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Asymmetric Amplification in Catalysis by *trans*-1,2-Diaminocyclohexane Bistriflamide

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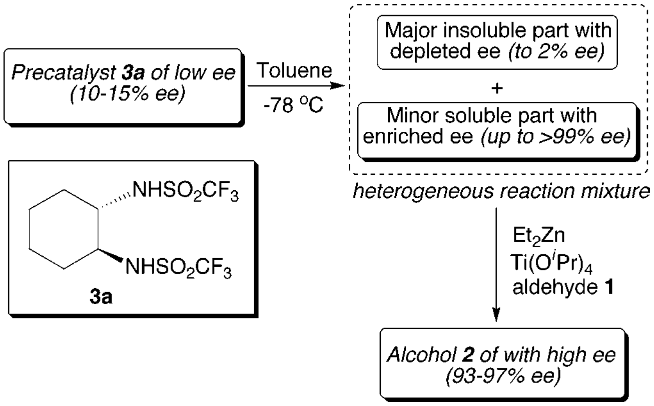
ABSTRACT



A strong asymmetric amplification is observed in the addition of diethylzinc on aromatic aldehydes in the presence of the bistriflamide of *trans*-1,2-diaminocyclohexane 3a. The asymmetric amplification originates from the insolubility of the catalyst precursor 3a of low enantiomeric excess (ee), with a concomitant large increase of ee for the minor soluble part of 3a. Controlled mono-N-acetylation of 3a (20% ee) at −78 °C allowed isolation of 4 possessing 90% ee.

Enantioselective addition of organozincs on aldehydes is of great synthetic importance.[1] One popular procedure is the system developed in 1989 by Ohno and Kobayashi, exemplified by the addition of diethylzinc on benzaldehyde **1a** at −78 °C in the presence of stoichiometric amounts of Ti(O^{i}Pr)$_4$ and 1 mol % equiv of a bissulfonamide derived from *trans*-1,2-diaminocyclohexane such as **3a** (Figure 1).[2] In the specific case of alcohol **2a**, ee's up to 97% have been observed. The authors kept **3a** and Ti(O^{i}Pr)$_4$ in toluene at 40 °C before cooling to −78 °C and adding Et$_2$Zn and aldehyde **1**. An alternate and convenient procedure, also giving 97% ee, was subsequently developed by Walsh et al., by mixing first **3a** and Et$_2$Zn at 23 °C before adding Ti(O^{i}Pr)$_4$ and aldehyde **1**.[3] The authors proposed a revised mechanism which is in agreement with the absence of a nonlinear effect. In 2002, we reported that the Ohno−Kobayashi protocol led to a strong asymmetric amplification,[4] and recently, we used this protocol in a sequential combination of two asymmetric amplifications;[5] the mechanistic

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(1) (a) Knochel, P.; Perea, J. J. A.; Jones, P. *Tetrahedron* **1998**, *54*, 8275−8319 and references therein. (b) Ostwald, R.; Chavant, P.-Y.; Stadtmuller, H.; Knochel, P. *J. Org. Chem.* **1994**, *59*, 4143−4153.

(2) (a) Takahashi, H.; Kawakita, T.; Yoshioka, M.; Kobayashi, S.; Ohno, M. *Tetrahedron Lett.* **1989**, *30*, 7095−7098. (b) Yoshioka, M.; Kawakita, T.; Ohno, M. *Tetrahedron Lett.* **1989**, *30*, 1657−1660. (c) Takahashi, H.; Kawakita, T.; Ohno, M.; Yoshioka, M.; Kobayashi, S. *Tetrahedron* **1992**, *48*, 5691−5700.

(3) (a) Pritchett, S.; Woodmansee, D. H.; Gantzel, P.; Walsh, P. J. *J. Am. Chem. Soc.* **1998**, *120*, 6423−6424. (b) Pritchett, S.; Woodmansee, D. H.; Gantzel, P.; Walsh, P. J. *Tetrahedron Lett.* **1998**, *39*, 5941−5942.

(4) Luukas, T. O.; Fenwick, D. R.; Kagan, H. B. *C. R. Chimie* **2002**, *5*, 487−491.

(5) Satyanarayana, T.; Kagan, H. B. *Chem.−Eur. J.* **2006**, *12*, 5785−5789.

