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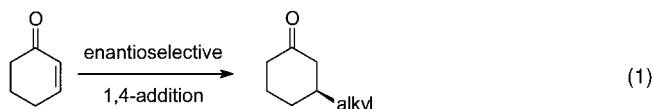
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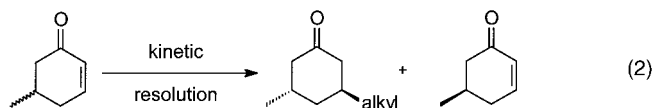
## Highly Enantioselective Copper–Phosphoramidite Catalyzed Kinetic Resolution of Chiral 2-Cyclohexenones\*\*

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, piperitone, and carvone are cheap, readily available, and widely used for this purpose.<sup>[1]</sup> 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.<sup>[2]</sup> 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.<sup>[3]</sup> 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 based on the copper–phosphoramidite catalyzed 1,4-addition to enones [Eq. (1)].<sup>[4]</sup>



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)]),<sup>[4]</sup> combined with the high *trans*-diastereoselectivity generally found in the addition of organometallic reagents to, for example, 5-alkyl-substituted 2-cyclohexenones,<sup>[5]</sup> should provide high selectivity in the kinetic resolution of such compounds [Eq. (2)].<sup>[6, 7]</sup>

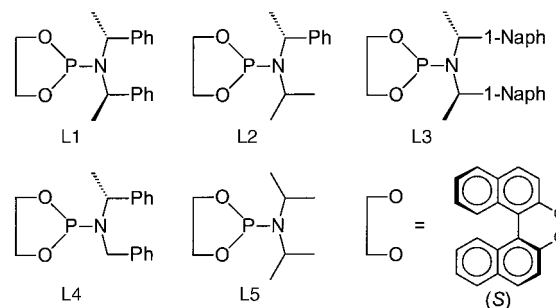


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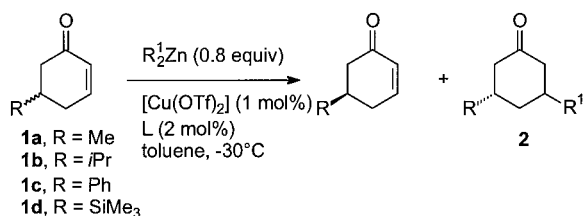
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To check the viability of this new approach we tested the ligands L1–L5 in the kinetic resolution of racemic 5-substituted 2-cyclohexenones **1a–d** under the conditions typical



for the asymmetric 1,4-addition as shown in Scheme 1. By using [Cu(OTf)<sub>2</sub>] (1 mol %), (*S,R,R*)-L1 (2 mol %), and Et<sub>2</sub>Zn (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).<sup>[8–10]</sup> 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.<sup>[11]</sup> Based on the expected *trans*-diastereoselectivity and the fact that the 1,4-addition of Et<sub>2</sub>Zn 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.<sup>[4d, 5, 12]</sup>

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**.<sup>[4b]</sup> 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.<sup>[13]</sup> 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)<sub>2</sub>] (18.1 mg, 0.05 mol %), (*S,R,R*)-L1 (54 mg, 0.10 mol %), and 0.55 equivalents of Et<sub>2</sub>Zn. Aqueous work up followed by column chromatography

Table 1. Kinetic resolution of 5-substituted 2-cyclohexenones **1a–d** according to Scheme 1.

