proton resonances were of equal intensity (cf. [{Yb(OR)(μ-OR)}$_2$], R = 2,6-*t*Bu$_2$-4-MeC$_6$H$_2$[14]), and very complex changes occurred on cooling (reversed on warming). Accordingly, some structural modification, possibly involving partial dissociation of THF, occurs on dissolution in C_7D_8. Nevertheless, the spectra at the two lowest temperatures investigated (213 and 193 K) showed two equal intensity H4 resonances, consistent with a symmetrical dimer. The ^{171}Yb chemical shift at room temperature is within the range[15] for dimeric Yb^{II} complexes and close to the value of $\delta = 536$[15] for [{Yb(NR$'_2$)(μ-OR)}$_2$](R$'$ = SiMe$_3$).

Crystallization from light petroleum appears to be a vital factor in isolation of **1**, and probably causes loss of THF from a monomeric [Yb(*t*Bu$_2$pz)$_2$(thf)$_n$] species. (Compound **1** in C_4D_8O shows only single *t*Bu and H4 resonances in the ^{1}H NMR spectrum.) Adoption of μ-η^2:η^2 bonding enables the Yb^{II} center to attain a higher degree of coordination saturation than is possible with the alternative arrangements of a five-coordinate monomer, [Yb(η^2-*t*Bu$_2$pz)$_2$(thf)], or a five-coordinate μ-η^1:η^1- bridged dimer. Moreover the latter structure would lead to severe steric repulsion between the 3- and 5-*t*Bu substituents of the bridging ligands and the terminal ligands, whereas adverse steric interactions are reduced with the μ-η^2:η^2-*t*Bu$_2$pz ligands. 3,5-Disubstituted (*t*Bu, Ph) pyrazolates are insufficiently bulky to stabilize low-coordinate (≤ 6) Ln^{III} complexes,[7] and ytterbium is eight-coordinate in **2**.[8]

Experimental Section

The compound described here is extremely air- and moisture-sensitive and consequently all operations were carried out in an inert atmosphere (purified Ar or N_2). Yb metal powder (3.46 g, 20.0 mmol), $HgPh_2$ (1.96 g, 5.56 mmol), and *t*Bu$_2$pzH (2.0 g, 11.1 mmol) in THF (30 mL) were heated at 60 °C for 30 h. Filtration of the red solution to remove excess Yb and precipitated Hg followed by evaporation of THF yielded a red solid which on crystallization from light petroleum at −20 °C afforded large red crystals of **1** (2.58 g 77 %). IR (Nujol): $\tilde{\nu}$ = 3122 w, 1601 w, 1562 w, 1500 s, 1432 s, 1404 ms, 1358 s, 1315 m, 1296 m, 1248 vs, 1231 s, 1206 s, 1104 vw, 1037 s, 1006 s, 991 s, 917 m, 882 m, 802 s, 782 s, 732 m, 724 s, 664 w, 626 m cm^{-1}; ^{1}H NMR (300 MHz, [C_7D_8], 0.02 M, 297 K): δ = 6.25 (s) and 6.13 (s) (total integration 4H, H4 pz), 3.40 (vbr, 8H; α-THF), 1.44 (s) and 1.33 (s) (total integration 80H,*t*Bu; β-THF); ^{1}H NMR (300 MHz, [C_4D_8O], 0.05 M, 297 K): δ = 5.89 (s, 4H, H4 pz), 1.29 (s, 72H; *t*Bu); ^{13}C {^{1}H} NMR (50 MHz, [C_6D_6], 0.02 M, 297 K): δ = 30.6, 31.4 (CH_3), 32.1, 32.2 ($C(CH_3)_3$), 96.9, 100.2 (C3,C5), 162.5, 164.0 (C4); ^{171}Yb NMR (52.5 MHz, 0.05 M in PhMe): δ = 557 ($\Delta\nu_{1/2}$ = 44 Hz) (relative to [(C_5Me_5)$_2$Yb(thf)$_2$]); Vis/near IR (4.14×10^{-3} M in THF; λ_{max} (ε)) = 386 (383), 429sh (283) nm; elemental analysis calcd for $C_{52}H_{92}N_8O_2Yb_2$: C 51.73, H 7.68, N 9.28, Yb 28.66; found: C 51.30, H 7.54, N 9.21, Yb 28.28.

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Lithium Ephedrinate Mediated Aldol Reaction of Arylacetonitriles: Thermodynamic Control of Enantioselectivity**

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A reaction in which enantioselectivity is thermodynamically controlled is termed an "asymmetric transformation".[1] Both homogeneous ("first kind") and crystallization-induced ("second kind") asymmetric transformations are synthetically attractive, since they offer the possibility of converting a racemic mixture into its enantiomers in quantitative yield. The aldol reaction would appear to be a logical choice for the

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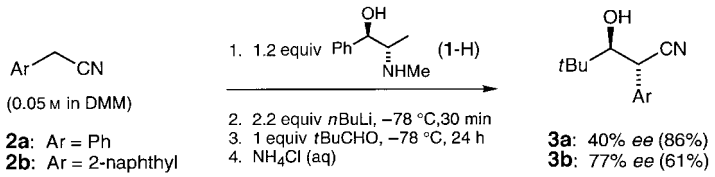
development of asymmetric transformations, given the documented facility of retro-aldol pathways. However, to date, no reversible enantioselective aldol reactions are known.

