Copper Phosphoramidite-Catalyzed Enantioselective Desymmetrization of meso-Cyclic Allylic Bisdiethyl Phosphates

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ABSTRACT

A highly regio-, diastereo-, and enantioselective desymmetrization of five-, six-, and seven-membered meso-cyclic allylic bis-diethyl phosphates (2a, 2b, and 2c, respectively) was obtained with diethylzinc, using catalytic amounts of [Cu(OTf)]_2 and phosphoramidite ligands 5. Enantiomeric excesses of up to 87, 94, and >98% were obtained for the addition of diethylzinc to cyclopentene, cyclohexene, and cycloheptene bis-diethyl phosphates, respectively.

meso-Cyclic allylic diols are powerful substrates for the construction of enantiomerically enriched functionalized products. Their desymmetrization has been realized by acylation or by allylic substitution, which can occur via S_{N}2 or S_{N}2′ (allylic displacement) mechanisms, with either retention or inversion.¹ The palladium-catalyzed desymmetrization, pioneered by Trost, is usually performed with soft nucleophiles and takes place via the S_{N}2 mechanism.² A somewhat related enantioselective ring opening of meso-

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the first case the reaction occurs via the S_N2 mechanism with retention (the nucleophile attacks from the same side of the allylic leaving group), in the second case the allylic displacement reaction takes place with inversion. Piarulli, Gennari, and co-workers have recently disclosed a new highly regio-, diastereo-, and enantioselective desymmetrization of meso-cyclic allylic bisdiethyl phosphates with organozinc reagents catalyzed by copper(I) complexes of chiral Schiff base ligands 1 (Scheme 1). In the case of meso-

4-cyclopentene-1,3-bisdieyl phosphate (2a), only the product arising from the allylic displacement (S_N2 mechanism with inversion (3a)) was obtained with excellent yield and enantiomeric excess (ee) up to 88% after screening a library of 125 Schiff-base ligands 1. Reaction of diethylzinc with meso-2-cyclohexene-1,4-bisdiethyl phosphate (2b), on the contrary, gave the allylic displacement products originating from either inversion (3b) or retention (4b) with good diastereoselectivity (81:19–4:96), depending on the solvent and the ligand used. However, very low ees were obtained. The reaction of meso-2-cycloheptene-1,4-bisdiethyl phosphate (2c) afforded only the product arising from the allylic displacement with inversion (3c), albeit with modest ee (up to 56%).

The Groningen group has demonstrated that phosphoramidites of general structure 5 serve as very effective ligands in a number of catalytic asymmetric carbon-carbon bond-forming reactions. These include the already mentioned copper-catalyzed ring opening of oxacyclic alkenes, the conjugate addition of dialkyliczincs to enones and nitroalkenes, the ring opening of vinyl epoxides, the desymmetrization of methyldiene cycloalkene oxides, the allylic alkylation of cinnamyl derivatives, and the rhodium-catalyzed addition of arylboronic acids.

In this paper we report a highly enantioselective desymmetrization of meso-4-cyclopentene-1,3-bisdieyl phosphate (2a), meso-2-cyclohexene-1,4-bisdiethyl phosphate (2b), and meso-2-cycloheptene-1,4-bisdiethyl phosphate (2c) with diethylzinc catalyzed by copper(I) complexes of phosphoramidite ligands 5 (Figure 1).

Copper complexes of ligands 5a–f were obtained in situ by stirring CuOTf with 2 equiv of the appropriate ligand in toluene (45 min, rt). Reaction of meso-4-cyclopentene-1,3-bisdieyl phosphate (2a), readily obtained from commercially available meso-4-cyclopentene-1,3-diol, with 2.0 equiv of Et2Zn in the presence of 10 mol % of the copper-phosphoramidite complexes afforded the product arising from allylic displacement with inversion (3a, R = Et) in variable yields and enantiomeric excesses (Table 1). In particular, the screening of the ligands revealed that good yields and enantiomeric excesses were obtained when phosphoramidite ligands with bulkier secondary amine substituents were used (entries 2–4). Varying the temperature with the best ligand 5b increased the enantiomeric excess to 87% at −40 °C (entry 7). Dimethylzinc was considerably less reactive than diethylzinc; the reaction had to be run at 0 °C to obtain 3a (R = Me) with a fair conversion (54%), still associated with a good ee (87%, Table 1, entry 10).

meso-2-Cyclohexene-1,4-bisdiethyl phosphate (2b) was obtained starting from cyclohexadiene via a palladium-

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(14) cis-4-Cyclopentene-1,3-diol was transformed into the corresponding bisdiethyl phosphate (2) by deprotonation with n-BuLi and reaction with diethylchlorophosphite in THF/TEMA (4/1); see: Yu, K. L.; Ko, K. Y.; Fraser-Reid, B. Synth. Commun. 1988, 465–468.