Entry	Ligand	Enone	R <sup>1</sup>	t [min]	Conv. [%] <sup>[a]</sup>	ee [%] <sup>[a]</sup>	s	Conf. <sup>[b]</sup>
1 <sup>[c]</sup>	( <i>S,R,R</i> )-L1	<b>1a</b>	Et	15	48	88	120	R
		<b>20</b>			<b>53</b>	<b>99</b>		
2	( <i>S,S,S</i> )-L1	<b>1a</b>	Et	15	42	62	24	R
3	( <i>S,R</i> )-L2	<b>1a</b>	Et	90	49	86	50	R
4	( <i>S,S</i> )-L2	<b>1a</b>	Et	45	51	90	42	R
5	( <i>S,R,R</i> )-L3	<b>1a</b>	Et	45	46	76	40	R
6	( <i>S,S,S</i> )-L3	<b>1a</b>	Et	90	19	12	3	R
7	( <i>S,R</i> )-L4	<b>1a</b>	Et	45	55	84	14	R
8	( <i>S,S</i> )-L4	<b>1a</b>	Et	60	62	75	6	R
9	( <i>S</i> )-L5	<b>1a</b>	Et	90	27	22	5	R
10	( <i>S,R,R</i> )-L1	<b>1b</b>	Et	10	54	96	39	–
11	( <i>S,R,R</i> )-L1	<b>1c</b>	Et	–	55	89 <sup>[d]</sup>	19	R
12	( <i>S,R,R</i> )-L1	<b>1d</b>	Et	5	56	86	14	–
13	( <i>S,R,R</i> )-L1	<b>1a</b>	<i>i</i> Pr	60	55	84	14	R
14 <sup>[e]</sup>	( <i>S,R,R</i> )-L1	<b>1a</b>	<i>n</i> Bu	15	49	93	>200	R
		<b>30</b>			<b>54</b>	>99		
15 <sup>[e]</sup>	( <i>S,R,R</i> )-L1	<b>1b</b>	<i>n</i> Bu	60	50	93	94	–
		<b>90</b>			<b>53</b>	<b>99</b>		
16 <sup>[e]</sup>	( <i>S,R,R</i> )-L1	<b>1d</b>	<i>n</i> Bu	15	44	78	>200	–
		<b>45</b>			<b>52</b>	>99		
17 <sup>[e]</sup>	( <i>S,R,R</i> )-L1	<b>1a</b>	Me	20	50	93	94	R
18 <sup>[e]</sup>	( <i>S,R,R</i> )-L1	<b>1b</b>	Me	25	48	85	66	R
19 <sup>[e]</sup>	( <i>S,R,R</i> )-L1	<b>1d</b>	Me	15	50	90	58	–

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

[b] Configuration of the unconverted enone. [c] Reaction run at  $-40^{\circ}\text{C}$ . [d] *ee* determined by chiral HPLC (see Supporting Information). [e] Reaction run at  $-35^{\circ}\text{C}$ .

yielded (*R*)-**1a** (3.6 g; 33%) with an *ee* > 99%.<sup>[14]</sup> <sup>13</sup>C NMR analysis of the isolated product **2** (R = Me, R<sup>1</sup> = Et) showed the presence of >95% of the *trans* diastereomer.<sup>[15]</sup>

Because the relatively small methyl group in **1a** already gives rise to high selectivity we expected that other 5-substituted substrates would also give selectivities high enough to be synthetically useful.<sup>[16]</sup> To our surprise a more bulky isopropyl group (**1b**) led to a slight decrease in the selectivity (*s* = 39; Table 1, entry 10), and substrate **1c** containing a phenyl group at the 5-position also gave a lower selectivity (*s* = 19; Table 1, entry 11) than **1a**. Resolution of the synthetically important 5-trimethylsilyl-2-cyclohexenone (**1d**) was also successful, providing 86% *ee* at 56% conversion (*s* = 14, Table 1, entry 12).<sup>[3a, 16b, 17]</sup>

We next turned our attention to the influence of the dialkylzinc reagent on the enantioselectivity in the kinetic resolution. We reasoned that using the more bulky *i*Pr<sub>2</sub>Zn reagent in the resolution of **1a** would lead to an even higher selectivity for the *trans* product than Et<sub>2</sub>Zn, 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 13). On the other hand the use of *n*Bu<sub>2</sub>Zn 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 *n*Bu<sub>2</sub>Zn than with Et<sub>2</sub>Zn (Table 1, entries 15 and 16) for both substrates **1b** and **1d**. In particular a remarkable increase in selectivity from *s* = 14 with Et<sub>2</sub>Zn to *s* > 200 with *n*Bu<sub>2</sub>Zn was observed for

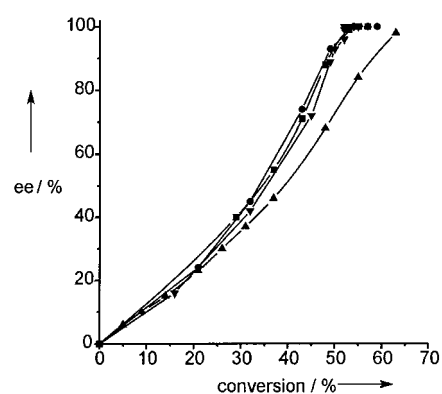


Figure 1. Plot of *ee* [%] against conversion [%] for the kinetic resolution of **1a** with (*S,R,R*)-L1, [Cu(OTf)<sub>2</sub>] and Et<sub>2</sub>Zn (■), *i*Pr<sub>2</sub>Zn (▲), *n*Bu<sub>2</sub>Zn (●), and Me<sub>2</sub>Zn (▼) (entries 1, 13, 14, and 17 in Table 1).

