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Bos, Pieter H.; Macia, Beatriz; Fernandez-Ibanez, M. Angeles; Minnaard, Adriaan J.; Feringa, Ben L.

Published in:
Organic & Biomolecular Chemistry

DOI:
10.1039/b917269f

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Document Version
Publisher's PDF, also known as Version of record

Publication date:
2010

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):
Catalytic asymmetric conjugate addition of dialkylzinc reagents to \(\alpha,\beta\)-unsaturated sulfones†

Pieter H. Bos, Beatriz Maciá, M. Ángeles Fernández-Ibáñez, Adriaan J. Minnaard and Ben L. Feringa*

Received 21st August 2009, Accepted 21st September 2009
First published as an Advance Article on the web 1st October 2009
DOI: 10.1039/b917269f

An efficient method is reported for the highly enantioselective copper-catalyzed conjugate addition of dialkylzinc reagents to \(\alpha,\beta\)-unsaturated sulfones using a monodentate phosphoramidite ligand.

The conjugate addition of organometallic reagents to \(\alpha,\beta\)-unsaturated compounds is one of the most versatile and widely used synthetic methods for carbon–carbon bond formation.† Enantioselective metal-catalyzed versions of this transformation are used as key-steps in the synthesis of numerous natural products and biologically active compounds and have been studied extensively over the past decade.‡

An important goal in extending the current methodology is the development of an enantioselective catalytic method for the addition of organometallic reagents to \(\alpha,\beta\)-unsaturated sulfones. Optically active sulfones with a stereocenter at the \(\beta\)-position are valuable intermediates in organic chemistry due to their ease of derivatization yielding a variety of building blocks, including aldehydes or ketones, alkenes, alkynes, alkanes and haloalkanes.¶

In 2007, Carretero et al.,§ and Charette and Desrosiers² both reported methodology for the catalytic asymmetric conjugate reduction of \(\beta,\beta\)-disubstituted \(\alpha,\beta\)-unsaturated sulfones leading to alkyl aryl sulfones. Using a hydroboration approach excellent yields and enantiomeric excesses were obtained.

A complementary approach to sulfones bearing \(\beta\) stereocenters is the asymmetric conjugate addition of organometallic reagents to \(\alpha,\beta\)-unsaturated sulfones. In 2004, Mauléon and Carretero reported a rhodium-catalyzed asymmetric conjugate addition of organoboronic acids to \(\alpha,\beta\)-unsaturated sulfones giving high to excellent yields and enantioselectivities.⁵

Recently, Charette et al. reported a method for the catalytic asymmetric conjugate addition of diorganozinc reagents to \(\beta\)-substituted vinyl sulfones using a bidentate phosphorus based ligand (Binap) and elevated temperatures (60 °C) with good results.⁷ Performing the reaction in benzene gave high yields and lower enantioselectivities while using THF gave an increase in ee, but lower yields. Our group recently developed a copper-catalyzed asymmetric conjugate addition of Grignard reagents to \(\alpha,\beta\)-unsaturated sulfones giving excellent results using a bidentate phosphorus based ligand (Tol-Binap) and aliphatic substrates.⁸

In this paper we describe the first asymmetric conjugate addition of diorganozinc reagents to \(\alpha,\beta\)-unsaturated sulfones using a monodentate phosphoramidite ligand (L1). Among all the ligands used so far in the field of copper-catalyzed conjugate addition of organometallic reagents, phosphoramidites stand out as readily accessible, inexpensive and easily modified.⁹ The excellent enantioselectivities that phosphoramidites give in the conjugate addition of dialkylzinc reagents to a variety of substrates have encouraged us to use them as ligands in the conjugate addition of diorganozinc reagents to \(\alpha,\beta\)-unsaturated sulfones.

Initially, we studied the addition of diethylzinc to \(\alpha,\beta\)-unsaturated sulfone 1a using phosphoramidite L1 (Fig. 1) at various temperatures and in different solvents (Table 1).