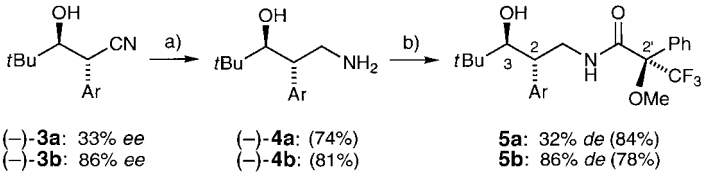
Herein we report the first example of a thermodynamically controlled enantioselective aldol reaction: Lithium ephedrinate (**1**-Li) mediates the addition of arylacetonitriles **2** to aldehydes with up to 86% *ee*. The β-hydroxynitriles *rac*-**3** are readily synthesized by the *anti*-selective aldol reaction of arylacetonitriles,[2] and are useful precursors for γ-amino alcohol neuronal reuptake inhibitors such as **4b**.[3] The use of nitriles in enantioselective aldol reactions is currently limited to acetonitrile[4] and 2-cyanopropionates.[5] To enable asymmetric synthesis of β-hydroxynitriles derived from **2**, we explored the use of a wide range of nonbasic, monobasic, and dibasic chelating chiral ligands. The best results were afforded by the use of 1.2 equivalents of **1**-Li (generated in situ by the addition of *n*BuLi to (1*R*,2*S*)-(−)-ephedrine (**1**-H)) in a 0.05 M solution of the nitrile in dimethoxymethane (DMM), as illustrated in Scheme 1 for the reaction of **2a** and **2b** with



Scheme 1. Aldol reaction of **2a** and **2b** with pivalaldehyde mediated by **1**-Li.

pivalaldehyde. In both cases the (2*S*,3*S*)-(−)-alcohols **3a** and **3b** are formed as pure *anti* compounds; the enantiomeric excesses were low (40% for **3a**) to moderate (77% for **3b**).

The absolute configurations were determined in the following way. Single-crystal X-ray determination of the (1*S*)-(+)-10-camphorsulfonic acid salt of (+)-*ent*-**4b**[6] (obtained by resolution of *rac*-**4b**, crystals from ethanol/water) established that (+)-*ent*-**4b** possessed the 2*R*,3*R* configuration. Reduction of (−)-**3b** afforded (−)-**4b**, thus indicating the 2*S*,3*S* configuration for (−)-**3b** (Scheme 2). Conversion of



Scheme 2. a) $LiAlH_4/AlCl_3$, Et_2O; NaOH (aq). b) Chloride salt of (+)-α-methoxy-α-trifluoromethylphenylacetyl chloride (1.1 equiv), CH_2Cl_2, NaOH (aq).

(−)-**3b** (86% *ee*) into the corresponding (*R*)-Mosher amide **5b** confirmed that reduction of **3b** was stereoselective.[7] Compound (−)-**3a** was assigned the 2*S*,3*S* configuration on the basis of its levorotation and the similarity of the ^{1}H NMR spectrum of the major (*R*)-Mosher amide **5a** to that of (2*S*,3*S*,2′*R*)-**5b**.

β-Amino alkoxides have been used previously as chiral controllers in 1,2-additions[8] and aldol reactions.[4, 9] However, our use of a 24-hour reaction time at −78 °C in the present case is unusual, and stems from the observation that initial enantioselectivities are near zero. The effect of reaction time on the enantiomeric excess in different reactions of **2a** and pivalaldehyde (0.025 M)[10] is depicted in Table 1. As can be

Table 1. Effect of reaction time on yield and enantiomeric excess of **3a** ($[\mathbf{2a}]_0 = 0.025$ M).[a]

t [h]	Yield [%][b]	*ee* [%][c]
1	73	7
2	81	16
6	67	29
12	83	33
24	79	36
48	72	32

[a] The values were determined from six individual reactions. [b] Yield of **3a** after chromatography (pure *anti* product according to ^{1}H NMR spectroscopy). [c] Determined by HPLC (Daicel Chiralcel OD).

seen, the yield is essentially maximized after 1 h, but the enantiomeric excess rises to a maximum value of approximately 34% after 12 h (curve A, Figure 1). Schlosser et al.