synthon **1d**. The use of Me<sub>2</sub>Zn 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.<sup>[18]</sup> 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 Me<sub>2</sub>Zn, which makes it easy to stop the reaction at the optimal conversion and *ee*.<sup>[19]</sup>

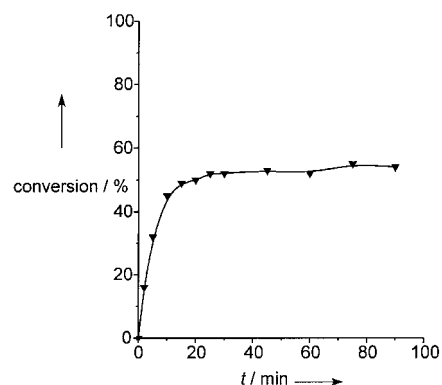
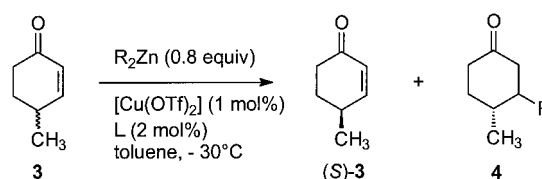


Figure 2. Plot of conversion [%] against time *t* for the kinetic resolution of **1a** with (*S,R,R*)-L1, [Cu(OTf)<sub>2</sub>], and Me<sub>2</sub>Zn (entry 17 in Table 1).

The results of the kinetic resolution of racemic 4-methyl-2-cyclohexenone (**3**) (Scheme 2) are summarized in Table 2.<sup>[8, 20]</sup> 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.<sup>[15]</sup> 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),



Scheme 2. Kinetic resolution of racemic 4-methyl-2-cyclohexenone (**3**).

Table 2. Kinetic resolution of **3** according to Scheme 2.

Entry	Ligand	R	t [min]	Conv. [%] <sup>[a]</sup>	ee [%] <sup>[a]</sup>	s
1 <sup>[b]</sup>	( <i>S,R,R</i> )-L1	Et	15	48	71	16
2	( <i>S,S,S</i> )-L1	Et	60	55	83	13
3	( <i>S,R,R</i> ) + ( <i>S,S,S</i> )-L1 (1:1)	Et	30	52	78	17
4	( <i>S,R</i> )-L2	Et	105	57	81	10
5	( <i>S,S</i> )-L2	Et	75	56	85	13
6	( <i>S,R,R</i> )-L4	Et	105	54	83	15
7	( <i>S,R,R</i> )-L4	Et	120	19	10	3
8 <sup>[c]</sup>	( <i>S,R,R</i> )-L1	Me	75	58	82	10
9 <sup>[c]</sup>	( <i>S,R,R</i> )-L1	<i>n</i> Bu	25	45	70	27

[a] Both conversion and *ee* determined by chiral GC in the presence of *n*-dodecane as internal standard (see Supporting Information). [b] Reaction performed at  $-40^{\circ}\text{C}$ . [c] Reaction performed at  $-35^{\circ}\text{C}$ .

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  $\text{Me}_2\text{Zn}$  instead of  $\text{Et}_2\text{Zn}$  led to a slight decrease in selectivity, whereas again the use of  $n\text{Bu}_2\text{Zn}$  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,R*)-L1-Cu(OTf)<sub>2</sub>] 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)<sub>2</sub>] (18 mg, 0.05 mmol) and (*S,R,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  $-30^{\circ}\text{C}$  and racemic **1a** (11.0 g, 100 mmol) and *n*-dodecane (4.0 mL) were added. After the mixture had been stirred for 10 min,  $\text{Et}_2\text{Zn}$  (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 51% conversion. Extra  $\text{Et}_2\text{Zn}$  (3.6 mL, 1.1 M solution in toluene) was added and after 3 h another sample was taken. GC analysis showed >99% *ee* and 55% conversion. The reaction mixture was quenched with 1 M HCl aq (150 mL), and the aqueous layer was extracted with  $\text{Et}_2\text{O}$  (3  $\times$  100 mL), and the combined organic layers were washed with brine and dried over  $\text{Na}_2\text{SO}_4$ . Filtration and evaporation of the solvents yielded a mixture of **1a**, addition product, and *n*-dodecane which were separated by column chromatography ( $\text{SiO}_2$ , hexanes/diethyl ether 4:1) to give (*R*)-(-)-**1a** (3.6 g, 33 mmol, 33%).  $[\alpha]_D^{20} = -87.3^{\circ}$  ( $c=0.81$ ,  $\text{CHCl}_3$ ).<sup>[3b]</sup> <sup>1</sup>H NMR (200 MHz,  $\text{CDCl}_3$ ):  $\delta=1.06$  (d,  $J=6.1$  Hz, 3H), 1.9–2.5 (m, 5H), 6.0 (m, 1H), 6.9 (m, 1H); <sup>13</sup>C NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta=21.06$  (q), 30.20 (d), 33.87 (t), 46.12 (t), 129.44 (d), 149.80 (d), 199.93 (s). GC analysis (Chiraldex G-TA) showed an *ee* > 99% (no (*S*)-**1a** was detected).