![Structure of ligand (S,R,R)-L1](image)

At −40 °C in toluene, full conversion was obtained after 3 days giving the product with excellent ee (entry 1). Upon increasing the reaction temperature full conversion was obtained in 24 h while the enantioselectivity remained excellent (entries 2–4). Upon direct addition of the substrate to the reaction mixture the enantiomeric

### Table 1 Optimization of solvent and temperature

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Temperature (°C)</th>
<th>Conversion (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>Toluene</td>
<td>−40</td>
<td>100 (72 h)</td>
</tr>
<tr>
<td>2a</td>
<td>Toluene</td>
<td>−25</td>
<td>100 (48 h)</td>
</tr>
<tr>
<td>3a</td>
<td>Toluene</td>
<td>−10</td>
<td>100 (24 h)</td>
</tr>
<tr>
<td>4a</td>
<td>Toluene</td>
<td>0</td>
<td>100 (24 h)</td>
</tr>
<tr>
<td>5a</td>
<td>Toluene</td>
<td>0</td>
<td>100 (24 h)</td>
</tr>
<tr>
<td>6a</td>
<td>THF</td>
<td>0</td>
<td>0 (24 h)</td>
</tr>
<tr>
<td>7a</td>
<td>Et₂O</td>
<td>0</td>
<td>25 (24 h)</td>
</tr>
<tr>
<td>8a</td>
<td>t-BuOMe</td>
<td>0</td>
<td>30 (24 h)</td>
</tr>
<tr>
<td>9a</td>
<td>DCM</td>
<td>0</td>
<td>12 (24 h)</td>
</tr>
</tbody>
</table>

*Conditions: 1 (1 equiv., 0.1 mmol), Et₂Zn (3.2 equiv.), Cu(OTf)₂ (5 mol%), (S,R,R)-L1 (10 mol%). Conversion determined by GC-MS. †Enantiomeric excess determined by chiral HPLC (See the ESI†). Determined by comparison with literature data based on the sign of optical rotation. °Slow addition of the substrate 1a over 5 h.

† Electronic supplementary information (ESI) available: General procedures for the synthesis of substrates and products; H and 13C NMR spectral data of all products. See DOI: 10.1039/b917269f
excess dropped only slightly (entry 5). Use of either ethereal solvents or DCM resulted in a large decrease in conversion (entries 6–9).

After optimization of reaction temperature and solvent the influence of the copper source was examined (Table 2).

The catalyst based on copper(II) triflate gave full conversion after 24 h and high enantiomeric excess. Changing the counterion of the copper source had a dramatic effect on the conversion after 24 h and high enantiomeric excess. Changing the counterion in influence of the copper source was examined (Table 2).

6–9). Solvents or DCM resulted in a large decrease in conversion (entries a–c).

In Table 2, the influence of the copper source on the conversion and enantiomeric excess was determined (Table 2). With the less reactive dimethylzinc no conversion was obtained after 24 h (entry 2). Di n-butylin gave less than 10% conversion after 24 h. Even after 5 days the conversion was not complete, nevertheless the product could be isolated in good yield and with moderate enantiomeric excess (entry 3). The more reactive disisopropylzinc gave full conversion after 24 h and both the isolated yield and enantiomeric excess dropped slightly compared with diethylzinc (entry 4). Unfortunately, the use of diphenylzinc did not give any reaction (entry 5).

Using optimized conditions we then studied the influence of the substituent pattern of the substrate on the conjugate addition of diethylzinc (Table 5). Because excellent results have been obtained using Grignard reagents on aliphatic substrates, we focused our efforts on a range of aromatic substrates for which excellent ee’s were found. Introduction of a chloride at the ortho position gave a drop in ee (entry 2). Moving the chloride further away from the phenyl gave good results.

Conditions: 1 (1 equiv., 0.1 mmol), Et2Zn (3.2 equiv.), Cu salt (5 mol%), (S,R,R)-L1 (10 mol%) in toluene at 0 °C. Conversion determined by GC-MS after 16 h. * Enantiomeric excess determined by chiral HPLC (See the ESI†). * Determined by comparison with literature data based on the sign of optical rotation.

\[ \begin{align*}
\text{Cu(Ot})_2 & \mid \text{Cu(OTf)}_2 & \mid \text{Cu} & \mid \text{CuCl} & \mid \text{CuBr} & \mid \text{CuOTf-benzene} \\
\text{Conversion}^a & \mid 100 & 0 & 5 & 40 & 85 \\
\text{ee}^d & \mid 88 & nd & nd & 85 & 83 \\
\end{align*} \]

* Conditions: 1 (1 equiv., 0.1 mmol), Et2Zn (3.2 equiv.), Cu salt (5 mol%), (S,R,R)-L1 (10 mol%) in toluene at 0 °C. Conversion determined by GC-MS after 16 h. * Enantiomeric excess determined by chiral HPLC (See the ESI†). * Determined by comparison with literature data based on the sign of optical rotation.

