Homogeneous Catalysis

In Situ Formation of a Heterobimetallic Chiral [(Salen)Ti^{IV}]/[(Salen)V^{V}] Catalyst for the Asymmetric Addition of TMSCN to Benzaldehyde**

Yuri N. Belokon, Michael North, Victor I. Maleev, Nikolay V. Voskoboev, Margarita A. Moskalenko, Alexander S. Peregudov, Andrey V. Dmitriev, Nikolai S. Ikonnikov, and Henri B. Kagan**

The wide potential of molecules with multiple (multidentate) Lewis acid sites that bind and chemically activate small organic molecules has been recognized for some time.[1] Quite recently, several groups made significant progress towards the design and use of chiral homo- and heterobimetallic complexes for asymmetric catalysis, with particularly important contributions reported by Shibasaki et al.[2] and Trost et al.[3] The former group developed an effective chiral bimetallic catalyst based on an alkali metal/lanthanoid complex for asymmetric Michael addition reactions, whereas the latter group elaborated on dinuclear zinc complexes of a chiral pentadentate ligand for asymmetric Henry and aldol condensation reactions. In the case of the asymmetric opening of epoxides catalyzed by chiral [(salen)Co] complexes (salen = *N,N'*-bis(salicylaldehydo)ethylenediamine),[4] the reaction involved two separate chiral salen–metal species in the rate-limiting step of the reaction, and subsequently, very efficient oligomeric catalysts were developed based on this principle.[5] It is reasonable to propose that many other established catalysts may operate via unrecognized polymetallic intermediates lying on the reaction coordinate; a large number of nonlinear effects observed in asymmetric catalytic reactions seem to indicate such a possibility.[6]

Homo- or heterobimetallic complexes have enormous potential to revolutionize asymmetric catalysis. They can activate both components of a bimolecular reaction simultaneously, overcome entropy barriers associated with bringing the two reagents together, minimize the energy barrier that arises from solvent–shell rearrangements during the reaction, and recognize prochiral faces or groups within the reagents through predetermination of the reaction trajectory.

Belokon', North and co-workers have developed an efficient catalyst based on dinuclear, chiral [{(salen)Ti^{IV}-(μ-O)}$_2$] precatalysts for the asymmetric addition of trimethylsilyl cyanide to aldehydes.[7] Kinetic studies indicated that two Ti^{IV} complexes were involved in the rate-limiting step of this reaction.[8] Subsequently, monomeric chiral ionic [(salen)V^{V}(O)]$^+$EtOSO$_3^-$ complexes were shown to be even more enantioselective in the same reaction, although the rate was almost two orders of magnitude slower than that with the analogous Ti^{IV} catalysts.[9] Kinetic studies indicated that two cationic V^{V} complexes were again involved in the rate-limiting step of the reaction.[9a]

Based on these results, we thought that a mixed-metal complex derived from Ti^{IV} and V^{V} might form an even better catalyst, which would exhibit the asymmetric induction associated with V^{V} complexes and the faster rates of reaction associated with Ti^{IV} catalysts. Furthermore, we considered complexes derived from enantiomeric ligands to study the interactions between the complexes, as mixed species could give rise to anomalies with respect to the independent metal catalysts. Herein, we report the performance of mixtures of [{((*R*,*R*)-salen)Ti^{IV}(μ-O)}$_2$] or [{((*S*,*S*)-salen)Ti^{IV}(μ-O)}$_2$], and ionic [((*S*,*S*)-salen)V^{V}(O)]$^+$EtOSO$_3^-$ or [((*R*,*R*)-salen)-V^{V}(O)]$^+$EtOSO$_3^-$ in the asymmetric addition of trimethylsilyl cyanide to benzaldehyde at different molar ratios of Ti/V.

