Kitamura, S. Suga, M. Niwa, R. Noyori, *J. Am. Chem. Soc.* **1995**, *117*, 4832 – 4842; c) N. Oguni, Y. Matsuda, T. Kaneko, *J. Am. Chem. Soc.* **1988**, *110*, 7877 – 7877; d) K. Mikami, Y. Motoyama, M. Terada, *J. Am. Chem. Soc.* **1994**, *116*, 2812 – 2820; K. Mikami, M. Terada, *Tetrahedron* **1992**, *48*, 5671 – 5680; M. Terada, K. Mikami, T. Nakai, *J. Chem. Soc. Chem. Commun.* **1990**, 1623 – 1624.

[3] a) K. Mikami, S. Matsukawa, *Nature* **1997**, *385*, 613 – 615; b) S. Matsukawa, K. Mikami, *Tetrahedron Asymm.* **1997**, *8*, 815 – 816; c) *Enantiomer* **1996**, *1*, 69 – 73; d) T. Ohkuma, H. Doucet, T. Pham, K. Mikami, T. Korenaga, M. Terada, R. Noyori, *J. Am. Chem. Soc.* **1998**, *120*, 1086 – 1087.

[4] For an opposite strategy of deactivation, see N. W. Alcock, J. M. Brown, P. J. Maddox, *J. Chem. Soc. Chem. Commun*. **1986**, 1532 – 1534; J. M. Brown, P. J. Maddox, *Chirality* **1991**, *3*, 345 – 354; K. Maruoka, H. Yamamoto, *J. Am. Chem. Soc.* **1989**, *111*, 789 – 790; J. W. Faller, J. Parr, *J. Am. Chem. Soc.* **1993**, *115*, 804 – 805.

[5] a) The activation barrier to axial torsion in selectively deuterated BIPHEP is measured to be only (22 ± 1) kcal, which suggests that axial rotation takes place at room temperature or above: O. Desponds, M. Schlosser, *Tetrahedron Lett*. **1996**, *37*, 47 – 48, and references therein; b) see also 6,6′-substituted analogues: G. Trabesinger, A. Albinati, N. Feiken, R. W. Kunz, P. S. Pregosin, M. Tschoerner, *J. Am. Chem. Soc.* **1997**, *119*, 6315 – 6323, and references therein.

[6] a) T. Ohkuma, H. Ooka, S. Hashiguchi, T. Ikariya, R. Noyori, *J. Am. Chem. Soc.* **1995**, *117*, 2675 – 2676; b) T. Ohkuma, H. Ooka, T. Ikariya, R. Noyori, *J. Am. Chem. Soc.* **1995**, *117*, 10417 – 10418; c) H. Doucet, T. Ohkuma, K. Murata, T. Yokozawa, M. Kozawa, E. Katayama, A. F. England, T. Ikariya, R. Noyori, *Angew. Chem.* **1998**, *110*, 1792 – 1796; *Angew. Chem. Int. Ed.* **1998**, *37*, 1703 – 1707.

[7] a) P. Mangeney, T. Tejero, A. Alexakis, F. Grosjean, J. Normant, *Synthesis* **1988**, 255 – 257; b) S. Pikul, E. J. Corey, *Org. Synth*. **1993**, *71*, 22 – 29.

[8] 3,5-Dimethylphenyl-BINAP: K. Mashima, Y. Matsumura, K. Kusano, H. Kumobayashi, N. Sayo, Y. Hori, T. Ishizaki, S. Akutagawa, H. Takaya, *J. Chem. Soc. Chem. Commun*. **1991**, 609 – 610.

[9] ^{1}H NMR ($CDCl_3$): (*S*)-DM-BINAP/$RuCl_2$/(*S*,*S*)-DPEN: $\delta = 3.02$, 3.16, 4.19; (*R*)-DM-BINAP/$RuCl_2$/(*S*,*S*)-DPEN: $\delta = 2.62$, 3.86, 4.43. ^{1}H NMR ($CDCl_3$/$(CD_3)_2CDOD$ 1/2): (*S*)-DM-BINAP/$RuCl_2$/(*S*,*S*)-DPEN: $\delta = 2.98$, 3.36, 4.21; (*R*)-DM-BINAP/$RuCl_2$/(*S*,*S*)-DPEN: $\delta =$ 2.60, 3.87, 4.42.

[10] Although the DM-BIPHEP/$RuCl_2$/DPEN complex was treated with DM-BINAP in 2-propanol, it was not observed by ^{1}H NMR spectroscopy.

[11] R. L. Chowdhury, J.-E. Bäckvall, *J. Chem. Soc. Chem. Commun*. **1991**, 1063 – 1064; K.-J. Haack, S. Hashiguchi, A. Fujii, T. Ikariya, R. Noyori, *Angew. Chem*. **1997**, *109*, 297 – 300; *Angew. Chem. Int. Ed. Engl*. **1997**, *36*, 285 – 288; R. Noyori, S. Hashiguchi, *Acc. Chem. Res.* **1997**, *30*, 97 – 102.

[12] P. D. Theisen, C. H. Heathcock, *J. Org. Chem.* **1988**, *53*, 2374 – 2378; W. H. Pirkle, S. D. Beare, *J. Am. Chem. Soc.* **1967**, *89*, 5485 – 5487.

