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Highly Enantioselective Copper – Phosphoramidite Catalyzed Kinetic Resolution of Chiral 2-Cyclohexenones™

Robert Naasz, Leggy A. Arnold, Adriaan J. Minnaard, and Ben L. Feringa*™

Chiral 2-cyclohexenones are attractive building blocks for the synthesis of a variety of natural products. A limited number of naturally occurring optically active cyclohexenones such as pulegone, pipertone, and carvone are cheap, readily available, and widely used for this purpose.[1] The development of routes to other optically active 2-cyclohexenones includes the preparation of nonnatural cyclohexenones from naturally occurring ones; for example, 4-methyl- and 5-methylcyclohexenone can be derived from pulegone and carvone.[2] Recently the groups of Corey and Sato introduced elegant methods for the synthesis of enantiomerically pure 2-cyclohexenones which can easily be converted into a variety of other chiral 2-cyclohexenones.[3] Although both methods are widely applicable they consist of multistep syntheses to obtain the desired 2-cyclohexenone synthons. On the other hand a variety of racemic 2-cyclohexenones is readily accessible. This encouraged us to develop a general method towards optically active 2-cyclohexenones by kinetic resolution of racemic 2-cyclohexenones catalyzed with the copper – phosphoramidite catalyzed 1,4-addition to enones [Eq. (1)].[4]

\[
\text{enantioselective} \quad \text{1,4-addition} \quad \text{alkyl}
\]

It was anticipated that the high enantioselectivity obtained with these catalysts in the 1,4-addition of diethylzinc to 2-cyclohexenone (> 98 % ee, [Eq. (1)]),[4] combined with the high trans-diastereoselectivity generally found in the addition of organometallic reagents to, for example, 5-alkyl-substituted 2-cyclohexenones,[5] should provide high selectivity in the kinetic resolution of such compounds [Eq. (2)].[6, 7]

\[
\text{kinetic} \quad \text{resolution} \quad \text{alkyl} \quad \text{kinetic} \quad \text{resolution} \quad \text{alkyl}
\]

To check the viability of this new approach we tested the ligands L1 – L5 in the kinetic resolution of racemic 5-substituted 2-cyclohexenones 1a – d under the conditions typical for the asymmetric 1,4-addition as shown in Scheme 1. By using [Cu(OTf)2] (1 mol %), (S,R,R)-L1 (2 mol %), and Et2Zn (0.8 equiv) in toluene at −40 °C for the resolution of (±)-5-methyl-2-cyclohexenone (1a) on a 1 mmol scale, an ee of 88 % was reached at 48 % conversion indicating a selectivity (s) of 120 (Table 1, entry 1).[8–10] Accordingly after 20 min 53 % conversion had taken place and unreacted 1a with 99 % ee was found. This high selectivity makes the resolution synthetically applicable.[11] Based on the expected trans-diastereoselectivity and the fact that the 1,4-addition of Et2Zn to 2-cyclohexenone in the presence of L1 produces (S)-3-ethylcyclohexanone we predicted the unreacted enantiomer to be (R)-1a which turned out to be correct.[4b, 5, 12]

