A General Strategy for Improving Enantiomeric Purities via the Tandem Use of Mirror-Image Catalysts

J. W. Faller* and Adrien R. Lavoie

Department of Chemistry, Yale University, New Haven, Connecticut 06520-8107

Received November 6, 2001

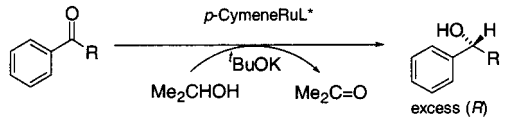
Summary: In situations where the asymmetric transfer hydrogenation catalysis of a given ketone gives moderate, though insufficiently high ee, the enantiomeric purity of the resulting alcohol can be enhanced via a subsequent asymmetric dehydrogenation with the antipode of the catalyst. Herein, we report on the theoretical and experimental aspects of this strategy.

Downloaded by CARLI CONSORTIUM on June 29, 2009
Published on April 4, 2002 on http://pubs.acs.org | doi: 10.1021/om010960+

Introduction

The development of new chiral catalysts often proceeds via modification of chiral ligands in order to improve the transfer of chirality to substrate. After *tuning* of the system by variations in electronic features, steric effects, or reaction conditions (e.g., solvent or temperature) one hopefully is able to achieve a catalyst that provides a product of acceptable optical purity.[1] However, even after extensive tuning there is often a point of diminishing returns wherein only modest product ee is obtained and the system will not yield a product of increased enantiomeric purity. With these concerns in mind, which are particularly relevant to investigation of asymmetric transfer hydrogenation catalysis, we have developed a general strategy which will allow for one to obtain ee's in excess of the original asymmetric transformation.[2,3] This method favorably exploits the microscopic reversibility of the aryl ketone/alcohol equilibrium, which has, until now, been considered to be a source of degradation of enantiomeric purity and yield.[4,5] We have referred to this new approach as tandem mirror-image resolution (TMIR).

Scheme 1



R = aliphatic substituent
L* = Ligand derived from (1*S*,2*R*)-*cis*-1-amino-2-indanol

Results and Discussion

The rationale for this strategy follows from consideration of the relative rate constants for the forward and reverse reactions of an asymmetric transfer hydrogenation shown in Scheme 1.[6−8] If the (*R*)-alcohol is formed in excess, then the forward rate constant for producing the (*R*)-product will be larger than that for producing the (*S*)-product. This observation is a function of the difference in the diastereomeric transition state energies ($\Delta\Delta G^{\ddagger}$, which is related to the difference in logarithms of rate constants and thus dependent on $k_R/k_S = k_{rel}$), with the transition state for the (*S*)-product ($\Delta G^{\ddagger}_S$) being of higher energy than for the (*R*)-product ($\Delta G^{\ddagger}_R$).[4d] Since a prochiral ketone is used, this is purely a kinetic phenomenon and is schematically represented in Figure 1.

It follows that the ratio of the products is determined by the ratio of the rate constants (k_{rel}). Since the products are enantiomers, one also observes that the same ratio of rate constants would be observed for the reverse reaction, which could be used for a conventional kinetic resolution if the racemic alcohols were available (eq 1).[4,9,10] The kinetic resolution should therefore provide the opposite enantiomer of the alcohol from that which was obtained in the forward direction (Scheme

(1) (a) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley: New York, 1994. (b) Brunner, H.; Zettlmeier, W. *Handbook of Enantioselective Catalysis*; VCH: Weinheim, 1993.

(2) For reviews on transfer hydrogenation see: (a) Zassinovich, G.; Mestroni, G. *Chem. Rev.* **1992**, *92*, 1051. (b) Brieger, G.; Nestrick, T. J. *Chem. Rev.* **1974**, *74*, 567. (k) Naota, T.; Takaya, H.; Murahashi, S. I. *Chem. Rev.* **1998**, *98*, 2599.