Super High Throughput Screening (SHTS) of Chiral Ligands and Activators: Asymmetric Activation of Chiral Diol – Zinc Catalysts by Chiral Nitrogen Activators for the Enantioselective Addition of Diethylzinc to Aldehydes**

Kuiling Ding, Akihiro Ishii, and Koichi Mikami*

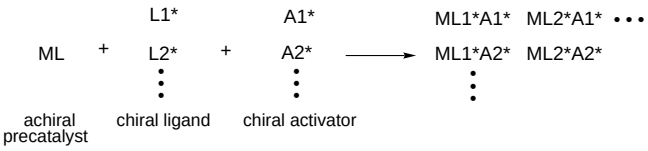
Combinatorial chemistry has been well recognized as a useful strategy for the discovery and optimization of bioactive drugs, coordination complexes, and solid-state materials.[1] Of the split-and-mix and parallel-matrix strategies, the latter is more employable for lead optimization, and high-throughput screening (HTS) is essential for tuning a variety of modifications.[2] However, only a limited number of investigations has so far been reported on the optimization of chiral ligands for metal complexes.[3] With HPLC or gas chromatography (GC) on chiral columns, it takes a tediously long time to separate enantiomeric products and then to determine the enantioselectivity of the reactions. The application of a detection system based on circular dichroism (CD) to HPLC on nonchiral stationary phases allows the simultaneous monitoring of the CD signal $\Delta\varepsilon$, the absorption ε, and their ratio $g = \Delta\varepsilon/\varepsilon$. The dissymmetry factor g is independent of concentration and is linearly related to the enantiomeric excess.[4] With this technique, the enantiomeric excess of the product could be determined within minutes without separation of the enantiomeric products. Therefore, combined application of the combinatorial chemistry (CC) factory (Dainippon Seiki, DNC) for reactions and HPLC-CD provide a highly efficient screening system, which we refer to as the super high throughput screening (SHTS) system, for finding the most effective catalyst through asymmetric activation.

Asymmetric activation of a chiral catalyst with a chiral additive may enhance the levels of catalyst efficiency and enantioselectivity.[5] The advantage of this approach over the deactivation strategy[6] is that the activated catalyst can produce a greater enantiomeric excess in the products than can the enantiomerically pure catalyst on its own. Sharpless et al. emphasized the importance of "chiral ligand accelation" through the construction of an asymmetric catalyst from an achiral precatalyst by ligand exchange with a chiral ligand.[7] Chiral catalysts thus obtained with chiral ligands (L1*, L2*,…) may be further evolved with chiral activators (A1*, A2*,…) into the most catalytically active and enantioselective chiral catalysts (Scheme 1).

[*] Prof. Dr. K. Mikami, Prof. Dr. K. Ding, A. Ishii
Department of Chemical Technology, Faculty of Engineering
Tokyo Institute of Technology
2-12-1 Ookayama, Meguro-ku, Tokyo 152 (Japan)
Fax: (+81) 3-5734-2776
E-mail: kmikami@o.cc.titech.ac.jp

[**] This work was aided by the Ministry of Education, Science, Sports and Culture of Japan (nos. 09238209 and 10208204). A UNESCO research fellowship for K. D. is gratefully acknowledged. We are grateful to Mr. Naotaka Sawada of Dainippon Seiki Co., Ltd., Dr. Akito Tanaka of Fujisawa Pharmaceutical Co., Ltd., and Mr. Kenichi Kudo of JASCO Corp. for their technical assistance.

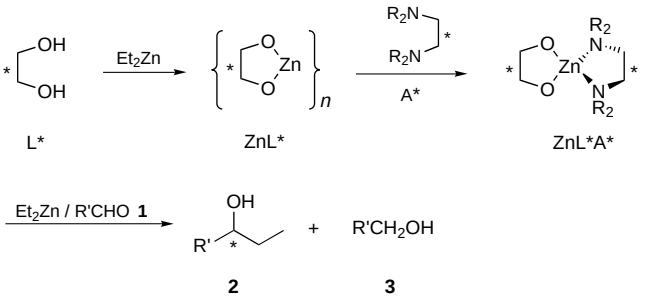
  1433-7851/99/3804-0497 $ 17.50+.50/0



Scheme 1. General principle for the creation of a catalyst system by asymmetric activation.

We now report the SHTS of parallel solution libraries of chiral ligands and activators for diol–zinc catalysts in the addition of diethylzinc to aldehydes by using the CC factory and HPLC-CD. For C–C bond forming reactions, enantioselective addition of diorganozinc reagents to aldehydes constitutes one of the most important and fundamental asymmetric reactions.[8] Since the initial report by Oguni and Omi,[9] various chiral ligands, including β-amino alcohols, have been used for this type of reaction.[10–12] However, less attention has been paid to C_2-symmetric chiral diols, probably due to their lower catalytic activity and enantioselectivity for the reaction.[13] Only very recently, some derivatives of 2,2′-dihydroxy-1,1′-binaphthyl (BINOL) were found to be effective,[14] but the simple BINOL itself is very inert to the reaction.