The [{((*R*,*R*)-salen)Ti^{IV}(μ-O)}$_2$] **1a** (or [{((*S*,*S*)-salen)-Ti^{IV}(μ-O)}$_2$], **1b**), and [((*R*,*R*)-salen)V^{V}(O)]$^+$EtOSO$_3^-$ **2a** (or [((*S*,*S*)-salen)V^{V}(O)]$^+$EtOSO$_3^-$, **2b**) catalysts (Scheme 1) were synthesized as described previously.[9b] The asymmetric addition of trimethylsilyl cyanide to benzaldehyde (Scheme 1) was catalyzed by **1a** or **2a** to give (*S*)-*O*-(trimethylsilyl)mandelonitrile (80 and 90% *ee*, respectively).[7,9] Use of **1b** or **2b** similarly led to (*R*)-*O*-(trimethylsilyl)mandelonitrile.

Use of a mixture of **1b** and **2a** as a catalyst in the reaction at a 1:1 molar ratio of Ti/V may be expected to result in: 1) Completely racemic product if a fast exchange of ligands between the two metal centers takes place. 2) Almost exclusive (*R*)-mandelonitrile formation at this ratio (and up to a 1:4 molar ratio of Ti/V) if **1b** and **2a** were independent. Above a 1:4 molar ratio of Ti/V, the enantiomeric excess of the product would decrease and at a 1:11 ratio of Ti/V, racemic product would be formed (see Figure 1, curve a). Accordingly, exclusive formation of (*S*)-mandelonitrile would be observed if a 1:1 mixture of **1a** and **2b** were used as a catalyst. 3) Formation of a mixed complex with novel catalytic properties, which could not be predicted in advance.

As the [(salen)Ti] catalyst is almost two orders of magnitude faster than the [(salen)V]$^+$ catalyst, one could expect the Ti catalyst to determine the absolute configuration

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[*] Prof. Dr. Y. N. Belokon, Dr. V. I. Maleev, Dr. M. A. Moskalenko, Prof. Dr. A. S. Peregudov, A. V. Dmitriev, Dr. N. S. Ikonnikov
A. N. Nesmeyanov Institute of Organo-Element Compounds
Russian Academy of Sciences
Vavilov 28, 119991 Moscow (Russian Federation)
Fax: (+95) 135-5085
E-mail: yubel@ineos.ac.ru

Prof. Dr. H. B. Kagan
Institut de Chimie Moléculaire et des Matériaux d'Orsay,
Laboratoire de Synthèse Asymétrique (UMR 8075)
Université de Paris-Sud
Bâtiment 420, 91405 Orsay Cedex (France)
Fax: (+33) 169-157-895
E-mail: kagan@icmo.u-psud.fr

Prof. M. North
Department of Chemistry, King's College
Strand, WC2R 2LS London (UK)

N. V. Voskoboev
Higher Chemical College, Russian Academy of Sciences
Miusskaya pl. 9, 125 047 Moscow (Russian Federation)

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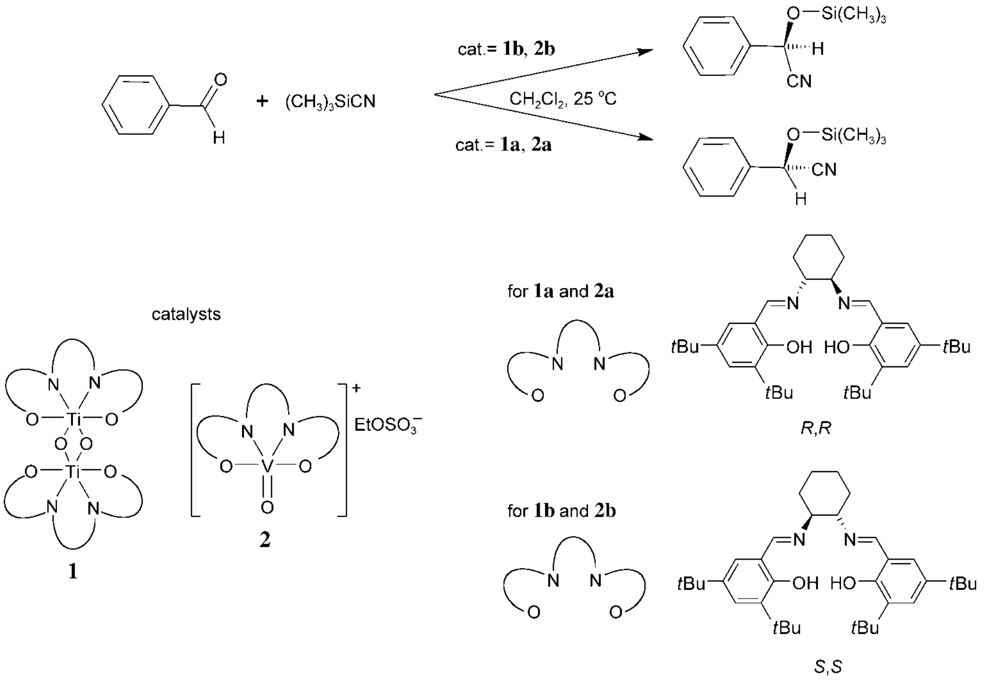