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- [1] a) T.-L. Ho, *Enantioselective Synthesis: Natural Products Synthesis from Chiral Terpenes*, Wiley, New York, **1992**; recent examples: b) S. Srikrishna, S. J. Gharpure, P. Praveen Kumar, *Tetrahedron Lett.* **2000**, *41*, 3177–3180; c) T. M. Meulemans, G. A. Stork, F. Z. Macaev, B. J. M. Jansen, A. De Groot, *J. Org. Chem.* **1999**, *64*, 9178–9188.  
 [2] a) A five-step synthesis of (*R*)-(+)-4-methyl-2-cyclohexenone starting from (+)-pulegone: H. W. Lee, S. K. Ji, I.-Y. C. Lee, J. H. Lee, *J. Org. Chem.* **1996**, *61*, 2542–2543; b) synthesis of optically pure 4-methyl-2-cyclohexenone from carvone: D. H. Hua, S. Venkataraman, *J. Org.*

*Chem.* **1988**, *53*, 1095–1097; c) (*R*)-(+)-5-methyl-2-cyclohexenone from (+)-pulegone: W. Oppolzer, M. Petrzilka, *Helv. Chim. Acta* **1978**, *61*, 2755–2762.

- [3] a) G. Sarakinos, E. J. Corey, *Org. Lett.* **1999**, *1*, 811–814; b) G. P.-J. Hareau, M. Koiwa, S. Hikichi, F. Sato, *J. Am. Chem. Soc.* **1999**, *121*, 3640–3650; c) T. Hanazawa, M. Koiwa, G. P.-J. Hareau, F. Sato, *Tetrahedron Lett.* **2000**, *41*, 2659–2662; d) G. P.-J. Hareau-Vittini, S. Hikichi, F. Sato, *Angew. Chem.* **1998**, *110*, 2221–2223; *Angew. Chem. Int. Ed.* **1998**, *37*, 2099–2101; e) S. Hikichi, G. P.-J. Hareau, F. Sato, *Tetrahedron Lett.* **1997**, *38*, 8299–8302.  
 [4] For two recent reviews see: a) B. L. Feringa, *Acc. Chem. Res.* **2000**, *33*, 346–353; b) L. A. Arnold, R. Imbos, A. Mandoli, A. H. M. De Vries, R. Naasz, B. L. Feringa, *Tetrahedron* **2000**, *56*, 2865–2878; see also: c) R. Naasz, L. A. Arnold, M. Pineschi, E. Keller, B. L. Feringa, *J. Am. Chem. Soc.* **1999**, *121*, 1104–1105; d) B. L. Feringa, M. Pineschi, L. A. Arnold, R. Imbos, A. H. M. De Vries, *Angew. Chem.* **1997**, *109*, 2733–2736; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2620–2623; e) A. H. M. De Vries, A. Meetsma, B. L. Feringa, *Angew. Chem.* **1996**, *108*, 2526–2528; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2374–2376; for other recent reports on the catalytic asymmetric 1,4-addition: f) I. H. Escher, A. Pfaltz, *Tetrahedron* **2000**, *56*, 2879–2888, and references therein; g) A. Alexakis, C. Benhaïm, X. Fournioux, A. van den Heuvel, J.-M. Levlève, S. March, S. Rosset, *Synlett* **1999**, 1811–1813, and references therein; h) M. Yan, Z.-Y. Zhou, A. S. C. Chan, *Chem. Commun.* **2000**, 115–116, and references therein.  
 [5] a) E. J. Corey, F. J. Hannon, *Tetrahedron Lett.* **1990**, *31*, 1393–1396; b) T. A. Blumenkopf, C. H. Heathcock, *J. Am. Chem. Soc.* **1983**, *105*, 2354–2358; c) N. L. Allinger, C. K. Riew, *Tetrahedron Lett.* **1966**, 1269–1272; d) C. H. Heathcock, T. C. Germroth, S. L. Graham, *J. Org. Chem.* **1979**, *44*, 4481–4487.  
