Electronic Supplementary Information (ESI)

A new approach to switching of enantioselectivity in NHC–Cu-catalyzed conjugate addition of alkylzincs to cyclic enones

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General. All chemicals were obtained from commercial sources and were used as received. Azolium chlorides 3-12 has been prepared according to our previous paper. $^1$H- and $^{13}$C-NMR spectra were recorded on spectrometers at 400 and 100 MHz, respectively. Flash column chromatography was executed on silica gel 60 (Merck, mesh: 230-400; particle size: 0.040-0.063 nm).

Procedure for preparation of 9. To a flask were added N-benzylbenzimidazole $^2$ (4.4 mmol), 1,4-dioxane (15 mL) and α-chloroacetamidine derived from chloroacetyl chloride and (S)-leucinol $^3$ (4 mmol). After stirring the reaction mixture at 110 ºC for 16 h, the solvent was removed under reduced pressure. The residue was dissolved in methanol, and then activated carbon (ca. 1 g) was added. After 16 h, the activated carbon was removed by filtration. The filtrate was concentrated under reduced pressure to obtain a solid, which was purified by reprecipitation using ethyl acetate and methanol to afford the corresponding coupling product as a white solid.

1-[2-((S)-1-hydroxy-4-methyl-2-pentanylamino)-2-oxoethyl]-3-benzylbenzimidazolium chloride (9): $^1$H-NMR (CDCl$_3$): $\delta$ 10.7 (s, 1H), 9.20 (d, $J = 8.2$ Hz, 1H), 7.99 (d, $J = 8.2$ Hz, 1H), 7.57–7.27 (m, 8H), 7.42–7.32 (m, 5H), 5.86 (d, $J = 16.0$ Hz, 1H), 5.79 (d, $J = 15.2$ Hz, 1H), 5.72 (d, $J = 15.2$ Hz, 1H), 5.64 (d, $J = 16.0$ Hz, 1H), 4.72 (br, 1H), 3.97 (br, 1H), 3.65–3.54 (m, 2H), 1.61–1.50 (m, 2H), 1.27–1.24 (m, 1H), 0.83 (d, $J = 6.4$ Hz, 3H), 0.78 (d, $J = 6.4$ Hz, 3H); $^{13}$C-NMR: $\delta$ 164.6, 143.6, 132.3, 132.2, 130.6, 129.3, 129.2, 127.9, 127.2, 126.9, 114.2, 113.0, 64.3, 51.5, 51.1, 49.8, 39.6, 24.8, 22.7, 22.3. Anal. Calc. for C$_{22}$H$_{28}$ClN$_3$O$_2$$\cdot$0.25H$_2$O: C, 65.01; H, 7.07; N, 10.34. Found: C, 64.67; H, 6.65; N, 10.08%.

General procedure for catalytic asymmetric reaction of cyclic enone with R$_2$Zn. To a solution of Cu(OTf)$_2$ (0.06 mmol) in dehydrated THF (9 mL) was added 9 (0.045 mmol). Then, the reaction vessel was cooled at 0 ºC, and enone (1 mmol) followed by R$_2$Zn (3 mmol, 1 mol/L in hexanes for Et$_2$Zn or in heptane for Bu$_2$Zn) were added. The color immediately changed from yellow to dark brown. After stirring at room temperature for 3 h, the reaction was quenched with 10% HCl aq. (ca. 5 mL). The resulting mixture was extracted with diisopropyl ether (15 mL x 3) and dried over Na$_2$SO$_4$. The product was purified by silica gel column chromatography (hexane/EtOAc = 9/1). Enantiomeric excess was measured by chiral GLC. The configuration assigned through comparison with GLC data in the literature.
3-Ethylcyclohexanone (2)

Enantiomeric excess was determined by chiral GLC (Supelco γ-Dex225, 70 °C, N₂ gas, linear velocity of 27.5 cm/s, Rt = 65 min (S), 69 min (R)).

Racemic compound

Table 1, Run 10 (S : R = 90.5 : 9.5)

Table 2, Run 7 (S : R = 29.5 : 70.5)
3-Butylcyclohexanone (13)
Enantiomeric excess was determined by chiral GLC (Supelco γ-Dex225, 90 °C, N₂ gas, linear velocity of 27.5 cm/s, Rt = 65 min (S), 67 min (R)).

Racemic compound

Table 3, Run 1 (S : R = 92 : 8)

Table 3, Run 2 (S : R = 26 : 74)
4,4-Dimethyl-3-ethylcyclohexanone

Enantiomeric excess was determined by chiral GLC (Supelco γ-Dex225, 85 °C, N₂ gas, linear velocity of 27.5 cm/s, Rt = 62 min (R), 64 min (S)).

Table 3, Run 3 (R : S = 86 : 14)

Table 3, Run 4 (R : S = 15 : 85)
3-Ethylcycloheptanone (16)

Enantiomeric excess was determined by chiral GLC (Supelco $\beta$-Dex225, 80 °C, N$_2$ gas, linear velocity of 27.5 cm/s, Rt = 63 min ($S$), 69 min ($R$)).

Racemic compound

Table 3, Run 5 ($S : R = 92 : 8$)

Table 3, Run 6 ($S : R = 9 : 91$)
3-Butylcloheptanone (17)
Enantiomeric excess was determined by chiral GLC (Agilent J&W Cyclodex-B, 100 °C, N₂ gas, linear velocity of 27.5 cm/s, Rt = 73 min (S), 75 min (R)).

Racemic compound

Table 3, Run 7 (S : R = 88 : 12)

Table 3, Run 8 (S : R = 11 : 89)
References
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$^{13}$C-NMR Spectra for 9
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$^{13}$C-NMR Spectra for 3-ethylcyclohexanone (2)
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