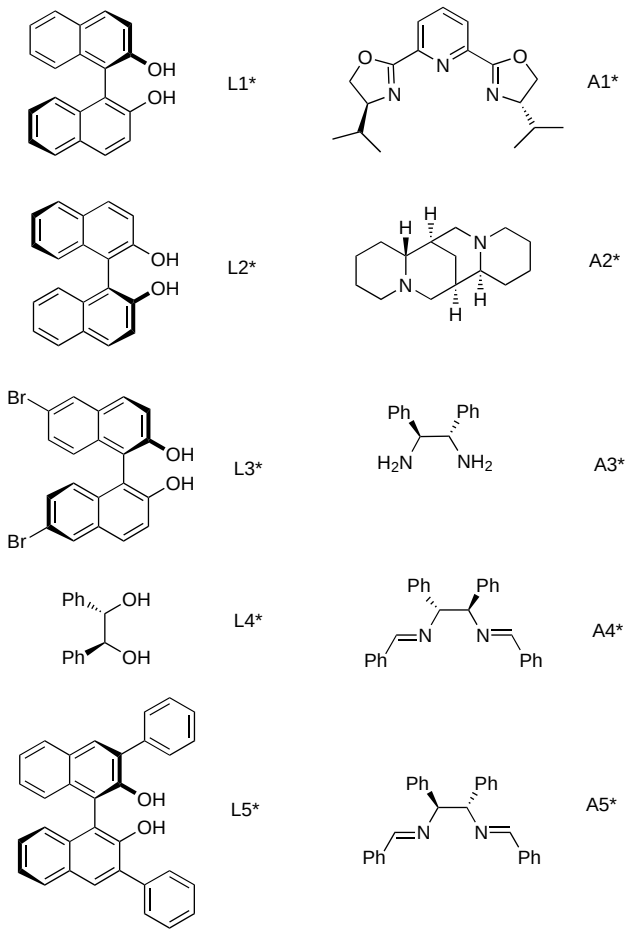
It is reasonable to assume that the active catalyst in the addition of diethylzinc to aldehydes is a monomeric zinc alkoxide; the cleavage of the higher aggregates could result in an activation of overall catalyst system.[15] As shown in Scheme 2, for activation of the diol–zinc catalyst system,



Scheme 2. Asymmetric activation of diol–zinc catalysts by nitrogen ligands.

addition of a chiral nitrogen ligand is most efficient because of its ability to coordinate so strongly to the zinc cation. As a result, a monomeric zinc complex is expected to be formed in a manner similar to that of a chiral salen–zinc complex (salen = *N*,*N*′-bis(salicylidene)ethylenediamine dianion).[16] Furthermore, bimolecular combination of chiral activators with the diol–zinc complexes should be more convenient than the unimolecular combination. Thus, we initially examined the primary combinatory library of chiral ligands (L1*–L5*) and chiral activators (A1*–A5*), from which the lead compound could be further optimized for the next generation of the chiral ligands and activators.

The reactions were carried out as described in the Experimental Section. As shown in Figure 1, under the experimental conditions we observed an effect of the activation in terms of catalyst efficiency (Figures 1a and b).



Enantioselectivity of the reaction is also increased by matched combination of diol ligands and nitrogen activators (Figure 1c). For example, L1* and A4* promote the reaction to give (*S*)-1-phenylpropanol with 8.2% *ee* (54% yield) and 1.1% ee (64% yield), respectively. However, the combined use of L1* and A4* quantitatively provides the product with 37.4% *ee* (*S*). The substitution of the 3- and 3′-positions with bulky phenyl groups further prevents the aggregation of BINOL/Zn and increases the enantioselectivity, the best combinations were found to be L5*/A4* and L5*/A5* to provide (*S*)-1-phenylpropanol with up to 65% *ee* and in quantitative yields.

On the basis of the results derived from primary combinatorial libraries, we then created a new library of diimines (activators; A4*–A15*) with 12 members by simple condensation of enantiopure 1,2-diphenylethylenediamine or 1,2-diaminocyclohexane with two equivalents of aromatic aldehydes respectively. As shown in Figure 2, all library members significantly activate the Zn(L5*) complex and produce 1-phenylpropanol in higher yields and with higher enantioselectivities than those complexes obtained by only using the ligands themselves. The reaction could be completed within minutes in the case of L5*/A9*. The chirality of the nitrogen activators has little effect on the configuration of the product, but may influence the enantioselectivity, particularly in the cases of L5* with A8*, A9*, A12*, or A13*. Therefore, the absolute configuration of product is determined primarily by that of the diol, which is consistent with the empirical rule