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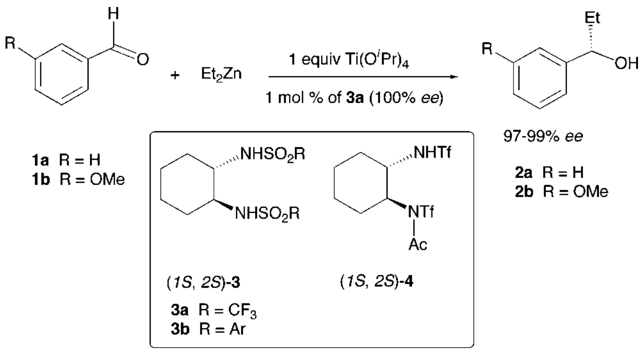

Figure 1. Addition of diethylzinc on aldehydes.

implications were shortly discussed.[4] We wish to report here that the asymmetric amplification associated to the Ohno–Kobayashi procedure is correlated with the insolubility of catalyst precursor **3a** in toluene. We previously observed that, when catalyst precursor **3a** and Ti(O^{i}Pr)$_4$ are first mixed in toluene and then heated at various temperatures, the system does not seem fully homogeneous.[6] To study this problem, we performed several experiments. First, it was found that the asymmetric amplification was unchanged if the catalyst precursor **3a** was heated *alone* at 55 °C in toluene, before cooling to −78 °C and then introducing all the reactants. The composition of the solutions was analyzed at −78 °C before addition of the reactants, by filtering the solid and evaporating the solvent. Results in toluene and in some other solvents are reported in Table 1.

Table 1. ee Enrichment of **3a** [10% ee with (1*R*,2*R*)-excess] in Various Solvents after a Resting Time of 10 min at −78 °C[a]

amount of **3a**[a] (mg)	solvent (1 mL)[b]	filtrate **3a** ee %[c] (amount)	precipitate **3a** ee %[c] (amount)
94.5	toluene	>96 (5.0 mg)	10 (82.0 mg)
94.5	toluene (1 mL) + hexane (1.5 mL)	>99[d] (3.0 mg)	11 (82.0 mg)
18.9	CH$_2$Cl$_2$	89 (3.0 mg)	7 (14.0 mg)
18.9	diethyl ether	50 (4.0 mg)	2 (13 mg)
18.9	toluene	>98 (1.5 mg)	2 (15 mg)

[a] A standard 0.25 M solution of 10% ee (1*R*,2*R*)-**3a** in EtOAc was prepared and used throughout all the above experiments. [b] EtOAc was removed under reduced pressure. 1 mL of toluene was added and warmed at 55 °C for 30 min and rapidly cooled to −78 °C followed by quick filtration by suction filtration. [c] ee of **3a** was determined by ^{19}F NMR using quinidine as the shift reagent. [d] The minor enantiomer was not detected in this case.

The data in Table 1 show that **3a** with an ee as small as 10% leaves a precatalyst in toluene at −78 °C with an ee higher than 96−98%. This interesting ee enrichment of **3a** in solution was also successfully transferred to products when **3a** was employed as the catalyst in Et$_2$Zn addition on aldehydes. By taking advantage of the information in Table 1, some catalytic reactions were undertaken (Table 2) using 3-methoxybenzaldehyde **2b**. ee enrichment of **3a** in these conditions (as high as 96−98% ee starting from 10% ee) very reasonably correlates with the enantiomeric excess of the product **2**. A reaction of Et$_2$Zn addition on **2b** using 15% ee **3a** performed in toluene at −78 °C gave the corresponding alcohol with 97% ee.

Table 2. Use of **3a** of Low ee as the Catalyst in the Reaction of Et$_2$Zn on Aldehyde **1b**[a]

entry	initial ee % of **3a**	conversion %	ee % of (*R*)-**2b**[b]
1	15.0	>95	97
2	10.0	>95	93

[a] (1*R*,2*R*)-**3a** (20 mol % equiv) dissolved in EtOAc was taken into a Schlenk tube, and EtOAc was removed under reduced pressure. 1 mL of toluene was added and warmed at 55 °C for 30 min. Then, it was rapidly cooled to −78 °C followed by the addition of all reactants. After 3 h, reactions were quenched with 1 N HCl. [b] Measured by HPLC on Chiralcel OD-H.