A good correlation was observed between the results with the ligands L1 – L5 in the 1,4-addition of diethylzinc to 2-cyclohexenone and the results in the kinetic resolution (Table 1, entries 1 – 9). The most successful ligands in the 1,4-addition, namely (S,R,R)-L1, (S,R)- and (S,S)-L2 (Table 1, entries 3 and 4), and (S,R,R)-L3 (Table 1, entry 5), also give the highest selectivity in the kinetic resolution of 1a.[10] Noteworthy is the fact that (S,R,R)-L1 gives a much faster reaction at −40 °C than all other ligands at −30 °C, reaching 48 % conversion after only 15 min.[13] This finding and the high selectivity obtained with (S,R,R)-L1 make it the obvious ligand of choice in these kinetic resolution experiments. The high activity of this catalyst also makes resolutions on a larger scale with lower catalyst loading possible. To demonstrate this a resolution experiment was performed on 1a (11.0 g, 100 mmol) with [Cu(OTf)2] (18.1 mg, 0.05 mol %), (S,R,R)-L1 (54 mg, 0.10 mol %), and 0.55 equivalents of Et2Zn. Aqueous work up followed by column chromatography...
Table 1. Kinetic resolution of 5-substituted 2-cyclohexenones 1a – d according to Scheme 1.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>Enone R'</th>
<th>t [min]</th>
<th>Conv. [%]</th>
<th>ee [%]</th>
<th>s</th>
<th>Conf.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1[a]</td>
<td>(S,R,R)-L1</td>
<td>1a</td>
<td>Et</td>
<td>15</td>
<td>48</td>
<td>88</td>
<td>120</td>
</tr>
<tr>
<td>2</td>
<td>(S,S,S)-L1</td>
<td>1a</td>
<td>Et</td>
<td>15</td>
<td>42</td>
<td>24</td>
<td>57</td>
</tr>
<tr>
<td>3</td>
<td>(S,R)-L2</td>
<td>1a</td>
<td>Et</td>
<td>90</td>
<td>49</td>
<td>86</td>
<td>50</td>
</tr>
<tr>
<td>4</td>
<td>(S,S)-L2</td>
<td>1a</td>
<td>Et</td>
<td>45</td>
<td>51</td>
<td>90</td>
<td>42</td>
</tr>
<tr>
<td>5</td>
<td>(S,R,R)-L3</td>
<td>1a</td>
<td>Et</td>
<td>45</td>
<td>46</td>
<td>76</td>
<td>40</td>
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<tr>
<td>6</td>
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<td>1a</td>
<td>Et</td>
<td>90</td>
<td>19</td>
<td>12</td>
<td>3</td>
</tr>
<tr>
<td>7</td>
<td>(S,R)-L4</td>
<td>1a</td>
<td>Et</td>
<td>45</td>
<td>55</td>
<td>84</td>
<td>14</td>
</tr>
<tr>
<td>8</td>
<td>(S,S)-L4</td>
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<td>Et</td>
<td>60</td>
<td>62</td>
<td>75</td>
<td>6</td>
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<td>90</td>
<td>27</td>
<td>22</td>
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<tr>
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<td>(S,R,R)-L1</td>
<td>1b</td>
<td>Et</td>
<td>10</td>
<td>54</td>
<td>96</td>
<td>39</td>
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<tr>
<td>11</td>
<td>(S,R,R)-L1</td>
<td>1c</td>
<td>Et</td>
<td>5</td>
<td>55</td>
<td>89</td>
<td>19</td>
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<tr>
<td>12</td>
<td>(S,R,R)-L1</td>
<td>1d</td>
<td>Et</td>
<td>5</td>
<td>56</td>
<td>86</td>
<td>14</td>
</tr>
<tr>
<td>13</td>
<td>(S,R,R)-L1</td>
<td>1d</td>
<td>nPr</td>
<td>60</td>
<td>55</td>
<td>84</td>
<td>14</td>
</tr>
<tr>
<td>14[a]</td>
<td>(S,R,R)-L1</td>
<td>1a</td>
<td>nBu</td>
<td>15</td>
<td>49</td>
<td>93</td>
<td>&gt; 200</td>
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<tr>
<td>15[a]</td>
<td>(S,R,R)-L1</td>
<td>1b</td>
<td>nBu</td>
<td>60</td>
<td>50</td>
<td>93</td>
<td>94</td>
</tr>
<tr>
<td>16[a]</td>
<td>(S,R,R)-L1</td>
<td>1d</td>
<td>nBu</td>
<td>15</td>
<td>44</td>
<td>78</td>
<td>&gt; 200</td>
</tr>
<tr>
<td>17[a]</td>
<td>(S,R,R)-L1</td>
<td>1a</td>
<td>Me</td>
<td>20</td>
<td>50</td>
<td>93</td>
<td>94</td>
</tr>
<tr>
<td>18[a]</td>
<td>(S,R,R)-L1</td>
<td>1b</td>
<td>Me</td>
<td>25</td>
<td>48</td>
<td>85</td>
<td>66</td>
</tr>
<tr>
<td>19[a]</td>
<td>(S,R,R)-L1</td>
<td>1d</td>
<td>Me</td>
<td>15</td>
<td>50</td>
<td>90</td>
<td>58</td>
</tr>
</tbody>
</table>

[a] Both conversion and ee determined by chiral GC in the presence of n-dodecane or n-hexadecane as internal standard (see Supporting Information).