Scheme 1. The asymmetric addition of trimethylsilyl cyanide to benzaldehyde.

of the resulting mandelonitrile. Theoretically, a mixture of **1b** and **2a** in a ratio of 1:2 should give (*R*)-mandelonitrile and a mixture of **1a** and **2b** should produce (*S*)-mandelonitrile. Unexpectedly, it was predominantly (*R*)-mandelonitrile that was formed in 82% *ee* when a 1:2 mixture of **1a** and **2b** was employed as catalyst, and the *S* product that was formed from a mixture of **1b** and **2a** as catalyst. These results are not consistent with either a fast exchange of ligands or with the independent function of the catalysts with respect to one another. The absolute configuration of the product appeared to be determined by the slower vanadium catalyst rather than by the faster titanium catalyst.

Figure 1 illustrates the variation of the enantiomeric excess and absolute configuration of the mandelonitrile trimethylsilyl ether as the mol% of a mixture of **1a** and **2b** (curve b) or **1b** and **2a** (curve c) was progressively varied from 100% of the titanium catalyst to 100% of the vanadium catalyst (calculated as a ratio of the metal ions and not the complexes; the total catalyst concentration was maintained at 3.1×10^{-4} M and assumes that both Ti and V catalysts are calculated as monomers). The results indicate that catalysis by titanium complexes was predominant only when the mol% of vanadium in the mixture was very low. Introduction of just 10 mol% of vanadium into the catalyst results in the formation of racemic product, and at a catalyst composition of 35% vanadium and 65% titanium, the vanadium appears already to determine the absolute configuration of the product.

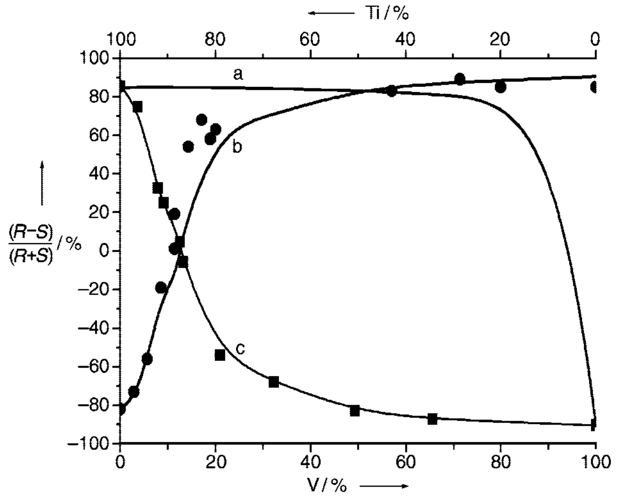
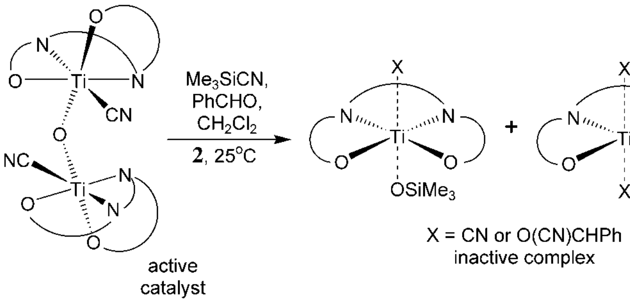


Figure 1. a) The calculated enantiomeric excess of the product if catalysts **1b** and **2a** work independently of one another (the sum of the total catalyst concentration is maintained at 3.1×10^{-4} M, and the relative reactivities of the two catalysts are taken into account); b) and c) The variation of enantiomeric excess and absolute configuration of mandelonitrile as the mol% of a mixture of **1a** and **2b** (curve b) or **1b** and **2a** (curve c) is varied from 100% of titanium-based catalyst to 100% of vanadium-based catalyst (calculated as a ratio of metal ions).