  1433-7851/99/3804-0498 $ 17.50+.50/0

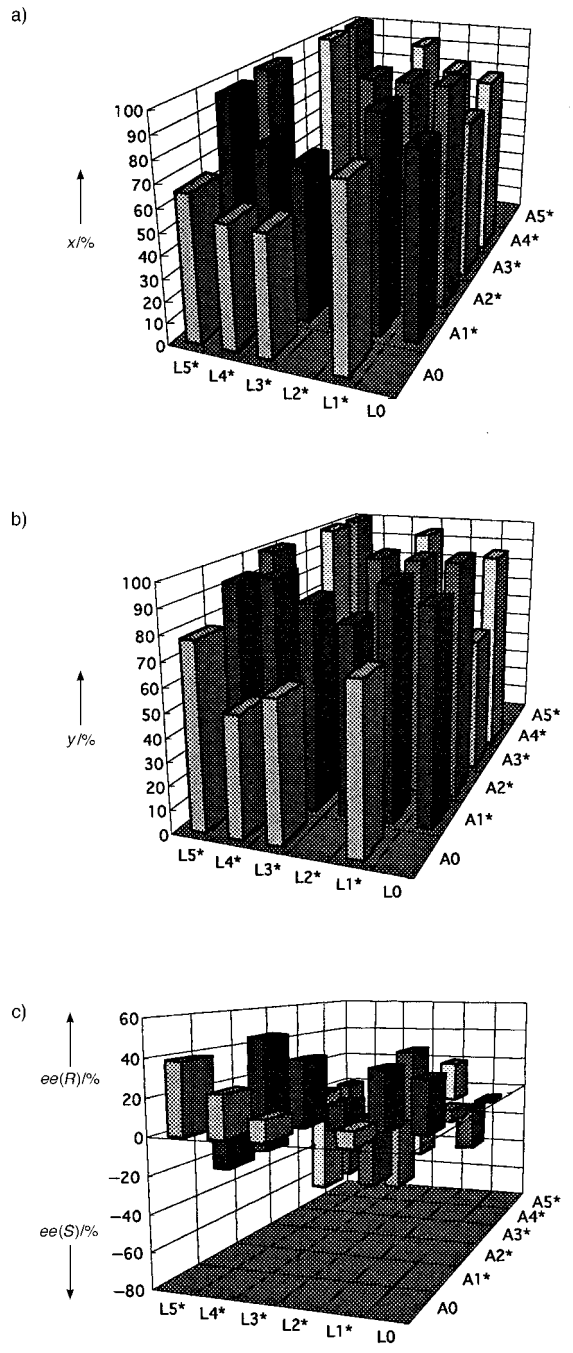


Figure 1. Random screening of chiral ligands L0 – L5* and activators A0 – A5* for the hydrogenation of aldehydes **1** to alcohols **2** and **3**. a) Conversion x of **1**; b) selectivity y of **2** versus **3**; c) enantiomeric excess of **2**.

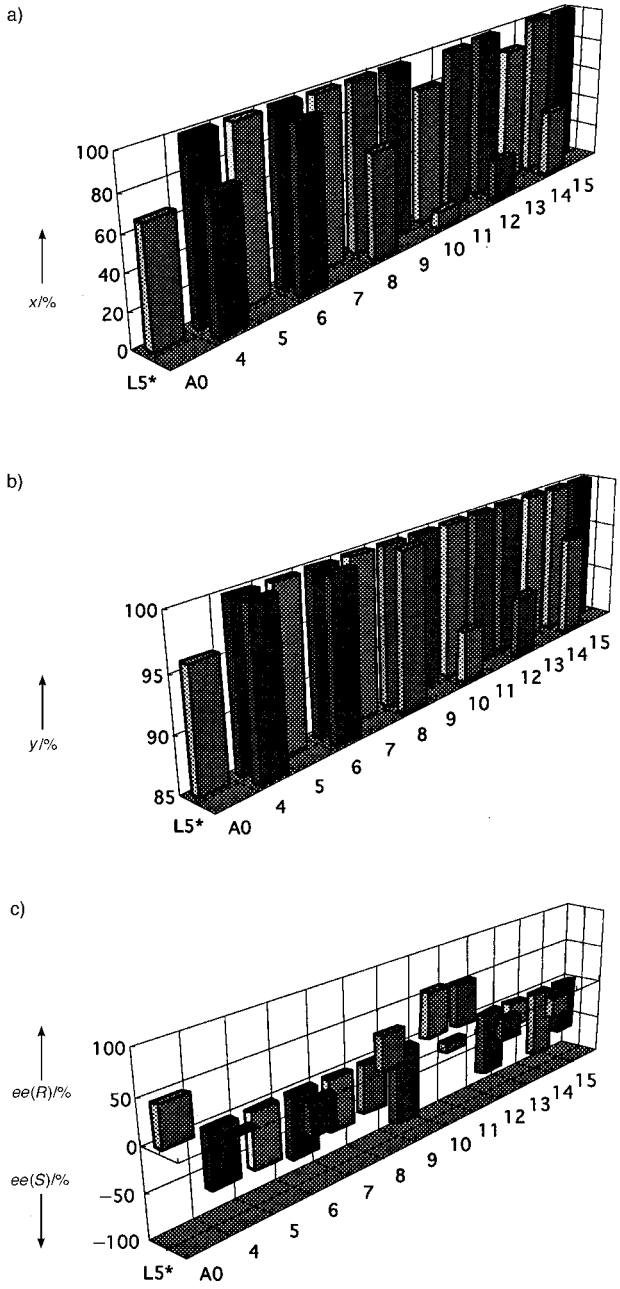
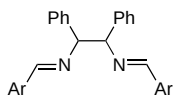
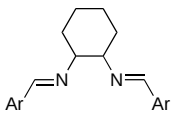


Figure 2. Screening of the second-generation library of chiral activators A0 – A15* in combination with chiral ligand L5* for the hydrogenation of aldehydes **1** to alcohols **2** and **3**. a) Conversion x of **1**; b) selectivity y of **2** versus **3**; c) enantiomeric excess of **2**.