 [6] Recent examples of nonenzymatic kinetic resolutions: a) S. Bellemin-Lapponnaz, J. Tweddell, G. Ruble, F. M. Breitling, G. C. Fu, *Chem. Commun.* **2000**, 1009–1010; b) J. Yun, S. L. Buchwald, *J. Org. Chem.* **2000**, *65*, 767–774; c) X. Feng, L. Shu, Y. Shi, *J. Am. Chem. Soc.* **1999**, *121*, 11002–11003; d) E. N. Jacobsen, *Acc. Chem. Res.* **2000**, *33*, 421–431; e) for a general introduction see: H. B. Kagan, J. C. Fiaud, *Top. Stereochem.* **1988**, *18*, 249–330.  
 [7] Kinetic resolution of 1,3-diene monoepoxides and alkynyl epoxides using copper–phosphoramidite complexes: a) F. Badalassi, P. Crotti, F. Macchia, M. Pineschi, A. Arnold, B. L. Feringa, *Tetrahedron Lett.* **1998**, *39*, 7795–7798; b) F. Bertozzi, P. Crotti, F. Macchia, M. Pineschi, A. Arnold, B. L. Feringa, *Tetrahedron Lett.* **1999**, *40*, 4893–4896.  
 [8] B.-D. Chong, Y.-I. Ji, S.-S. Oh, J.-D. Yang, W. Baik, S. Koo, *J. Org. Chem.* **1997**, *62*, 9323–9325.  
 [9] Selectivity factor  $s = [(\text{rate of fast-reacting enantiomer})/(\text{rate of slow-reacting enantiomer})] = \ln[(1-c)(1-ee)]/\ln[(1-c)(1+ee)]$ . See also ref. [6e].  
 [10] For an example of natural product synthesis starting from optically pure **1a** see ref. [2c].  
 [11] As a rule of thumb  $s < 15$  is insufficient for practical purposes,  $15 < s < 30$  is moderate to good and  $s > 30$  is excellent; K. Faber, *Biotransformation in Organic Chemistry*, Springer, Berlin, **1992**, p. 34.  
 [12] All absolute configurations were determined by comparison of the optical rotation of an isolated sample of unreacted starting material with optical rotations reported in literature: See ref. [3b] and references therein. Optical rotation of **1d**: ref. [16b].  
 [13] Resolution experiments with (*S,R,R*)-L1 at  $-30^{\circ}\text{C}$  gave approximately the same selectivity but were too fast to be accurately monitored in time, giving over 50% conversion after 5 min.  
 [14] This somewhat reduced yield of isolated product (33% of a maximum of 45%) is caused by the high volatility of **1a**, which results in loss of product during removal of the solvents.  
 [15] S. Berrada, P. Metzner, *Bull. Soc. Chim. Fr.* **1986**, 817–821.  
 [16] a) Racemic **1b** and **1c** were prepared according to: R. L. Frank, H. K. Hall, Jr., *J. Am. Chem. Soc.* **1950**, *72*, 1645–1648; b) for the synthesis and kinetic resolution of racemic **1d** see: M. Asaoka, K. Shima, H. Takei, *Tetrahedron Lett.* **1987**, *28*, 5669–5672.  
 [17] M. Asaoka, K. Shima, H. Takei, *J. Chem. Soc. Chem. Commun.* **1988**, 430–431.  
 [18] a) C. H. Wong, G. M. Whitesides, *Enzymes in Synthetic Organic Chemistry*, Elsevier, London, **1994**; b) A. D. Cuiper, M. L. C. E. Kouwijzer, P. D. J. Grootenhuys, R. M. Kellogg, B. L. Feringa, *J. Org.*

*Chem.* **1999**, *64*, 9529–9537; c) H. van der Deen, A. D. Cuiper, R. P. Hof, A. van Oeveren, B. L. Feringa, R. M. Kellogg, *J. Am. Chem. Soc.* **1996**, *118*, 3801–3803.