There are at least two interpretations of these results: One is the formation of a catalytically active, mixed titanium–vanadium complex, which overrides the original titanium- and vanadium-based catalysts; the vanadium-based portion of the mixed catalyst is then responsible for the determination of the configuration of the mandelonitrile. The second possibility is that the vanadium precatalyst **2** is involved in the deactivation of the titanium precatalyst **1** by catalyzing a side reaction. Such a side reaction might result from the attack of trimethylsilyl cyanide at the remaining oxygen bridge of a bimetallic [(salen)Ti] complex that forms during the catalytic cycle[8] to result in the formation of inactive mononuclear complexes (Scheme 2).[9b]



Scheme 2. Formation of inactive mononuclear complexes.

To distinguish between these two possibilities, we studied the variation in the enantiomeric excess of the product during the course of the reaction and measured the reaction kinetics at various ratios of Ti/V. The formation of a mixed complex (once complete) would result in the formation of the product with a constant enantiomeric excess throughout the reaction. In contrast, the destruction of the titanium catalyst mediated by complex **2** should result in a change in the enantiomeric excess (and even the absolute configuration) of the mandelonitrile trimethylsilyl ether during the reaction. Furthermore, there should be a significant decrease in the rate of the reaction relative to the reaction catalyzed by pure **1** at the same initial concentration.

Figure 2 shows the variation of the enantiomeric excess of mandelonitrile trimethylsilyl ether with the reaction yield for **1a**, **2b**, and mixtures of **1a** and **2b**. There was no observed variation in the enantiomeric excess with the reaction yield (or time) for either of the pure catalysts (Figure 2, curves a and b). In contrast, very significant changes were observed for a mixture composed of 90% titanium and 10% vanadium (calculated as a ratio of metal ions; Figure 2, curve e). At 75% conversion, (*S*)-mandelonitrile trimethylsilyl ether was formed. Extrapolation of the curve to the beginning of the reaction leads to approximately 60–70% *ee* of the *S* product. At 80% conversion the product became a racemic mixture and predominantly *R* product was formed, albeit with a very low enantiomeric excess (see also Figure 1). The rate of the reaction was significantly diminished (Figure 3), in line with the removal of the more-active titanium-based catalyst from the reaction mixture. These results seem to be consistent with the suppression of the activity of complex **1** by the complex **2**.

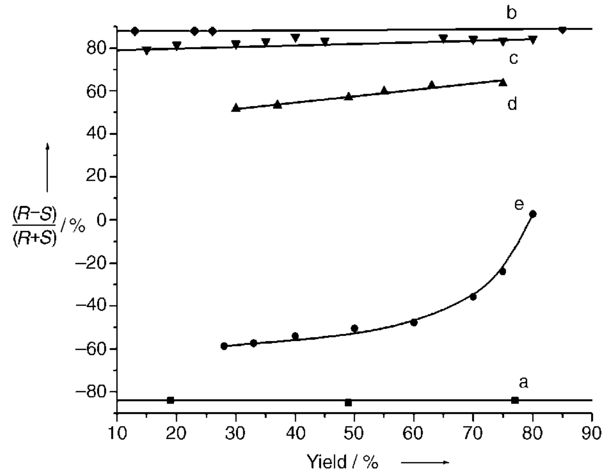


Figure 2. Variation of the enantiomeric excess of mandelonitrile trimethylsilyl ether with yield at different ratios of Ti/V: a) pure **1a**; b) pure **2b**; c) a mixture of **1a** and **2b** with Ti/V = 1:1; d) a mixture of **1a** and **2b** with Ti/V = 4:1; e) a mixture of **1a** and **2b** with Ti/V = 10:1.