	Ar
A4*: *S,S*	Ph
A5*: *R,R*	Ph
A6*: *S,S*	2,6-$Cl_2C_6H_3$
A7*: *R,R*	2,6-$Cl_2C_6H_3$
A8*: *S,S*	2,4,6-$Me_3C_6H_2$
A9*: *R,R*	2,4,6-$Me_3C_6H_2$



	Ar
A10*: *S,S*	Ph
A11*: *R,R*	Ph
A12*: *S,S*	2,6-$Cl_2C_6H_3$
A13*: *R,R*	2,6-$Cl_2C_6H_3$
A14*: *S,S*	2,4,6-$Me_3C_6H_2$
A15*: *R,R*	2,4,6-$Me_3C_6H_2$

drawn by Noyori.[8a] The steric hindrance of the chiral activators was found to be crucial, and hence activator A9* provides the best results (100 % yield, 90 % *ee*)

The reaction catalyzed by the best combination L5*/A9* was further optimized by lowering the reaction temperature to − 78 °C. We were pleased to find that (*S*)-1-phenylpropanol was obtained with 99 % *ee* and in quantitative yield (Table 1). Even when 2 mol % of L5*/A9* was used for the reaction, (*S*)-phenylpropanol can be obtained with 97 % *ee* and in 100 % yield. Under the optimized conditions, the combination of L5* and A9* is proven to be extremely effective for the addition of diethylzinc to a range of aldehydes (Table 1).

  1433-7851/99/3804-0499 $ 17.50+.50/0

Table 1. Asymmetric addition of Et_2Zn to aldehydes in the presence of L5*/A9* to provide alcohol **2**.

Entry	R	Yield [%] of **2**[a]	*ee* [%] of **2**[b]	Config.[c]
1	phenyl	100	99.0	*S*
2	phenyl[d]	100	97.0	*S*
3	*p*-methoxyphenyl	100	98.5	n.d.
4	*m*-methoxyphenyl[e]	100	96.4	n.d.
5	*p*-chlorophenyl	99	98.5	*S*
6	*p*-*tert*-butylphenyl	100	99.0	n.d.
7	β-naphthyl	100	93.8	*S*
8	α-naphthyl	93	91.5	*S*

[a] Yield of isolated **2** based on the consumed aldehydes. [b] Determined by HPLC on a Daicel OD-H column unless otherwise noted. [c] Assigned by comparison of chiroptical values with those in the literature. n.d. = not determined. [d] 2 mol % of L5*/A9* was used. [e] Determined by HPLC on a Chiracel OB-H column.

In summary, we have successfully developed a new strategy for super high throughput screening of chiral ligands and activators by employment of the CC factory and HPLC-CD. This SHTS technique combined with our concept of asymmetric activation will provide a very powerful methodology for finding the best activated catalyst.[17]

Experimental Section

General procedure for SHTS: All reactions were performed under nitrogen. Weighed amounts of chiral ligands L* (0.01 mmol) or chiral activators A* (0.01 mmol) or both (0.01 mmol each) were introduced into 1-mL polypropylene microtubes. CH_2Cl_2 (100 μL) and Et_2Zn (200 μL, 1M in hexane) were added with micropipetters. The microtubes were then set up in the CC factory to maintain the temperature at 0 °C for 30 min, and finally benzaldehyde (11 μL, 0.1 mmol) was introduced. After agitation for 20 h at 0 °C, the tubes were opened. The programed quench with water and extraction with ethyl acetate were performed by the CC factory. The product mixtures were then submitted to a JASCO CD-995 instrument with an autosampler on a CrestPak C18S column (4.6 × 150 mm) with CH_3CN/H_2O (1/1) as eluent. The retention time for 1-phenylpropanol is 3.0 min. Based on the dissymmetry factor *g* measured for 1-phenylpropanol with known enantiomeric excesses at 275 nm, the enantiomeric excesses of the products could be calculated conveniently.

Optimized procedure: Under argon to a predried flask were added L5* (44 mg, 0.1 mmol), A9* (47 mg, 0.1 mmol), CH_2Cl_2 (1 mL), and diethylzinc (2 mL of 1M solution in hexane, 2 mmol) at room temperature. The flask was cooled to −78 °C, and then benzaldehyde (106 mg, 1 mmol) was introduced dropwise by a microsyringe. After the reaction mixture was stirred at −78 °C for 4 h and then at −20 °C for 1 h, water (2 mL) was added to quench the reaction. The aqueous layer was extracted with diethyl ether, and the combined organic phase was washed with brine and then dried over anhydrous $MgSO_4$. After removal of the solvent, the residue was analyzed by ^1H NMR spectroscopy to determine the benzaldehyde conversion and product ratio. The crude product was purified by column chromatography on silica gel with EtOAc/hexane (1/5) as eluent to give pure 1-phenylpropanol as a colorless liquid in quantitative yield and with 99 % *ee*; HPLC on Daicel OD-H column: eluent hexane/2-propanol (99/1); flow rate 0.8 mL min^{-1}; UV detection at λ = 254 nm; retention time = 22.9 min (*R* enantiomer), 26.0 min (*S* enantiomer).

Received: August 25, 1998 [Z12329IE]
German version: *Angew. Chem.* **1999**, *111*, 519 – 523

Keywords: asymmetric activation · asymmetric catalysis · binaphthol · combinatorial chemistry · zinc

[1] Special issues on combinatoral chemistry: a) *Acc. Chem. Res.* **1996**, *29*(3); b) *Chem. Eng. News* **1996**, *74*(4); reviews: c) F. Balkenhohl, C. B. Hunnefeld, A. Lansky, C. Zechel, *Angew. Chem.* **1996**, *108*, 2437 – 2476; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2288 – 2337; d) C. Gennari, H. P. Nestler, U. Piarulli, B. Salom, *Liebigs Ann.* **1997**, 637 – 647; e) *Combinatorial Chemistry: Synthesis and Application* (Eds.: S. R. Wilson, A. W. Czarink), Wiley, New York, **1997**.