(15) Reactions at −40 or −20 °C showed poor conversions (15–20%) associated with slightly better ees (90–93%).
catalyzed 1,4-diacetoxylolation,\textsuperscript{16} followed by hydrolysis and phosphorylation using the same procedure as for the five-membered substrate 2a.\textsuperscript{14} Reaction with Et\textsubscript{2}Zn afforded variable proportions of two products, namely, those arising from the allylic displacement (S\textsubscript{N}2) with either inversion (3b) or retention (4b) (Table 2). In particular, small ligands (e.g., 5a, entry 1) and higher reaction temperatures (cf. entries 7–9, 10–11) afforded larger proportions of product 4b, whereas ligands bearing bulkier amine substituents and lower temperatures favored the formation of product 3b. An enantiomeric excess of up to 82\% was obtained for the product arising from allylic displacement (S\textsubscript{N}2) with inversion, using ligand 5b at −60 °C, albeit in rather low yield (entry 2). Increasing the reaction temperature to −40 °C improved both the yield (77\%) and the enantiomeric excess (90\%, entry 7). Interestingly, ligand 5c comprising S-BINOL and the S,S-diamine moiety afforded a very promising 76\% ee at −60 °C (entry 3), which could be improved to 94\%, with 69\% yield, by increasing the temperature to −40 °C (entry 10). It should be noted that this is one of the few cases where the matched combination arises in 5 from S-BINOL and the S,S-diamine.\textsuperscript{10,11} Product 4b, on the other hand, was always isolated as a racemic mixture.

Reaction of the seven-membered-ring substrate 2c (Table 3), obtained following the same route as for 2b, afforded only the product arising from allylic displacement (S\textsubscript{N}2) with inversion (3c) with excellent enantiomeric excess (>98\%).

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|c|c|}
\hline
entry & ligand & R & T (°C) & product yield (\%) & ee % (configuration) \\
\hline
1 & 5a & Et & −60 & 10 & 24 (R,R) \\
2 & 5b & Et & −60 & >98 & 74 (R,R) \\
3 & 5c & Et & −60 & 20 & 60 (R,R) \\
4 & 5d & Et & −60 & 30 & 58 (R,R) \\
5 & 5e & Et & −60 & 65 & 10 (R,R) \\
6 & 5f & Et & −60 & 13 & 0 (R,R) \\
7 & 5b & Et & −40 & >98 & 87 (R,R) \\
8 & 5b & Et & −20 & >98 & 84 (R,R) \\
9 & 5b & Et & 0 & >98 & 81 (R,R) \\
10 & 5b & Me & 0 & 54 & 87 (R,R) \\
\hline
\end{tabular}
\caption{Allylic Alkylation of 2a with R\textsubscript{2}Zn in the Presence of Copper Complexes of Phosphoramidites 5a−f}
\end{table}

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|c|c|}
\hline
entry & ligand & R & T (°C) & product yield (\%) & 3b/4b & ee % of 3b (configuration) \\
\hline
1 & 5a & Et & −60 & 13 & 31/69 & 35 (R,R) \\
2 & 5b & Et & −60 & 35 & 76/24 & 82 (R,R) \\
3 & 5c & Et & −60 & 16 & 87/13 & 76 (R,R) \\
4 & 5d & Et & −3 & 3 & 79/21 & 68 (R,R) \\
5 & 5e & Et & −60 & 10 & 69/31 & 48 (R,R) \\
6 & 5f & Et & −60 & 0 & 85 & 44/56 & 52 (R,R) \\
7 & 5b & −40 & 77 & 87/13 & 90 (R,R) \\
8 & 5b & −20 & 89 & 67/33 & 84 (R,R) \\
9 & 5b & 0 & 85 & 44/56 & 52 (R,R) \\
10 & 5c & −40 & 69 & 85/15 & 94 (R,R) \\
11 & 5c & −20 & 88 & 68/32 & 93 (R,R) \\
\hline
\end{tabular}
\caption{Allylic Alkylation of 2b with Et\textsubscript{2}Zn in the Presence of Copper Complexes of Phosphoramidites 5a−f}
\end{table}
(C=O)−C−CF₃ fragment in one plane. The signals assigned to the methyl group of the ethyl substituent in the 2-position and to the vinylic proton in the 3-position of the seven-membered ring appeared at a higher field in the more abundant diastereomeric ester than the signals of the corresponding protons in the minor diastereomer; therefore, the absolute configuration of the major ester was assigned as \((R,R)\).²⁰