It can also be seen that the *R* product is formed even during the first 20% of the reaction as the amount of vanadium in the catalytic mixture increased from 10 to 20% (Figure 2, curve d) and then to 50% (Figure 2, curve c). The variation of the enantiomeric excess with the yield diminished as the percentage of vanadium increased, and at a ratio of 1:1 Ti/V, the enantiomeric excess remained constant throughout the reaction.

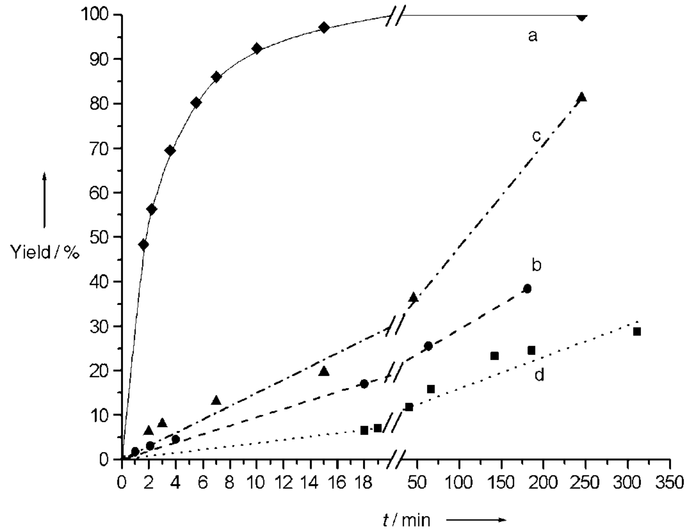


Figure 3. Variation of the yield of mandelonitrile with time as monitored by ^{1}H NMR spectroscopy at 25 °C (CD$_2$Cl$_2$ solutions) for the reaction catalyzed by: a) pure **1a**, b) pure **2b**, c) a mixture of **1a** and **2b** with Ti/V = 1:1, d) a mixture of **1a** and **2b** Ti/V = 10:1.

The rate of the reaction catalyzed by pure **1a** or **2b** or by a 1:1 mixture of the two catalysts was monitored by ^{1}H NMR spectroscopy (CD$_2$Cl$_2$ solutions, Figure 3). Both the disappearance of benzaldehyde and the appearance of the reaction product lead to identical results. The rate of the reaction obeyed second-order kinetics with reasonable correlation coefficients of 0.99 for **1a** and 0.98 for each of the other three cases (**2b**, and 1:1 and 10:1 mixtures of Ti/V). Rate constants (k) were calculated for reactions catalyzed by pure **1a**, pure **2b**, a 1:1 mixture of Ti and V, and a 10:1 mixture of Ti and V ($k = 1.62\times10^{-2}$, 3.21×10^{-4}, 5.86×10^{-4}, and $2.79\times10^{-4}\,\text{M}^{-1}\text{s}^{-1}$, respectively).

The variation of the apparent initial zero-order rate constant with the composition of the catalyst follows a bell-shaped profile, provided that at least 10% vanadium-based catalyst was present (monitored by UV/Vis spectroscopy of CH$_2$Cl$_2$ solutions, Figure 4). The maximum rate constant was observed at a Ti/V ratio of 1:1, which corresponded to 33 mol% of **1b** and 67 mol% of **2a**. Thus it appears that a new