In this case 2-naphthyl substituted sulfone was used.

Table 5 Asymmetric conjugate addition of Et2Zn to α,β-unsaturated sulfones

<table>
<thead>
<tr>
<th>R</th>
<th>Product Yield(^{a}) (%)</th>
<th>ee(^d) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph</td>
<td>2a</td>
<td>70</td>
</tr>
<tr>
<td>o-Cl Phenyl</td>
<td>3a</td>
<td>85</td>
</tr>
<tr>
<td>m-Cl Phenyl</td>
<td>4a</td>
<td>66</td>
</tr>
<tr>
<td>p-Cl Phenyl</td>
<td>5a</td>
<td>68</td>
</tr>
<tr>
<td>p-Me Phenyl</td>
<td>6a</td>
<td>46</td>
</tr>
<tr>
<td>p-CF3 Phenyl</td>
<td>7a</td>
<td>84</td>
</tr>
<tr>
<td>p-i-Pr Phenyl</td>
<td>8a</td>
<td>52</td>
</tr>
<tr>
<td>p-Br Phenyl</td>
<td>9a</td>
<td>86</td>
</tr>
<tr>
<td>2-Naphthyl</td>
<td>10a</td>
<td>83</td>
</tr>
</tbody>
</table>

* Conditions: 1 (1 equiv., 0.25 mmol), Et2Zn (3.2 equiv.), Cu(OTf)2 (7.5 mol%), (S,R,R)-L1 (11 mol%) in toluene at 0 °C. Full conversion after 24 h determined by GC-MS. * Isolated yield. * Enantiomeric excess determined by chiral HPLC (See the ESI†). * Determined by comparison with literature data based on the sign of optical rotation. * Slow addition of the substrate over 5 h. * Incomplete conversion.

In Table 4, the addition of various diorganozinc reagents to sulfone 1 was examined (Table 4). Using optimized conditions we then studied the influence of the substituent pattern of the substrate on the conjugate addition of diethylzinc (Table 5). Because excellent results have been obtained using Grignard reagents on aliphatic substrates, we focused our efforts on a range of aromatic substrates for which excellent ee’s were found. Introduction of a chloride at the ortho position gave a drop in ee (entry 2). Moving the chloride further away from the phenyl gave good results.

Conditions: 1 (1 equiv., 0.25 mmol), Et2Zn (3.2 equiv.), Cu(OTf)2 (7.5 mol%), (S,R,R)-L1 (11 mol%) in toluene at 0 °C. Conversion determined by chiral HPLC (See the ESI†). * Determined by comparison with literature data based on the sign of optical rotation. * Slow addition of the substrate over 5 h. * Incomplete conversion.
reaction centre increased the enantiomeric excess (entries 2–4). We attribute this effect to steric hindrance.

In the instance of electron donating substituents such as the para methyl and para isopropyl substituted substrates full conversion was not achieved after 24 h giving lower isolated yields. Fortunately, the lower reaction rate did not negatively influence the enantiomeric excess and excellent ee’s were obtained (entries 5 and 7). Furthermore, para trifluoromethyl-, p-bromo- and 2-naphthyl-substituted substrates gave good yields and excellent enantiomeric excesses (entries 6, 8 and 9).

In summary, we have developed a highly enantioselective copper-catalyzed conjugate addition of dialkylzinc reagents to a range of aromatic α,β-unsaturated sulfones using a monodentate phosphoramidite ligand. This procedure provided β-substituted 2-pyridyl sulfones in moderate to good yields (46–86%) and good to excellent enantiomeric excess (70–96%) and is complementary to our recent publication on the addition of Grignard reagents to aliphatic substrates. These enantioenriched sulfones are potentially useful intermediates in the preparation of a wide variety of functionalized chiral building blocks.

Acknowledgements

Financial support from The Netherlands Organization for Scientific Research (NWO-CW) is acknowledged. We thank T. D. Tiemersma-Wegman (GC and HPLC) and A. Kiewiet (MS) for technical assistance (Stratingh Institute for Chemistry, University of Groningen).

Notes and references


11 This dependence is in contrast to that reported for the asymmetric conjugate addition of Grignard reagents to α,β-unsaturated sulfones where the nature of the counterion hardly had an effect on conversion and enantioselectivity, see ref. 8.