(3) For selected examples of highly enantioselective and catalytic ketone hydrogenation see: (a) Mikami, K.; Korenaga, T.; Terada, M.; Ohkuma, T.; Pham, T.; Noyori, R. *Angew. Chem., Int. Ed.* **1999**, *38*, 495. (b) Noyori, R.; Hashiguchi, S. *Acc. Chem. Res.* **1997**, *30*, 97. (c) Doucet, H.; Ohkuma, T.; Murata, K.; Yokozawa, T.; Kozawa, M.; Katayama, E.; England, A. F.; Ikariya, T.; Noyori, R. *Angew. Chem., Int. Ed.* **1998**, *37*, 1703. (d) Noyori, R.; Ohkuma, T. *Pure Appl. Chem.* **1999**, *71*, 1493. (e) Petra, D. G. I.; Kamer, P. C. J.; van Leeuwen, P. W. N. M.; Goubitz, K.; Van Loon, A. M.; de Vries, J. G.; Schoemaker, H. E. *Eur. J. Inorg. Chem.* **1999**, 2335. (f) Okano, K.; Murata, K.; Ikariya, T. *Tetrahedron Lett.* **2000**, *41*, 9277. (g) Ohkuma, T.; Koizumi, M.; Yoshida, M.; Noyori, R. *Org. Lett.* **2000**, *2*, 1749. (h) Haack, K.-J.; Hashiguchi, S.; Fujii, A.; Ikariya, T.; Noyori, R. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 285. (i) Corey, E. J.; Helal, C. J. *Tetrahedron Lett.* **1995**, *36*, 9153. (j) Yamada, I.; Noyori, R. *Org. Lett.* **2000**, *2*, 3425.

(4) Kinetic resolutions: (a) Kagan, H. B.; Fiaud, J. C. In *Topics in Stereochemistry*; Eliel, E. L., Silen, S. H., Eds.; John Wiley & Sons: New York, 1988; Vol. 18, pp 249−330. (b) Sih, C. J.; Wu, S. H. In *Topics in Stereochemistry*; Eliel, E. L., Silen, S. H., Eds.; John Wiley & Sons: New York, 1988; Vol. 19, pp 63−125. (c) Blackmond, D. G. *J. Am. Chem. Soc.* **2001**, *123*, 545−553. (d) Keith, J. M.; Larrow, J. F.; Jacobsen, E. N. *Adv. Synth. Catal.* **2001**, *343*, 5. (e) Faber, K. *Chem. Eur. J.* **2001**, *7*, 5005.

(5) (a) Palmer, M.; Walsgrove, T.; Wills, M. *J. Org. Chem.* **1997**, *62*, 5226. (b) Palmer, M. J.; Wills, M. *Tetrahedron: Asymmetry* **1999**, *10*, 2045.

(6) Faller, J. W.; Lavoie, A. R. *Org. Lett.* **2001**, *3*, 3703.

(7) Horeau[8b] has previously established a relationship between the conversion (*C*), the initial ee (ee), and the final ee (EE), and $k_{rel} = S$ for a partially resolved system: $(1 - C)^{S-1} = [(1 - EE)/(1 - ee)][(1 + ee)^S/(1 + EE)^S]$. Figure 2 was constructed using this equation. We have also derived a convenient expression for determining k_{rel} in the kinetic resolution phase, where *X* is the mole fraction of a component at the start of the reaction.

$$\frac{k_S}{k_R} = \frac{\ln[(1 - C)(1 - EE)(2X_S)^{-1}]}{\ln[(1 - C)(1 + EE)(2X_R)^{-1}]}$$

Since EE cannot be negative, this equation applies for $k_S > k_R$. An analogous expression for k_R/k_S holds for $k_R > k_S$. This equation reduces to the one suggested by Sharpless[9] for the racemic case.

(8) For theoretical accounts of kinetic resolutions beginning from enantioimpure substrates see: (a) Brandt, J.; Jochum, C.; Ugi, I.; Jochum, P. *Tetrahedron* **1977**, *33*, 1353. (b) Horeau, A. *Tetrahedron* **1975**, *31*, 1307.

(9) Martin, V. S.; Woodard, S, S.; Katsuki, T.; Yamada, Y.; Ikeda, M.; Sharpless, K. B. *J. Am. Chem. Soc.* **1981**, *103*, 6237.