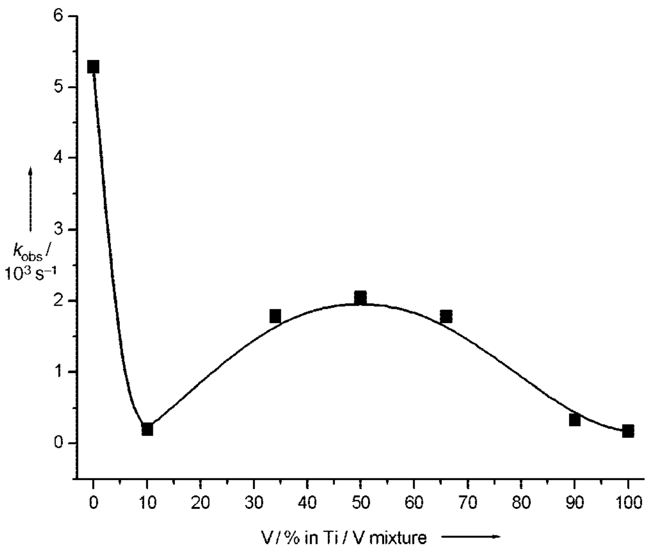


Figure 4. Observed zero-order rate constants of the reaction in CH_2Cl_2 at 20 °C catalyzed by complexes **1a** and **2b** with different ratios of titanium and vanadium.

catalyst was formed from **1b** and **2a** (or **1a** and **2b**) in the reaction mixture, which consisted of one V^V ion and one Ti^{IV} ion, with the resultant stereochemistry determined by the vanadium part of the catalyst and its kinetic behavior largely determined by its titanium-derived portion.

The variation in the *ee* observed in the early stages of the reaction with large ratios of up to 4:1 Ti/V can be explained by the mixed catalyst being formed slowly during this time. Hence, in the early stages of the reaction some titanium-based catalyst **1b** (or **1a**) is still present and catalyzes the formation of (*R*)-mandelonitrile trimethylsilyl ether (or the *S* product in the case of **1a**). However, once all of the titanium catalyst has been either inactivated or converted into a mixed catalyst, only the *S* product is formed. Thus, the enantiomeric excess varies in the early stages of the reaction and then remains almost constant.

With a mixture of catalysts **1b** and **2b** (i.e. both derived from (*S,S*)-cyclohexanediamine) in a 1:1 ratio of Ti/V, (*R*)-mandelonitrile trimethylsilyl ether was obtained in 95 % yield with 89 % *ee* after 30 min at 25 °C. A mixture of **1b** and **2a** under the same conditions gave (*S*)-mandelonitrile in 30 % yield (Figure 3) with 82 % *ee* (Figure 2). This is also consistent with the formation of a mixed complex, as pure **2b** would have produced only 20 % of the product under these conditions. As the formation of the mixed complex would be expected to take place at any titanium/vanadium ratio, it is most likely that this complex, rather than the vanadium complex **2**, catalyzes the decomposition of the titanium-based catalyst **1** by the route shown in Scheme 2 or in some other way.

In summary, we have shown that a mixture of two salen-derived V^V and Ti^{IV} complexes results in the formation of a mixed complex, which exhibits catalytic properties derived from both homometallic species. The mixed complex, besides its ability to catalyze asymmetric trimethylsilylcyanation reactions, appears to induce the inactivation (by TMSCN) of any remaining [(salen)Ti] catalyst (Scheme 2). We believe that this behavior is unique to a mixture of chiral catalysts and we are currently trying to extend this concept to some other classes of organometallic catalysts.

Experimental Section

General. Dichloromethane or CD_2Cl_2 were purified as described earlier.[10] Trimethylsilyl cyanide was purchased from Aldrich and freshly distilled before use. Catalysts **1a**,**b** and **2a**,**b** were prepared as described previously.[9b] Kinetics experiments were run in oven-dried glassware under an argon atmosphere. Kinetics measurements were conducted on a "Specord M40" spectrophotometer. Enantiomeric excesses were determined with chiral GC: DP-TFA-γ-CD, fused-silica capillary column (25 m × 0.23 mm), He as the carrier gas (T = 110 °C).

Kinetic experiments were carried out in a flask under thermostat control at 21 ± 0.5 °C. Standard solutions of **1** (2.46×10^{-6} mol) and **2** (4.75×10^{-6} mol) dissolved in dichloromethane (14 mL and 13.5 mL, respectively) were employed to give the initial concentration of the catalysts (3.52×10^{-4} M, calculated as the concentration of the metal ions). Solutions of catalysts were freshly prepared before use and were left for 20 min before samples (1.75 mL) of either the solutions of pure complexes or mixtures of **1** and **2** in the desired ratio (maintaining the total volume 1.75 mL) were mixed under argon and stirred for 15 min. The solution of the catalyst was then added to benzaldehyde (0.1 mL). After 2 min, TMSCN (0.15 mL) was added to the mixture. The resultant total concentration of the metal ions was 3.1×10^{-4} M. Samples (0.01 mL) were taken at appropriate intervals as the reaction progressed and diluted with dry CH_2Cl_2 (5 mL) to quench the reaction. The resulting solution was then analyzed by UV/Vis spectrophotometry at the maximum absorption band for benzaldehyde (246 nm in CH_2Cl_2). The absorption data were used to determine the concentration of benzaldehyde.