We have also noticed reactions becoming quite slow for low ee's of the precatalyst, as already reported.[4] This is in agreement with the great differences of solubility of enantiopure and racemic **3a**. It is the reason the catalyst loading has been increased here from 1 mol % equiv to 20 mol % equiv to speed up the reaction. The melting points of enantiopure and racemic **3a** are 189 and 240 °C, respectively (measured using DSC). This is a good indication of the racemate formation in the crystallization of *rac*-**3a**. It is interesting to point out that N-acetylation of **3a** (20% ee) by 20 mol % equiv of acetyl chloride in toluene at −78 °C in the presence of NEt$_3$ (20 mol % equiv) allowed recovery of the monoacetyl derivative **4** (90% ee) in agreement with the expected high ee of the soluble part of **3a**.

Nonlinear effects in asymmetric catalysis have attracted a lot of interest since the initial report in 1986[7] and led to many developments (some reviews: refs 8−11). Asymmetric amplification [(+)-nonlinear effect] is interesting from both synthetic and mechanistic points of view (some reviews : refs 11 and 12) and is very helpful in asymmetric autocatalysis.[12−14] Recently, Blackmond and co-workers

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(6) In our paper from 2002 (ref 4), we hypothesized that (+)-NLE in this reaction could be due to the reservoir effect where a diastereomeric organometallic species of *racemic composition* would be formed external to the catalytic system and did not consider the insolubility issue.

(7) Puchot, C.; Samuel, O.; Dunach, E.; Zhao, S.; Agami, C.; Kagan, H. B. *J. Am. Chem. Soc.* **1986**, *108*, 2353−2357.

(8) Girard, C.; Kagan, H. B. *Angew. Chem., Int. Ed.* **1998**, *37*, 2922−2959.

(9) Avalos, M.; Babiano, R.; Cintas, P.; Jimenèz, J. L.; Palacios, J. C. *Tetrahedron: Asymmetry* **2000**, *11*, 2845−2874.

(10) Kagan, H. B.; Luukas, T. O. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Berlin, 1999; Vol. 1, pp 101−118.

(11) Kagan, H. B.; Fenwick, D. R. *Top. Stereochem.* **1999**, *22*, 257−296.

(12) Soai, K.; Shibata, T.; Sato, I. *Acc. Chem. Res.* **2000**, *33*, 382−390.

(13) Soai, K.; Shibata, T.; Morioka, H.; Choji, K. *Nature* **1995**, *378*, 767−768.

(14) Blackmond, D. G. *Adv. Synth. Catal.* **2002**, *344*, 156−158.

investigated several examples of asymmetric amplifications involving organocatalysts.[15,16] They discovered that the partial solubility of an enantioimpure catalyst such as proline may lead to a substantial increase of ee for the soluble part. This is common to the numerous amino acids that give rise to a racemate crystallization. In that case, the soluble part has a high ee which is determined by the eutectic composition of the system. We noticed a similar situation with bistriflate **3a**. We calculated the eutectic composition from the values of the melting points of racemic and enantiopure **3a** according to the procedure given in refs 17 and 18 and found a value of 96% ee. This is virtually the same as the eutectic composition in the solubility diagram, i.e., in the tertiary phase system.[19] Therefore, we took this 96% ee as the eutectic composition of saturated solutions of **3a** in a solvent. However, it is lower than the measured ee of saturated solutions of **3a** in toluene or a toluene/hexane mixture (entries 1, 2, and 5; Table 1). Possibly, this arises from the fast cooling of the solution from 55 °C to −78 °C, giving the deposit of a large amount of racemic crystals without allowing the system to reach to an equilibrium of eutectic composition.[20] This explains reactions that become sluggish with a low ee of **3a**. Also, solvent presence can have an effect on the eutectic composition.[16b] The controlled mono-N-acetylation of **3a** (20% ee) into **4a** (90% ee) clearly shows that it is possible to trap the soluble and enantioenriched **3a** chemically at −78 °C. To verify the fact that (+)-NLE in this reaction is solely due to the ee enrichment of **3a** in solution (arising from the insolubility of the racemic part of **3a**) and not due to the involvement of any kind of homochiral and heterochiral organometallic complexes, we have performed a reaction following a procedure similar to the one reported by Walsh.[3] First, Et_2Zn was added to a partially soluble solution of **3a** with 26% ee in toluene at room temperature which resulted in the quick formation of a clear homogeneous solution. When this mixture was then cooled to −78 °C followed by the addition of $Ti(O^iPr)_4$ and benzaldehyde, it provided the corresponding product **2a** with 21% ee, indicating the absence of NLE which is consistent with results obtained by Walsh.[3] This result clearly excludes the possible involvement of homochiral and heterochiral aggregates of organometallic species. Thus, the (+)-NLE in this reaction arises exclusively from the ee enrichment of **3a** in solution. One can now envisage taking advantage of the high ee of partially soluble **3a** at −78 °C in running catalytic reactions other than organozinc additions on aldehydes. We are looking for such possibilities.