10.1021/om010960+ CCC: $22.00 © 2002 American Chemical Society
Publication on Web 04/04/2002

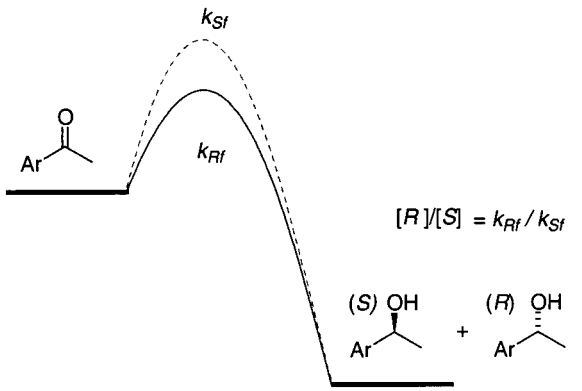
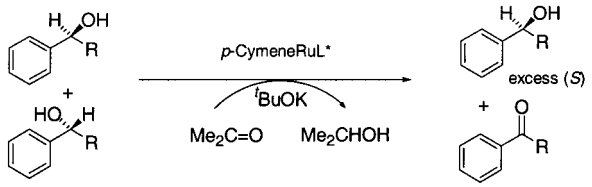
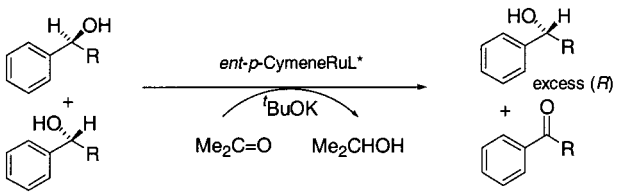


Figure 1. Reaction coordinate for hydrogenation/dehydrogenation with a chiral catalyst.

Scheme 2



Scheme 3



2), as we have demonstrated elsewhere.[6] If, however, one uses the opposite enantiomer of the original catalyst (from hydrogenation reaction), one should consume the other product enantiomer (Scheme 3). Consequently, if one produces an alcohol of modest enantiomeric purity via a catalytic asymmetric transfer hydrogenation, use of the opposite catalyst enantiomer in the reverse reaction (kinetic resolution) should enhance the ee of the product.

$$\left.\begin{aligned} k_{Sb} &= k_{Sf} / K_{eq} \\ k_{Rb} &= k_{Rf} / K_{eq} \end{aligned}\right\} \qquad k_{rel} = \frac{k_{Rb}}{k_{Sb}} = \frac{k_{Rf}}{k_{Sf}}$$

Since high yields are generally observed in transfer hydrogenations, one may well be willing to sacrifice some yield for an improvement in ee. In general, a kinetic resolution will allow one to achieve high ee, if enough material is consumed (an ideal result would be 50% conversion with 100% ee starting from racemic material given that $k_{rel} = \infty$).[4] However, with TMIR one has a *head start* on the kinetic resolution. Take, for example, the situation in which one quantitatively obtains the product alcohol in 70% ee from the transfer hydrogenation. Following this up with a kinetic resolution allows one to obtain ~60% yield (40% conversion back to ketone) with ~95% ee (see Figure 2) by employing the opposite enantiomer of the catalyst. Since the original ketone is a product in the kinetic resolution process, the scheme is amenable to repeated cycles; *hence one has a practical way to convert virtually all of the starting ketone to product alcohol of any desired optical purity.*

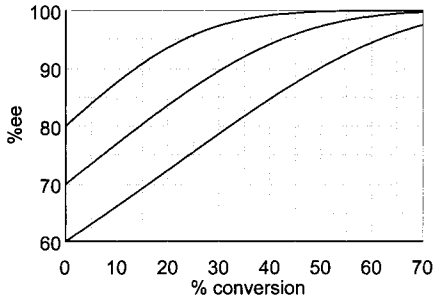


Figure 2. Predicted ee of remaining alcohol as a function of conversion back to ketone from starting enantioenriched alcohols of 60, 70, and 80% ee. The k_{rel} for each starting point is that predicted from the ratio necessary to obtain the observed ee in the hydrogenation step, i.e., 4, 5.67, and 9, respectively.

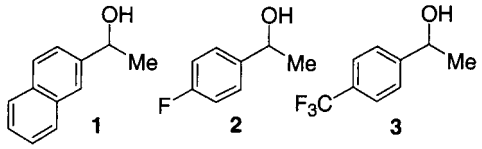


Figure 3. Aryl alcohols tested to illustrate the tandem hydrogenation/kinetic resolution strategy.

Table 1. Catalytic Data for the Kinetic Resolution of Partially Resolved Aryl Alcohols. All Reaction Temperatures Were +25 °C (ee_i and EE_f refer to the initial and final ee's, respectively)

substrate	time (h)	% conv	ee_i	EE_f
1[a]	7.0	25	89 (*S*)	97 (*S*)
2[a]	14.0	9	84 (*S*)	90 (*S*)
3[b]	26.0	12	85 (*S*)	91 (*S*)

[a] In 25 mL of acetone. [b] In 50 mL of acetone.