Figure 1. Plot of ee [%] against conversion [%] for the kinetic resolution of 1a with (S,R,R)-L1, [Cu(OTf)2] and Et2Zn ( ), iPr2Zn ( ), nBu2Zn ( ), and Me2Zn ( ) (entries 1, 13, 14, and 17 in Table 1).

Figure 2. Plot of conversion [%] against time t for the kinetic resolution of 1a with (S,R,R)-L1, [Cu(OTf)2], and Me2Zn (entry 17 in Table 1).

The results of the kinetic resolution of racemic 4-methyl-2-cyclohexenone (3) (Scheme 2) are summarized in Table 2.[6, 20] The selectivity was lower than that observed for most of the 5-substituted 2-cyclohexenones as could be expected from the lower trans selectivity in the 1,4-addition to 4-substituted 2-cyclohexenones.[15] Again (S,R,R)-L1 was the most successful ligand with s = 16 but in this case the peculiar observation was made that (S,S,S)-L1 performed nearly as well (s = 13), which makes it easy to stop the reaction at the optimal conversion and ee.[19]

We next turned our attention to the influence of the dialkyldivinyl reagent on the enantioselectivity in the kinetic resolution. We reasoned that using the more bulky iPr2Zn reagent in the resolution of 1a would lead to an even higher selectivity for the trans product than Et2Zn, and consequently would give a higher s value. Surprisingly the opposite was observed and the selectivity decreased drastically to s = 14 (Table 1, compare entries 1 and 10). On the other hand the use of nBu2Zn led to a significant increase in selectivity to s > 200, showing that an ee of 99 % is reached at 51 % conversion (Table 1, entry 14). The results for the kinetic resolution of 1a with different zinc reagents are graphically summarized in Figure 1.

To our delight the selectivity was higher with nBu2Zn than with Et2Zn (Table 1, entries 15 and 16) for both substrates 1b and 1d. In particular a remarkable increase in selectivity from s = 14 with Et2Zn to s > 200 with nBu2Zn was observed for synthon 1d. The use of Me2Zn also gave excellent selectivities in the resolution of 1a, 1b, and 1d (Table 1, entries 17 – 19). In a number of enzymatic kinetic resolutions a fast and stereoselective reaction of one enantiomer of the racemic substrate takes place, while the other is not converted even after prolonged reaction.[18] We approach this near perfect situation in the kinetic resolution of 1a as the reaction virtually ceases at 50 % conversion (Figure 2) in the presence of one equivalent of Me2Zn, which makes it easy to stop the reaction at the optimal conversion and ee.[19]

![Scheme 2](image-url)
whereas the resolution with a 1:1 mixture of the two diastereomers of L1 gave a selectivity of 17 (Table 2, entries 1–3). The use of Me₂Zn instead of Et₂Zn led to a slight decrease in selectivity, whereas again the use of nBu₂Zn led to an increase in selectivity to s = 27 (Table 2, entries 8 and 9).

The high selectivities (s up to and above 200) obtained with the [(S,R)-L1-Cu(OTf)] complex in the catalytic kinetic resolution of 1a–d and 3 make this an excellent method for obtaining these valuable building blocks with an ee > 99 %. Furthermore the high selectivity and high activity of this catalyst enabled us to successfully perform a resolution of 1a on a multigram scale.

Experimental Section

Resolution of racemic 1a on 100 mmol scale: In flame-dried glassware under an argon atmosphere [Cu(OTf)] (18 mg, 0.05 mmol) and [(S,R)-L1] (54 mg, 0.10 mmol) were dissolved in dry toluene (100 mL). After stirring at room temperature for 1 h the colorless solution was cooled to −30 °C and racemic 1a (110 g, 100 mmol) and n-dodecane (4.0 mL) were added. After the mixture had been stirred for 10 min, Et₂Zn (50 mL of 1.1 M solution in toluene, 55 mmol) was added dropwise by syringe over 5 min. A sample (0.1 mL) was taken after reaction overnight and analyzed by chiral GC (see Supporting Information) showing 1a with 93 % ee at 5 % conversion. Extra Et₂Zn (3.6 mL, 11 mmol in toluene) was added and after 3 h another sample was taken. GC analysis showed >99 % ee and 55 % conversion. The mixture reaction was quenched with 1M HCl aq (150 mL), and the aqueous layer was extracted with Et₂O (3 × 100 mL), and the combined organic layers were washed with brine and dried over Na₂SO₄. Filtration and evaporation of the solvents yielded a mixture of addition product, and dodecane which were separated by column chromatography (SiO₂, hexanes/diethyl ether 4:1) to give (R)-(−)-1a (3.6 g, 33 mmol, 33 %). [α]D²⁰ = −873° (c = 0.81, CHCl₃).[19] H NMR (200 MHz, CDCl₃): = 1.06 (d, J = 6.1 Hz, 3H), 1.9–2.5 (m, 5H), 6.0 (m, 1H), 6.9 (m, 1H); ¹³C NMR (300 MHz, CDCl₃): δ = 21.60 (q), 30.20 (d), 33.87 (t), 46.12 (t), 129.44 (d), 149.80 (d), 199.93 (s). GC analysis (Chiralex G-TA) showed an ee > 99 % (no (S)-1a was detected).