The plot $ee_{auxiliary} = f(ee_{product})$ is a sensitive tool for investigating catalytic systems. The various procedures of catalyst preparation may or may not generate a nonlinear effect. In the present case, the asymmetric amplification observed with the Ohno−Kobayashi protocol is clearly associated to the strong increase in ee of the precatalyst **3a** for the fraction present in solution. It may also be noted here that the presence of NLE does not indicate the involvement of two or more chiral ligands in the catalytic cycle. This conclusion emphasizes the importance of complementary studies to draw mechanistic conclusions based on the observed NLE.

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Supporting Information Available: Experimental procedures, DSC plots, and the eutectic composition determination. This material is available free of charge via the Internet at http://pubs.acs.org.

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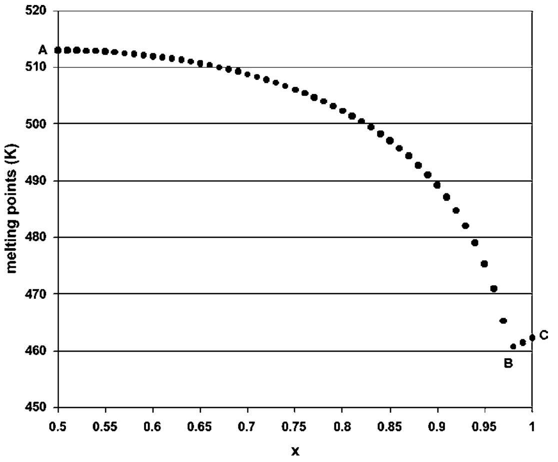
(15) Mathew, S. P.; Iwamura, H.; Blackmond, D. G. *Angew. Chem., Int. Ed.* **2004**, *43*, 3317−3321.

(16) (a) Klussmann, M.; Iwamura, H.; Mathews, S. P.; Wells, D. H., Jr.; Pandya, U.; Armstrong, A.; Blackmond, D. G. *Nature* **2006**, *441*, 521−525. (b) Klussmann, M.; White, A. J. P.; Armstrong, A.; Blackmond, D. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 7985−7989.

(17) Calculations of the eutectic composition:



(a) the Schröder−Van Laar equation [$\ln x = \Delta Hf_{enant}/R(1/T_{enant} - 1/T)$][18a] defines the part of the curve (BC part of the below plot) where the mixture behaves like a conglomerate, and (b) the Prigogine−Defay equation [$\ln 4x(1 - x) = 2\Delta Hf_{rac}/R(1/T_{rac} - 1/T')$][18b] allows us to draw the part of the curve (AB part of the below plot) where the mixture behaves like a racemic compound. In (a) and (b), ΔHf_{enant} (5556 cal/mol), ΔHf_{rac} (10 697 cal/mol), T_{enant} (462 K), and T_{rac} (513 K) are enthalpies of fusion and melting points, respectively, of enantiopure and racemic compounds **3a** (measured on DSC) at 25 °C→300 °C→25 °C (at 2 °C/min) and x = mole fraction of the more abundant enantiomer ($0.5 < x < 1$).

(18) (a) *Enantiomers, Racemates and Resolutions*; Jacques, J., Collet, A., Wilen, S. H., Eds.; John Wiley: New York, 1981; Chapter 2.2, Section 2.2.3, pp 46−47. (b) *Enantiomers, Racemates and Resolutions*; Jacques, J., Collet, A., Wilen, S. H., Eds.; John Wiley: New York, 1981; Chapter 2.3, Section 2.3.2, pp 90−91.

(19) *Enantiomers, Racemates and Resolutions*; Jacques, J., Collet, A., Wilen, S. H., Eds.; John Wiley: New York, 1981; Section 5.1.11, pp 289−290.

(20) In the case of racemate crystallization (if the solubility of racemate crystals is lower than enantiopure crystals), it is in fact possible to obtain a pure enantiomer from solution when the crystallization is carried out rapidly in a small quantity of solvent without allowing the system to reach the solubility equilibrium, i.e., the eutectic composition.[21]

(21) *Enantiomers, Racemates and Resolutions*; Jacques, J., Collet, A., Wilen, S. H., Eds.; John Wiley: New York, 1981; Chapter 3.3, Section 3.3.3, pp 195−196.