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

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General procedure for the kinetic resolution of 1a, 1b, 1d and 3 on an analytical scale:

All resolution were performed on a 1 mmol scale with 1 mol% Cu(OTf)$_2$ and 2 mol% of the phosphoramidite ligand with n-dodecane as internal standard according to the general procedure (vide infra).

Typical experimental procedure for the resolution of racemic 1a on an analytical scale; In flame dried glassware under an argon atmosphere 3.6 mg (0.01 mmol) Cu(OTf)$_2$ and 10.8 mg (0.02 mmol) (S,R,R)-L1 were dissolved in 10 ml of dry toluene. After stirring at RT for 1 h the colorless solution was cooled to -40°C and 110 mg (1.0 mmol) racemic 1a and 40 iL n-dodecane (internal standard) were added. After stirring for 10 min 0.73 mL Et$_2$Zn (1.1 M
in toluene, 0.8 mmol) was added. Samples of 0.2 mL were taken after 2, 5, 10, 15, 20, 25, 30, 45 and 60 min. The samples were quenched in 1 mL Et₂O saturated with water and filtered over a small plug of silica. The silica plugs were thoroughly rinsed with the “wet” Et₂O. Both conversion and ee were determined by chiral GC. Chiraldex G-TA, 50 m × 0.25 mm, He-flow: 1.0 mL/min, 100°C isotherm. \( T_{\text{ret}} \) 13.4 min (n-dodecane), \( T_{\text{ret}} \) 21.6 min ((S)-1a), \( T_{\text{ret}} \) 22.7 min ((R)-1a).

Determination of conversion and ee for 1a.
In all cases ee and conversion were determined by GC on a Chiraldex G-TA column (vide supra) except for the resolution performed with Me₂Zn because in this case the peaks of (S)-1a and addition product showed overlap. Ee and conversion were therefore measured on a Chiraldex A-TA column.

Determination of conversion and ee for 1b.
Ee and conversion were determined by GC on a Hydrodex-B-3P column, 25 m × 0.25 mm, He-flow: 0.9 mL/min. Initial temp: 90°C, initial time: 10 min, rate: 5°C/min, final temp: 150°C. \( T_{\text{ret}} \) 17.5 min (n-dodecane), \( T_{\text{ret}} \) 21.9 min ((S)-1b), \( T_{\text{ret}} \) 22.1 min ((R)-1b).
Determination of conversion and ee for 1d.

Ee and conversion were determined by GC on a CP-Chirasil-Dex CB column, 25 m x 0.25 mm, He-flow: 1.0 mL/min. Initial temp: 125°C, initial time: 20 min, rate: 10°C/min, final temp: 175°C. \( T_{\text{ret}} \) 6.0 min (\( n \)-dodecane), \( T_{\text{ret}} \) 10.9 min ((S)-1d), \( T_{\text{ret}} \) 11.4 min ((R)-1d).

Determination of conversion and ee for 3.

Ee and conversion were determined by GC on a ChiralDex G-TA column, 50 m x 0.25 mm, He-flow: 1.0 mL/min, 100°C isothermic. \( T_{\text{ret}} \) 13.4 min (\( n \)-dodecane), \( T_{\text{ret}} \) 20.1 min ((R)-3), \( T_{\text{ret}} \) 20.8 min ((S)-3).

Procedure for the kinetic resolution of 1c.

In flame dried glassware under an argon atmosphere 10.5 mg (0.03 mmol) Cu(OTf)\(_2\) and 31.3 mg (0.06 mmol) \((S,R,R)\)-L1 were dissolved in 20 ml of dry toluene. After stirring at RT for 1 h the colorless solution was cooled to -35°C and 1.0 g (5.8 mmol) racemic 1c and 0.40 mL \( n \)-hexadecane (internal standard) were added. After stirring for 10 min 2.85 mL Et\(_2\)Zn (1.1 M in toluene, 3.1 mmol) was added. After stirring overnight at -35°C a sample (0.2 mL) was taken. The sample was quenched in 1 mL Et\(_2\)O saturated with water and filtered over a small plug of silica. The silica plug was thoroughly rinsed with the
wet Et<sub>2</sub>O. Analyses on a DB-1 (J&W) GC column showed that
the conversion was 55%. The reaction mixture was quenched
with 20 mL of 1N HCl (aq) and the aqueous layer was
extracted with Et<sub>2</sub>O (3 × 25 mL) and the combined organic
layers were washed with brine and dried over Na<sub>2</sub>SO<sub>4</sub>. Filteration and evaporation of the solvents yielded a
mixture of 1c, addition product and n-hexadecane which
were seperated by column chromatography (SiO<sub>2</sub>, hexanes-
ether: 5-1) giving 378 mg (2.2 mmol, 38%) of (R)-(−)-1c.

α<sub>0</sub><sup>20</sup> = −37.9° (c = 1.97, CHCl<sub>3</sub>). <sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>): 2.5-2.8 (m, 4H), 3.4, (m, 1H), 6.1-6.2 (m, 1H), 7.0-7.1
(m, 1H), 7.2-7.4 (m, 5H). <sup>13</sup>C-NMR (300MHz, CDCl<sub>3</sub>): 33.64
(t), 40.91 (d), 44.81 (t), 126.64 (d), 126.94 (d), 128.72 (d), 129.73 (d), 143.13 (s), 149.47 (d), 199.15
(s). HPLC analysis (Chiralcel OJ, heptane-isopropanol: 95-5, flowrate 1.0 mL/min, 220 nm) showed ee = 89%.