[2] *High Throughput Screening* (Ed.: J. P. Devlin), Marcel Dekker, New York, **1997**.

[3] For examples, see a) M. S. Sigman, E. N. Jacobsen, *J. Am. Chem. Soc.* **1998**, *120*, 4901 – 4902; b) K. Burgess, H.-J. Lim, A. M. Porte, G. A. Sulikowski, *Angew. Chem.* **1996**, *108*, 192 – 194; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 220 – 222; c) B. M. Cole, K. D. Shimizu, C. A. Krueger, J. P. A. Harrity, M. L. Snapper, A. H. Hoveyda, *Angew. Chem.* **1996**, *108*, 1776 – 1779 *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1667 – 1671; d) G. Liu; J. A. Ellman, *J. Org. Chem.* **1995**, *60*, 7712 – 7713.

[4] For the application of a CD detection system to measure optical purity by HPLC on nonchiral stationary phases, see a) C. Bertucci, P. Salvadori, L. F. L. Guimaraes, *J. Chromatogr. A* **1994**, *666*, 535 – 539; b) P. Salvadori, C. Bertucci, C. Rosini, *Chirality* **1991**, *3*, 376 – 385; c) A. F. Drake, J. M. Gould, S. F. Mason, *J. Chromatogr.* **1980**, *202*, 239 – 245.

[5] a) K. Mikami, S. Matsukawa, *Nature* **1997**, *385*, 613 – 615; b) S. Matsukawa, K. Mikami, *Tetrahedron: Asymmetry* **1995**, *6*, 2571 – 2574; c) S. Matsukawa, K. Mikami, *Tetrahedron: Asymmetry* **1997**, *8*, 815 – 816; d) S. Matsukawa, K. Mikami, *Enantiomer* **1996**, *1*, 69 – 73; e) T. Ohkuma, H. Doucet, T. Pham, K. Mikami, T. Korenaga, M. Terada, R. Noyori, *J. Am. Chem. Soc.* **1998**, *120*, 1086 – 1087; f) S. Casolari, P. G. Cozzi, P. Orioli, E. Tagliavini, A. Umani-Ronchi, *Chem. Commun.* **1997**, 2123 – 2123; g) C. M. Yu, H. S. Choi, W. H. Jung, H. J. Kim, J. Shin, *Chem. Commun.* **1997**, 761 – 762; h) C. M. Yu, S. K. Yoon, W. H. Joon, H. S. Choi, K. Baek, *Chem. Commun.* **1997**, 763 – 764.

[6] a) K. Maruoka, Y. Yamamoto, *J. Am. Chem. Soc.* **1989**, *111*, 789 – 790; b) J. W. Faller, D. W. Sams, X. Liu, *J. Am. Chem. Soc.* **1993**, *115*, 804 – 805; c) J. W. Faller, D. W. Sams, X. Liu, *J. Am. Chem. Soc.* **1996**, *118*, 1217 – 1218; d) J. W. Faller, M. Tokunaga, *Tetrahedron Lett.* **1993**, *34*, 7359 – 7362; e) R. Sablong, J. A. Osborn, J. W. Faller, *J. Organomet. Chem.* **1997**, *527*, 65 – 70; f) N. W. Alcock, J. M. Brown, P. J. Maddox, *J. Chem. Soc. Chem. Commun.* **1986**, 1532 – 1534; g) J. M. Brown, P. J. Maddox, *Chirality* **1991**, *3*, 345 – 354; h) J. W. Faller, M. R. Mazzieri, J. T. Nguyen, J. Parr, M. Tokunaga, *Pure Appl. Chem.* **1994**, *66*, 1463 – 1469.

[7] D. J. Berrisford, C. Bolm, K. B. Sharpless, *Angew. Chem.* **1995**, *107*, 1159 – 1171; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1059 – 1070.

[8] For a general discussion, see a) R. Noyori, *Asymmetric Catalysis in Organic Synthesis*, Wiley, New York, **1994**; b) *Catalytic Asymmetric Synthesis* (Ed.: I. Ojima), VCH, New York, **1993**; c) *Advances in Catalytic Processes*, *Vol. 1* (Ed.: M. P. Doyle), JAI Press, Greenwich, USA, **1995**; d) H. B. Kagan, *Comprehensive Organic Chemistry*, *Vol. 8*, Pergamon, Oxford, **1992**; e) *Handbook of Enantioselective Catalysis* (Eds.: H. Brunner, W. Zettlmeier), VCH, New York, **1993**; reviews: f) R. Noyori, M. Kitamura, *Angew. Chem.* **1991**, *103*, 34 – 55; *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 49 – 69; g) K. Soai, S. Niwa, *Chem. Rev.* **1992**, *92*, 833 – 885; h) "Stereoselective Synthesis": R. M. Devant, H. E. Radunz, *Methoden Org. Chem.* (*Houben-Weyl) 4th ed. 19951 –*, Vol. E21b, **1996**, pp. 1314 – 1334.