^1H NMR spectroscopy experiments were run in a similar manner in CD_2Cl_2, and the kinetics of the reaction in NMR tubes were monitored by the disappearance of the benzaldehyde resonances at $\delta = 10.01$ (s, CHO) or 7.65 ppm (t, *p*-Ph). The formation of mandelonitrile was monitored by the increase in the signal at $\delta = 5.54$ ppm (s, CH), which is attributed to the CH group of the reaction product. The rate law was calculated from the second-order reaction rates:

$$k = \frac{1}{t}\frac{1}{(a-b)}\ln\frac{b(a-x)}{a(b-x)}$$

For enantiomeric excess analyses, samples were taken in the same manner; the only variation was a dilution of the sample with hexane (5 mL) followed by filtration through a small silica-filled column (2 × 0.5 cm; hexane/EtOAc 5:1) to remove the catalysts.

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[1] J. D. Wuest, *Acc. Chem. Res.* **1999**, *32*, 81–89.

[2] a) M. Shibasaki, M. Kanai, K. Funabashi, *Chem. Commun.* **2002**, 1989–1999, and references therein; b) R. Takita, T. Ohshima, M. Shibasaki, *Tetrahedron Lett.* **2002**, *43*, 4661–4665.

[3] a) B. Trost, V. S. C. Yeh, *Angew. Chem.* **2002**, *114*, 889–891; *Angew. Chem. Int. Ed.* **2002**, *41*, 861–863, and references therein; b) B. M. Trost, J. L. Gunzner, T. Yasukata, *Tetrahedron Lett.* **2001**, *42*, 3775–3778.

[4] a) M. Ready, E. N. Jacobsen, *J. Am. Chem. Soc.* **2001**, *123*, 2687–2688; b) D. E. White, E. N. Jacobsen, *Tetrahedron: Asymmetry* **2003**, *14*, 3633–3638.

[5] J. M. Ready, E. N. Jacobsen, *Angew. Chem.* **2002**, *114*, 1432–1435; *Angew. Chem. Int. Ed.* **2002**, *41*, 1374–1377.

[6] C. Girard, H. B. Kagan, *Angew. Chem.* **1998**, *110*, 3088–3127; *Angew. Chem. Int. Ed.* **1998**, *37*, 2922–2959.

[7] Yu. N. Belokon', S. Caveda-Cepas, B. Green, N. S. Ikonnikov, V. N. Krustalev, V. S. Larichev, M. A. Moscalenko, M. North, C. Orizu, V. I. Tararov, M. Tasinazzo, G. I. Timofeeva, L. V. Yashkina, *J. Am. Chem. Soc.* **1999**, *121*, 3968–3973.

[8] Yu. N. Belokon', B. Green, N. S. Ikonnikov, V. S. Larichev, B. V. Lokshin, M. A. Moskalenko, M. North, C. Orizu, A. S. Peregudov, G. I. Timofeeva, *Eur. J. Org. Chem.* **2000**, 2655–2661.

[9] a) Yu. N. Belokon', M. North, T. Parsons, *Org. Lett.* **2000**, *11*, 1617–1619; b) Yu. N. Belokon', A. V. Gutnov, M. A. Moskalenko, L. V. Yashkina, N. S. Ikonnikov, N. V. Voskoboev, V. N. Khrustalev, M. North, *Helv. Chim. Acta* **2002**, *85*, 3301–3312.

[10] A. J. Gordon, R. A. Ford, *The Chemist's Companion: A Handbook of Practical Data, Techniques, and References*, Wiley, New York **1972**, p. 437.