The curves in Figure 1 assume first-order kinetics. Other expressions could be relevant if first-order kinetics are not followed,[4] nonlinear effects are present,[10] complex rate laws are involved,[4c] or competing pathways are present (particularly if one yields racemic product and thus reduces apparent values of $k_R/k_S = k_{rel}$). Fortunately, even some complex systems have limits that follow simple first-order expressions.[4c] Perhaps the most useful criterion is that the experimentally determined k_{rel} does not vary with percent conversion for a kinetic resolution following simple kinetics.

We tested this approach using enantioenriched alcohols which were obtained via the transfer hydrogenation of the respective ketones with the catalyst derived from $(p\text{-CyRuCl}_2)_2$ and *cis*-1-amino-2-indanol. This system has previously been shown by Palmer et al. to be effective for transfer hydrogenations[5] and by us to be effective for kinetic resolutions.[6] The substrates and results are shown in Figure 3 and Table 1, respectively.

As predicted by the curves in Figure 2, the ee's for the product alcohols were increased above that of the initial transfer hydrogenation reaction. In the case of 1-(2′-naphthyl)ethanol, an initial ee = 89% (*S*) was increased to 97% (*S*) by utilization of the antipode of

(10) (a) Luukas, T. O.; Girard, C.; Fenwick, D. R.; Kagan, H. B. *J. Am. Chem. Soc.* **1999**, *121*, 9299. (b) Girard, C.; Kagan, H. B. Angew. *Chem.-Int. Edit.* **1998**, *37*, 2923. (c) Johnson, D. W.; Singleton, D. A. *J. Am. Chem. Soc.* **1999**, *121*, 9307.

Downloaded by CARLI CONSORTIUM on June 29, 2009
Published on April 4, 2002 on http://pubs.acs.org | doi: 10.1021/om010960+

the catalyst that reduced the ketone.[7,11] It should also be noted that the optical purities of two other substrates (4′-fluorophenylethanol and 4′-trifluoromethylphenylethanol) were also improved with this method though with less enantioenrichment.

In general it is accepted that a kinetic resolution can lead to essentially enantiopure material given that the reaction is run to high enough conversion. However, in our hands this catalytic system led to a gradual decrease in ee beyond the conversions that are reported in Table 1. We believe that this may arise from either decomposition of the catalyst or an inherent catalyst racemization process that has a rate constant (k_{rac}) competitive with k_{rel} for kinetic resolution. We have also observed this behavior where ee begins to decrease at higher conversions for other conventional kinetic resolutions with the catalysts derived from *cis*-1-amino-2-indanol. The magnitude of this problem appears to decrease if lower catalyst loadings are used; however, longer time intervals are needed to reach the same percent conversion. In these cases, the effective k_{rel} varies with amount of conversion (% C), which probably indicates a concurrent racemization process. The conditions chosen were those originally reported for the transfer hydrogenation of the ketones.[5] One might anticipate that optimization of conditions (e.g., variations in base concentration) may reduce this problem. The purpose of these experiments was to demonstrate the concept. Other catalysts may well be free of this limitation, and we are exploring other alternatives.

In conclusion, an original strategy for the refinement of enantiomeric purity has been proposed. This hypothesis has been experimentally validated by using tandem hydrogenation and kinetic resolution reactions. The method potentially allows for one to take full advantage of the microscopic reversibility of the ketone/alcohol couple which has, until this point, been regarded as an undesirable source of enantiopurity and yield degradation. We anticipate that this method will be extended to other systems and will be useful for synthetic applications which demand improved enantioselectivity.

