>
<td>3</td>
<td>2c (Ph, 1-Pr, Et)</td>
<td>55</td>
<td>50 (5)</td>
</tr>
<tr>
<td>4</td>
<td>2d (Ph, Me, t-Bu)</td>
<td>61</td>
<td>38 (5)</td>
</tr>
<tr>
<td>5</td>
<td>2e (Ph, Et, Et)</td>
<td>100</td>
<td>86 (5)</td>
</tr>
<tr>
<td>6</td>
<td>2f (Ph, t-Pr, Et)</td>
<td>93</td>
<td>81 (+)</td>
</tr>
<tr>
<td>7</td>
<td>2g (4-CH3C6H4, Me, Et)</td>
<td>75</td>
<td>77 (5)</td>
</tr>
<tr>
<td>8</td>
<td>2h (4-CH3OC6H4, Me, Et)</td>
<td>87</td>
<td>76 (+)</td>
</tr>
<tr>
<td>9</td>
<td>2i (4-CIC6H4, Me, Et)</td>
<td>100</td>
<td>&gt;99 (+)</td>
</tr>
<tr>
<td>10</td>
<td>2j (4-Buc6H4, Me, Et)</td>
<td>100</td>
<td>97 (+)</td>
</tr>
<tr>
<td>11</td>
<td>2k (4-NO2C6H4, Me, Et)</td>
<td>100</td>
<td>80 (+)</td>
</tr>
<tr>
<td>12</td>
<td>2l (3-NO2C6H4, Me, Et)</td>
<td>40</td>
<td>89 (+)</td>
</tr>
<tr>
<td>13</td>
<td>2m (2-thienyl, Me, Et)</td>
<td>88</td>
<td>83 (+)</td>
</tr>
</tbody>
</table>

* Reaction conditions: substrate 2 (0.25 mmol), CuF(PPh3)3·2MeOH (5 mol %), (S,R,R)-1b (6 mol %), PMHS (4 equiv), t-BuOH (4 equiv) in THF at room temperature for 24 h.
* Degrees of conversion were determined by 1H NMR.
* Isolated yield in parentheses.

(1) The ee values were determined by HPLC on a chiral column (Chiralcel OD-H, chiralcel OD-H column; flow rate: 0.5 mL/min; eluent: hexane/i-PrOH (99.5:0.5); detection at 210 nm; t1 = 11.93 min, t2 = 22.87 min; ee = 82%.

4. General

4.1. Ethyl (S)-3-phenylbutanoate 3a

1H NMR (400 MHz, CDCl3): δ 1.18 (t, J = 7.1 Hz, 3H), 1.30 (d, J = 7.0 Hz, 3H), 2.52–2.64 (m, 2H), 3.25–3.29 (m, 1H), 4.07 (q, J = 7.1 Hz, 2H), 7.19–7.23 (m, 3H), 7.28–7.31 (m, 2H), [α]D = +9.3 (c 1.43, CHCl3). HPLC analysis: chiralcel OD-H column; flow rate: 0.5 mL/min; eluent: hexane/i-PrOH (99.5:0.5); detection at 210 nm; t1 = 11.93 min, t2 = 22.87 min; ee = 82%.

4.2. Methyl (S)-3-phenylbutanoate 3b

1H NMR (400 MHz, CDCl3): δ 1.30 (d, J = 7.0 Hz, 3H), 2.52–2.66 (m, 2H), 3.25–3.31 (m, 1H), 3.67 (s, 3H), 7.18–7.23 (m, 3H), 7.28–7.32 (m, 2H), [α]D = +7.3 (c 1.36, CHCl3). HPLC analysis: chiralcel OD-H column; flow rate: 0.5 mL/min; eluent: hexane/i-PrOH (99.5:0.5); detection at 215 nm; t1 = 11.97 min, t2 = 23.15 min; ee = 44%.

4.2. iso-Propyl (S)-3-phenylbutanoate 3c

1H NMR (400 MHz, CDCl3): δ 1.12 (d, J = 6.2 Hz, 3H), 1.17 (d, J = 6.2 Hz, 3H), 1.30 (d, J = 6.9 Hz, 3H), 2.50–2.61 (m, 2H), 3.24–3.27 (m, 1H), 4.93–4.96 (m, 1H), 7.17–7.21 (m, 3H), 7.26–7.31 (m, 2H), [α]D = +5.2 (c 1.28, CHCl3). HPLC analysis: chiralcel OD-H column; flow rate: 0.5 mL/min; eluent: hexane/i-PrOH (99.5:0.5); detection at 215 nm; t1 = 9.20 min, t2 = 10.29 min; ee = 50%.

4.2. tert-Butyl (S)-3-phenylbutanoate 3d

1H NMR (500 MHz, CDCl3): δ 1.28 (d, J = 7.0 Hz, 3H), 1.35 (s, 9H), 2.45 (dd, J = 7.3, 14.7 Hz, 1H), 2.52 (dd, J = 8.1, 14.7 Hz, 1H),
2H).

4.2.12. Ethyl (+)-3-(3-nitrophenyl)butanoate 3l

4.2.6. Ethyl (+)-4-methyl-3-phenylpentanoate 3f

4.2.7. Ethyl (S)-3-(4-methylphenyl)butanoate 3e

4.2.8. Ethyl (S)-3-(4-chlorophenyl)butanoate 3d

4.2.10. Ethyl (S)-3-(4-bromophenyl)butanoate 3c

4.2.11. Ethyl (S)-3-(4-nitrophenyl)butanoate 3b

4.2.12. Ethyl (S)-3-(3-nitrophenyl)butanoate 3a

References


Acknowledgments

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