To test the applicability of this synthetic methodology to more functionalized substrates, we performed the reaction on compound 6,²¹ a derivative of conduritol A, using 5b as the ligand (Scheme 2).

Much to our delight, compound 7, derived from allylic displacement (S₉₂') with inversion, was obtained in 52% yield (74% based on recovered 6) as a single diastereomer, in 86% enantiomeric excess.²²,²³ It is worth noting that a fully functionalized cyclohexane derivative, containing four contiguous stereocenters and a double bond, was obtained as a single diastereomer and in high enantiomeric excess from an achiral starting material.

In summary, we have developed a highly regio-, diastereo-, and enantioselective desymmetrization of five-, six-, and seven-membered \(meso\)-cyclic allylic bis-diethyl phosphates (2a, 2b, and 2c, respectively) with diethylzinc using catalytic amounts of \([\text{Cu(OTf)}]_2\) and phosphoramidite ligands. Studies toward the extension of the scope of this reaction, using different organozinc reagents and other functionalized substrates, are currently underway in our laboratories.

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Supporting Information Available: Experimental details and characterization data, including \(^{1}H\), \(^{31}P\), and \(^{13}C\) NMR, IR, MS, and HRMS spectra and GC conditions. This material is available free of charge via the Internet at http://pubs.acs.org.

Table 3. Allylic Alkylation of 2a with \(\text{Et}_2\text{Zn}\) in the Presence of Copper Complexes of Phosphoramidites 5a−e

<table>
<thead>
<tr>
<th>entry</th>
<th>ligand</th>
<th>(T) (°C)</th>
<th>product yield (%)</th>
<th>ee% (configuration)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5a</td>
<td>−60</td>
<td>5</td>
<td>nd</td>
</tr>
<tr>
<td>2</td>
<td>5b</td>
<td>−60</td>
<td>81</td>
<td>&gt;98 (R,R)</td>
</tr>
<tr>
<td>3</td>
<td>5c</td>
<td>−40</td>
<td>85</td>
<td>&gt;98 (R,R)</td>
</tr>
<tr>
<td>4</td>
<td>5b</td>
<td>−40</td>
<td>86</td>
<td>&gt;98 (R,R)</td>
</tr>
<tr>
<td>5</td>
<td>5c</td>
<td>−40</td>
<td>86</td>
<td>&gt;98 (R,R)</td>
</tr>
</tbody>
</table>

a Reaction conditions: \([\text{Cu(OTf)}]_2\cdot\text{C}_6\text{H}_6\) (0.05 equiv), ligand 5 (0.2 equiv), \(\text{Et}_2\text{Zn}\) (2.0 equiv), 2c (1.0 equiv), toluene, 15 h. b Isolated yield. c Determined by \(^{1}H\) NMR analysis of the Mosher esters, after reduction of the phosphate ester to alcohol with \(\text{LiAlH}_4\) in diethyl ether (quantitative yield). d Absolute configuration was determined by analysis of the Mosher ester (see text).

Scheme 2. Desymmetrization of Functionalized Substrate 6

\(\text{Et}_2\text{Zn}\) \([\text{Cu(OTf)}]_2\cdot\text{C}_6\text{H}_6\), 5b, 6, 7

a Reaction conditions: \([\text{Cu(OTf)}]_2\cdot\text{C}_6\text{H}_6\) (0.05 equiv), ligand 5b (0.2 equiv), \(\text{Et}_2\text{Zn}\) (2.0 equiv), 6 (1.0 equiv).