- [19] Currently, we do not have an explanation as to why the selectivity factor is not higher ( $s > 200$ ) in this resolution as could be expected from Figure 2. A possible explanation is that the kinetics are more complicated with  $\text{Me}_2\text{Zn}$  than with the other zinc reagents in which case the formula given in reference [9] is no longer valid.
- [20] Resolution of racemic **3** through a Diels–Alder process: B. Wegener, M. Hansen, E. Winterfeldt, *Tetrahedron: Asymmetry* **1993**, *4*, 345–350; example of natural product synthesis starting from (*S*)-**3**: S. Potvin, P. Canonne, *Tetrahedron: Asymmetry* **1996**, *7*, 2821–2824.

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

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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.<sup>[1]</sup> Parallel kinetic resolution (PKR) is an interesting strategy recently introduced, in which both enantiomers of a racemate can be converted into useful products.<sup>[2]</sup> This conceptual variation often requires the use of two different stoichiometric chiral reagents in parallel.<sup>[3]</sup> Parallel reactions under non-stoichiometric conditions have previously been described in the asymmetric Bayer–Villiger oxidation of racemic ketones, by means of enzymatic methods<sup>[4]</sup> or chiral catalysts,<sup>[5]</sup> and in the intramolecular cyclopropanation of racemic allylic diazoacetates catalyzed by chiral rhodium complexes.<sup>[6]</sup> 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.

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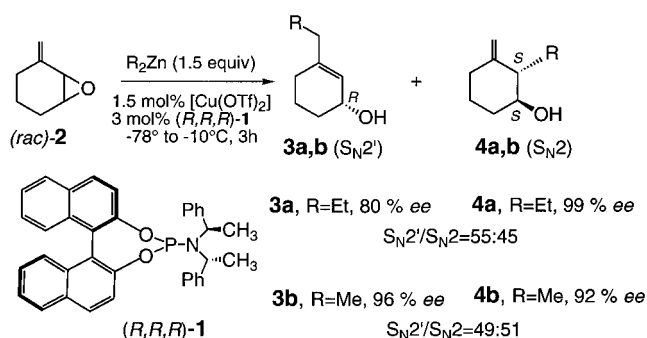
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Herein we report the first highly stereocontrolled transformation of a racemic mixture by an organometallic reagent and a chiral catalyst to give separable regioisomeric products.

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.<sup>[7a]</sup> When racemic vinyl epoxide **2** was treated with excess  $\text{Et}_2\text{Zn}$  (1.5 equiv) in the presence of the catalyst prepared in situ from  $[\text{Cu}(\text{OTf})_2]$  (1.5 mol %) (Tf = triflate =  $\text{OSO}_2\text{CF}_3$ ) and (*R,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  $\text{S}_{\text{N}}2'$ -addition product (*R*)-**3a** (46% yield, 80% *ee*; Scheme 1) together with the regioisomeric alcohol



Scheme 1. Enantioselective and regiodivergent addition of  $\text{R}_2\text{Zn}$  to racemic **2** catalyzed by  $[\text{Cu}(\text{OTf})_2]/(\text{R,R,R})$ -**1**.

(1*S*,2*S*)-**4a** (37% yield) having a surprising 99% *ee*! The progress of the reaction in terms of the conversion and enantioselectivities (Figure 1a and 1b, respectively) was therefore closely monitored.<sup>[8]</sup> 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  $\text{S}_{\text{N}}2'$ -regioselectivity to yield (*R*)-**3a** (15 min at  $-78^\circ\text{C}$ ), whereas the second slower one which provided (1*S*,2*S*)-**4a** ( $-10^\circ\text{C}$  and 3 h to go to completion) exhibited a complementary  $\text{S}_{\text{N}}2$  regioselectivity. In fact, after 15 min at  $-78^\circ\text{C}$ , the remaining vinyloxirane (1*S*,2*R*)-**2** (62% conversion) was enantiomerically pure, ( $>98\%$  *ee*)<sup>[9]</sup> and it reacted with nearly complete regioselectivity, and with complete *anti* stereoselectivity, at the 2-position. The catalyzed addition of  $\text{Me}_2\text{Zn}$  followed an even more pronounced regiodivergent behavior, affording, after complete conversion of **2**, (*R*)-**3b** (49% GC yield, 96% *ee*) and (1*S*,2*S*)-**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 ( $\text{S}_{\text{N}}2'/\text{S}_{\text{N}}2=98:2$ ), 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.<sup>[10]</sup> Probably the initially formed  $\pi$  complex **2A**<sup>[11][12]</sup> undergoes an oxidative addition resulting in the formation of