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Herein we report the first highly stereocontrolled transformation of a racemic mixture by an organometallic reagent and a chiral catalyst to give separable regioisomeric products.

Recently, we described a new catalytic kinetic resolution of racemic vinyloxiranes with dialkylzinc reagents (0.50 equiv) by using copper complexes of non-racemic phosphoramidite as chiral catalysts. When racemic vinyl epoxide 2 was treated with excess Et₂Zn (1.5 equiv) in the presence of the catalyst prepared in situ from [Cu(OTf)]₂ (1.5 mol %) (Ti = triflate = OSO₂CF₃) and (R,R)-1 (3 mol %), complete conversion of 2 took place in 3 h to give, after usual work-up and chromatographic purification (see Experimental Section), the corresponding S₈2⁻-addition product (R)-3a (46 % yield, 80 % ee; Scheme 1) together with the regioisomeric alcohol (S,S,2)-4a (37 % yield) having a surprising 99 % ee! The progress of the reaction in terms of the the conversion and enantioselectivities (Figure 1a and 1b, respectively) was therefore closely monitored.

The peculiarity of this reaction stems from the fact that regioisomeric products were derived from opposite enantiomers of 2 in two clearly distinct phases: The first one was very fast, proceeding with SN₂ regioselectivity, and with complete anti stereoselectivity, and with complete anti stereochemistry, at the 2-position. The catalyzed addition of Me₂Zn followed an even more pronounced regiodivergent behavior, affording, after complete conversion of 2, (R)-3b (49 % GC yield, 96 % ee) and (S,S,2)-4b (51 % GC yield, 92 % ee) (Scheme 1).

The complementary enantiomer-dependent regioselectivity was also demonstrated by a reaction carried out with the racemic catalyst (R,R,R)(S,S,S)-1. In this case, the conjugate-addition product 3 was obtained with almost complete regioselectivity (S₈2⁻/S₈₂⁻ = 98:2), clearly indicating that chiral recognition leads to enantio- and regiodivergent reactivity when the reaction is performed with the chiral catalyst.

The mechanism for the copper-catalyzed organometallic addition reactions has been discussed in a number of reports. Probably the initially formed π complex 2A undergoes an oxidative addition resulting in the formation of

**Highly Enantioselective Regiodivergent and Catalytic Parallel Kinetic Resolution**

Fabio Bertozzi, Paolo Cotti, Franco Macchia, Mauro Pineschi,* and Ben L. Feringa*

The development of new methodologies for the preparation of chiral compounds of high optical purity by means of asymmetric catalysis is presently an area of great importance in organic chemistry. Kinetic resolution of a racemic mixture with a chiral reagent is a well-documented strategy in which a maximum of only one half of the racemic starting material is converted into non-racemic products. Parallel kinetic resolution (PKR) is an interesting strategy recently introduced, in which both enantiomers of a racemate can be converted into useful products. This conceptual variation often requires the use of different stoichiometric chiral reagents in parallel. Parallel reactions under non-stoichiometric conditions have previously been described in the asymmetric Bayer–Villiger oxidation of racemic ketones, by means of enzymatic methods or chiral catalysts, and in the intramolecular cyclopropanation of racemic allylic diazoacetates catalyzed by chiral rhodium complexes. The latter is the only example of a PKR reaction involving the formation of a C–C bond. In this special case, there are distinct reactivities for both enantiomers: one enantiomer gave intramolecular cyclopropanation, whereas the other enantiomer was transformed by means of a hydride abstraction/elimination into achiral compounds.