[9] N. Oguni, T. Omi, *Tetrahedron Lett.* **1984**, *25*, 2823 – 2824.

[10] For examples of titanium complexes as catalysts, see a) D. Seebach, A. K. Beck, B. Schmidt, Y. M. Wang, *Tetrahedron* **1994**, *50*, 4363 – 4384; b) D. Seebach, L. Behrendt, D. Felix, *Angew. Chem.* **1991**, *103*, 100 – 101; *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 99 – 101; c) J. Qiu, C. Guo, X. Zhang, *J. Org. Chem.* **1997**, *62*, 2665 – 2668; d) F. Y. Zhang, C. W. Yip, R. Cao, A. S. C. Chan, *Tetrahedron: Asymmetry* **1997**, *8*, 585 – 589; e) F. Y. Zhang, A. S. C. Chan, *Tetrahedron: Asymmetry* **1997**, *8*, 3651 – 3655; f) T. Takahashi, T. Kawakita, M. Ohno, M. Yoshioka, S. Kobayashi, *Tetrahedron* **1992**, *48*, 5691 – 5700; g) M. Mori, T. Nakai, *Tetrahedron Lett.* **1997**, *38*, 6233 – 6236; h) W. Brieden, R. Ostwald, P. Knochel, *Angew. Chem.* **1993**, *105*, 629 – 631; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 582 – 584; i) S. Pritchett, D. H. Woodmansee, P. Gantzel, P. J. Walsh, *J. Am. Chem. Soc.* **1998**, *120*, 6423 – 6424.

[11] For asymmetric autocatalysis, see a) K. Soai, T. Shibata, H. Morioka, K. Choji, *Nature* **1995**, *378*, 767 – 768; b) T. Shibata, H. Morioka, T. Hayase, K. Choji, K. Soai, *J. Am. Chem. Soc.* **1996**, *118*, 471 – 742;

  1433-7851/99/3804-0500 $ 17.50+.50/0

c) S. J. Li, Y. Z. Jiang, A. Q. Mi, G. S. Yang, *J. Chem. Soc. Dalton Trans. 1* **1993**, 885 – 886; d) K. Soai, T. Shibata, *J. Synth. Org. Chem. Jpn*. **1997**, *55*(11), 72 – 83.

[12] For planar chiral heterocycles as ligands, see a) P. I. Dosa, J. C. Ruble, G. C. Fu, *J. Org. Chem*. **1997**, *62*, 444 – 445; for examples of β-amino thiols as ligands, see b) J. Kang, J. W. Lee, J. I. Kim, *J. Chem. Soc. Chem. Commun*. **1994**, 2009 – 2010; c) Y. Arai, N. Nagata, Y. Masaki, *Chem. Pharm. Bull*. **1995**, *43*, 2243 – 2245; d) E. Rijnberg, N. J. Hovestad, A. W. Kleij, J. T. B. H. Jastrzebski, J. Boersma, M. D. Janssen, A. L. Spek, G. van Koten, *Organometallics* **1997**, *16*, 2847 – 2857; for β-amino thiocarboxylate as ligand, see e) M.-J. Jin, S.-J. Ahn, K.-S. Lee, *Tetrahedron Lett*. **1996**, *37*, 8767 – 8770; for piperazines as chiral ligands, see f) S. Niwa, K. Soai, *J. Chem. Soc. Perkin Trans.1* **1991**, 2717 – 2272; g) T. Shono, N. Kise, E. Shirakawa, H. Matsumoto, E. Okazaki, *J. Org. Chem*. **1991**, *56*, 3063 – 3067; for oxazaborolidines as ligands, see h) N. N. Joshi, M. Srebnik, H. C. Brown, *Tetrahedron Lett*. **1989**, *30*, 5551 – 5554.

[13] a) C. Rosini, L. Franzini, D. Pini, P. Salvadori, *Tetrahedron: Asymmetry* **1990**, *1*, 587 – 588; b) K. R. K. Prasad, N. N. Joshi, *Tetrahedron: Asymmetry* **1996**, *7*, 1957 – 1960.

[14] a) H. Kitajima, K. Ito, Y. Aoki, T. Katsuki, *Bull. Chem. Soc. Jpn*. **1997**, *70*, 207 – 217; b) Q. S. Hu, W. S. Huang, D. Vitharana, X. F. Zhang, L. Pu, *J. Am. Chem. Soc.* **1997**, *119*, 12454 – 12464; c) W. S. Huang, Q. S. Hu, L. Pu, *J. Org. Chem.* **1998**, *63*, 1364 – 1365; d) Q. S. Hu, W. S. Huang, L. Pu, *J. Org. Chem*. **1998**, *63*, 2798 – 2799.

[15] a) C. Bolm, J. Muller, *Tetrahedron* **1994**, *50*, 4355 – 4362. For example, $[Zn(acac)_2]$ (acac = acetylacetone) has a trimeric structure, but the tri(3-phenylpyrazol-1-yl)borate complex of zinc is a monomer: b) M. J. Bennett, F. A. Cotton, R. Eiss, R. C. Elder, *Nature* **1967**, *213*, 174; c) A. Kremer-Aach, W. Klaui, R. Bell, A. Strerath, H. Wunderlich, D. Mootz, *Inorg. Chem*. **1997**, *36*, 1552 – 1563. Very recently, Denmark et al. reported an excellent example of deaggregation of a sulfonamide – zinc complex with nitrogen ligands: d) S. E. Denmark, S. P. O'Connor, S. R. Wilson, *Angew. Chem.* **1998**, *110*, 1162 – 1165; *Angew. Chem. Int. Ed.* **1998**, *37*, 1149 – 1151.