Downloaded by CARLI CONSORTIUM on June 29, 2009
Published on April 4, 2002 on http://pubs.acs.org | doi: 10.1021/om010960+

Experimental Section

All synthetic manipulations were carried out using standard Schlenk techniques under an inert atmosphere. Reagent grade 2-propanol (Brand-Nu Laboratories) was distilled from CaH_2 and was degassed with freeze−pump−thaw cycles (3×) prior to use. Technical grade acetone was distilled under reduced pressure (1×) prior to use. Et_2O (Fisher Scientific), all ketones (Aldrich), (1*R*,2*S*)-(+)-*cis*-1-amino-2-indanol (Aldrich), and (1*S*,2*R*)-(−)-*cis*-1-amino-2-indanol (Strem) were used without further purification. $(p\text{-CyRuCl}_2)_2$[12] was prepared according to literature procedures. The enantiomeric excess in each product was determined by chiral GC analysis using a Hewlett-Packard 5890A gas chromatograph with a Cyclodex-B chiral column. The absolute configuration of each isolated product was determined by correlation with published specific rotations.[5a,13] Optical rotations were measured on a Perkin-Elmer model 341 polarimeter at 589 nm and 25.0 °C, using a 1 dm path length. ^{1}H NMR spectra were recorded on either a Bruker 500 MHz or a Bruker 400 MHz spectrometer, and chemical shifts were in ppm relative to residual solvent peaks (^{1}H).

Transfer Hydrogenation. A typical experimental procedure is described.[5a] A flame-dried Schlenk flask was charged with $(p\text{-CyRuCl}_2)_2$ (7.7 mg, 0.013 mmol), (1*R*,2*S*)-(+)-*cis*-1-amino-2-indanol (7.5 mg, 0.05 mmol), and a stir bar. To these components was added 2-propanol (5 mL, dried/degassed), and the resultant solution was heated (100 °C) for 20 min, followed by cooling to ambient temperature. This solution was added to a mixture of the desired ketone (5.0 mmol) in 2-propanol (45 mL). The reaction was initiated with the addition of a solution of ^{t}BuOK (1.25 mL, 0.1 M in 2-propanol) at 25 °C. Once the reaction was complete (as determined by GLC analysis), the solvent was removed under reduced pressure, and the resultant brown oil was subjected to flash chromatography (silica gel-60, Et_2O). Subsequent evaporation under reduced pressure yielded clear oils in each case. ^{1}H NMR spectral data for the resultant products were consistent with previously reported results.[5a,13]

Kinetic Resolution. It should be noted that the use of pure alcohols (absent of the parent ketone) should provide the best results in the kinetic resolution, as it improves interference from back reactions. The removal of the starting ketone should not be essential and in ideal cases could remain in the kinetic resolution step. The most important step, however, is the removal of catalyst used for the initial hydrogenation.

A typical experimental procedure is described.[6] A flame-dried Schlenk flask was charged with $(p\text{-CyRuCl}_2)_2$ (28 mg, 0.048 mmol), (1*S*,2*R*)-(−)-*cis*-1-amino-2-indanol (28 mg, 0.188 mmol), and a stir bar. To these components was added acetone (5 mL), and the resultant solution was heated (100 °C) for 20 min, followed by cooling to ambient temperature. This solution was added to a mixture of the desired nonracemic alcohol (0.5 mmol) in acetone (20 mL). The reaction was initiated with the addition of a solution of ^{t}BuOK (2.0 mL, 0.1 M in 2-propanol). After the desired time, an aliquot of the catalytic solution (1 mL) was removed via syringe and was evaporated under reduced pressure. The resultant oil was subjected to flash chromatography (silica gel-60, Et_2O) and subsequent evaporation under reduced pressure to yield clear oils in each case.

Acknowledgment. We thank the National Science Foundation (Grant CHE0092222) for support of this research.

Supporting Information Available: Tables containing the calculated k_{rel} values for substrates 1−3; derivation of equation for ee as a function of % C. This material is available free of charge via the Internet at http://pubs.acs.org.

OM010960+

(11) This value for EE_f and % conversion fits is lower than the theoretically predicted value obtained with the Horeau equation.[7] We have previously measured the k_{rel} (from a kinetic resolution) for 1-(2′-naphthyl)ethanol to be >5.[6] When a value of $k_{rel} = 6$ is substituted into the equation, a conversion of 26% is obtained. The observed EE_f = 89% would suggest a $k_{rel} = 17$. This suggests a degradation of enantiomeric purity and effective k_{rel} over the course of the reaction. (See Supporting Information for more details.)

(12) Bennett, M. A.; Huang, T.-N.; Matheson, T. W.; Smith, A. K. *Inorg. Synth*. **1981**, 21, 74.
(13) Nakamura, K.; Matsuda, T. *J. Org. Chem*. **1998**, *63*, 8957 (see Supporting Information).