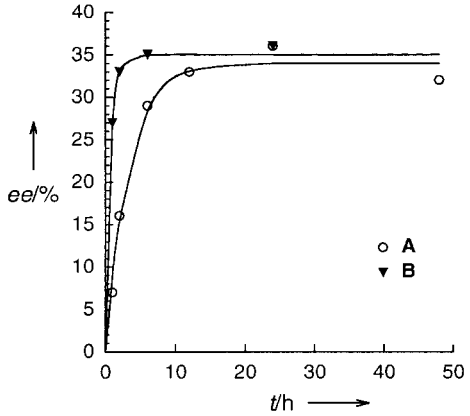
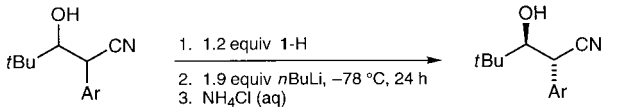


Figure 1. Enantiomeric excess of **3a** as a function of reaction time ($[\mathbf{2a}]_0 = 0.025$ M). Curve A: data from separate reactions (Table 1). Curve B: data from a single reaction.

observed a similar dependence of the enantiomeric excess on the reaction time for the carboxylation of sparteine-ligated lithium *N*-BOC-*N*-methylbenzylamine (BOC = *tert*-butoxycarbonyl).[11] As a check, another reaction was performed, and aliquots of the reaction mixture were periodically withdrawn and analyzed directly; these data are shown in curve B of Figure 1. These two series of experiments clearly indicate that enantioselectivity is thermodynamically controlled and that the aldol reaction is reversible.

We have previously established that diastereoselectivity in the reaction of lithiated **2a** and cyclohexanecarbaldehyde in THF at −78 °C within 30 min is kinetically controlled.[2c] The change to thermodynamic control in the present case is most likely due to the 48-fold increase in the reaction time, but the assistance of DMM or **1**-Li cannot be ruled out. As a final proof that the aldol reaction of nitriles was reversible over a 24-hour period at −78 °C, racemic *anti*-aldols *rac*-**3a**, **b** were individually resubjected to the reaction conditions (Scheme 3



rac-**3a, b** (2*RS*,3*RS*) (0.05 M in DMM)

3a: 31% *ee* (64%)
3b: 86% *ee* (75%)

Scheme 3. Deracemization of *rac*-**3a** and *rac*-**3b** mediated by **1**-Li.

and Experimental Section). Suprisingly, no deracemization[12] took place in the presence of even a slight excess of *n*BuLi. However, reactions performed with "substoichiometric" amounts of base (1.9 equiv) were successful: **3a** and **3b** are recovered with 31% and 86% *ee*, respectively, values close to those obtained in the corresponding aldol reactions (Scheme 1). Additional evidence for operation of a retro-aldol pathway is provided by the observation of small amounts of starting nitriles **2a** and **2b** (3–8%) in the crude product mixture. No precipitate was observed during the reaction, which indicates that **3a** and **3b** are formed as a result of an asymmetric reaction of the first kind.

At this point it is possible to outline a possible mechanism for asymmetric induction. Lithium alkoxides, including **1**-Li,[13] are known to be aggregated in ether solvents. We propose that the lithium alkoxides of both **3** and *ent*-**3** form mixed aggregates with **1**-Li. These mixed aggregates are diastereomeric and differ in energy; retro-aldol reaction establishes the equililibrium concentration of these diastereomers, which upon quenching gives rise to enantiomerically enriched **3**.

Noncovalently linked chiral controllers have been successfully applied in a great number of crystallization-driven asymmetric transformations.[1, 14] However, effective use of noncovalently linked chiral controllers in homogeneous asymmetric transformations is rarely achieved. In reactions which deracemize a single stereogenic center Pirkle et al.,[15] Hoppe et al.,[14] and Hoffmann et al.[16] have achieved asymmetric induction approaching 80% *ee*. Beak et al. have achieved up to 98% *ee* (at 10% conversion) by using a limiting reagent to "quench" a homogeneous asymmetric transformation of an organolithium compound.[17] The current work is noteworthy in view of the high enantiomeric excess obtained (86%), and the fact that two stereogenic centers are simultaneously deracemized.

Experimental Section

Deracemization of *rac*-**3b:** An oven-dried 50-mL flask was charged with *rac*-**3b**[2a] (126.5 mg, 0.5 mmol) and **1**-H (100 mg, 0.6 mmol) and purged with N_2. Then 10 mL of DMM (freshly distilled from Na/benzophenone) were added, and the solution was cooled to −78 °C. *n*BuLi (2.31 M in hexane, 0.4 mL, 0.92 mmol) was added, and after 24 hours at −78 °C the reaction was quenched by addition of a saturated aqueous solution of NH_4Cl (1.0 mL). Standard workup and column chromatography (EtOAc/hexane 15/85) afforded 94.3 mg of **3b** (75%). The spectral data matched that of *rac*-**3b**.[2b] HPLC analysis indicated 86% *ee* (Daicel Chiralcel OD, EtOH/hexane 5/95, 1 mL min^{-1}; t_{ret} = 13.0 (2*S*,3*S*), 16.6 min (2*R*,3*R*)). Recrystallization (toluene/hexane) gave 48 mg of **3b** (34%) with 95% *ee*; $[\alpha]_D = -74.0°$ (21 °C, c = 1.01 in $CHCl_3$).

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