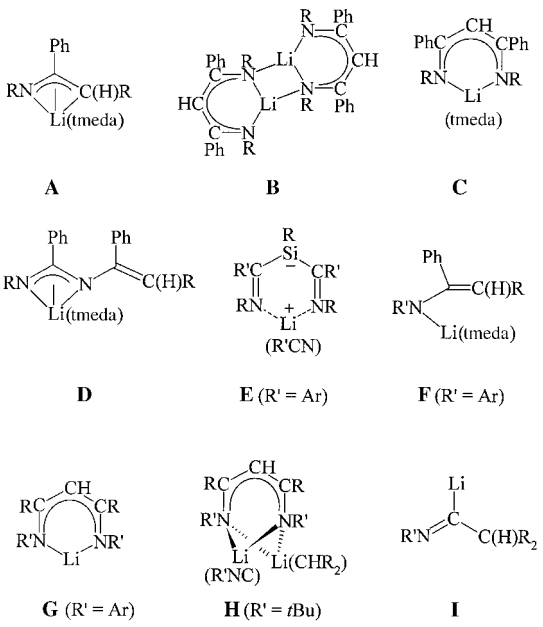
[16] P. G. Cozzi, A. Papa, A. Umani-Ronchi, *Tetrahedron Lett*. **1996**, 37, 4613 – 4616.

[17] Recently, IR thermography was employed for qualitative analysis of catalytic (asymmetric) processes: in homogeneous catalysis: M. T. Reetz, M. H. Becker, K. M. Kuhling, A. Holzwarth, *Angew. Chem.* **1998**, *110*, 2792-2795; *Angew. Chem. Int. Ed.* **1998**, *37*, 2647 – 2650 (we thank Prof. Dr. Manfred T. Reetz for kindly sending us a copy of this manuscript prior to publication); in heterogeneous catalysis: G. Georgiades, V. A. Self, P. A. Sermon, *Angew. Chem.* **1987**, *99*, 1050 – 1052; *Angew. Chem. Int. Ed. Engl*. **1987**, *87*, 1042 – 1043; b) F. C. Moates, M. Somani, J. Annamalai, J. T. Richardson, D. Luss, R. C. Willson, *Ind. Eng. Chem. Res.* **1996**, *35*, 4801 – 4803; c) D. E. Bergbreiter, *Chemtract: Org. Chem*. **1997**, *10*, 683 – 686; d) S. J. Tayler, J. P. Morken, *Science* **1998**, *280*, 267 – 270, and references cited therein. IR thermography may be applied for quantitative analysis of catalytic asymmetric processes in the near future.

A 1-Aza-2-silacyclobut-3-ene and an Alkyne from $[Li\{Si(SiMe_3)_3\}(thf)_3]$ and the Isocyanide 2,6-$Me_2C_6H_3NC$

Peter B. Hitchcock, Michael F. Lappert,* and Marcus Layh

The interaction of a trimethylsilylmethyllithium reagent $Li[CH_{3-n}(SiMe_3)_n]$ ($n = 1$, 2, or 3) and an α-H-free nitrile R′CN can yield a 1-azaallyl-, β-diketiminato-, or 1,3-diazaallyllithium, depending on n, the nature of R′, the stoichiometry, and the absence or presence of a neutral coligand. Examples of such products from $LiCHR_2$ ($R = SiMe_3$) and PhCN are **A**,[1] **B**,[2] **C**,[3] or **D**,[1] each formed by initial insertion of PhCN into the Li–C bond of $Li(CHR_2)$ and a 1,3-Me_3Si shift from C to N, followed for **B** – **D** by insertion of a further PhCN molecule into an Li–N or Li–C bond of **A** and a final 1,3-Me_3Si N → N or C → N shift. This chemistry was extended to the lithium silyl and germyl congeners of $LiCR_3$. Thus, $[Li(SiR_3)(thf)_3]$ with 2,6-$Me_2C_6H_3CN$ (ArCN) yielded the zwitterionic 3-sila-β-diketiminatolithium complex **E**, a process involving a hitherto unprecedented 1,3-Me_3Si shift from Si to N.[4] We also previously demonstrated that from $LiCHR_2$ and an isocyanide R′NC, a similar diversity of



products **F** – **H** is available, each formed via successively the 1:1 adduct and the lithioaldimine **I**.[1] Compound **I**, by a 1,2-Me_3Si C → C shift, is transformed into **F**, which by a similar sequence generates **G** and **H**.

We now report the results presented in Scheme 1: Treatment of $[Li(SiR_3)(thf)_3]$ [5] with the isocyanide ArNC yields

[*] Prof. M. F. Lappert, Dr. P. B. Hitchcock, Dr. M. Layh
School of Chemistry, Physics and Environmental Science
University of Sussex
Brighton BN1 9QJ (UK)
Fax: (+44) 1273 – 677196
E-mail: m.f.lappert@sussex.ac.uk

[**] We thank EPSRC for a fellowship for M.L. and other support.

  1433-7851/99/3804-0501 $ 17.50+.50/0