ORGANIC LETTERS

2001
Vol. 3, No. 23
3703−3706

Enantioselective Routes to Both Enantiomers of Aryl Alcohols with a Single Catalyst Antipode: Ru and Os Transfer Hydrogenation Catalysts

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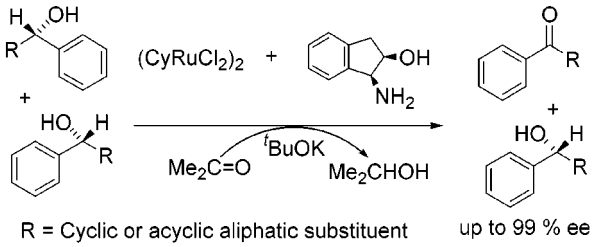
Received August 23, 2001

ABSTRACT



The kinetic resolution of secondary aryl alcohols has been investigated. When $(CyRuCl_2)_2$, (1*R*,2*S*)-(+)-*cis*-1-amino-2-indanol, and KOH or ^{t}BuOK (catalyst 1) were combined in the presence of (±)-alcohols, ee's > 90% were generally observed. When applied to the kinetic resolution of (±)-indanol and (±)-tetralol, ee's = 99% (*R*) were observed. In addition, the asymmetric transfer hydrogenation of ketones was investigated with a catalyst, 2, generated in situ from $(CyOsCl_2)_2$, (1*R*,2*S*)-(+)-*cis*-1-amino-2-indanol, and ^{t}BuOK, yielding ee's of up to 98% (*S*).

The development of new and original chiral catalysts often proceeds via modification of chiral auxiliaries in order to improve the transfer of chirality to substrate. However, once an enantioselective catalyst is discovered, it is often desirable to enhance the scope of the system to allow the production of both enantiomers of the product in high enantiomeric purity. Such a transformation is usually accomplished by employing the opposite enantiomer of the catalyst, which is often obtained using the enantiomeric ligand in a transition metal catalyst. However, in cases where only one antipode of the ligand is available, this approach is not an option.[1]

An ideal situation in this case would be the development of a methodology that could use the same catalyst to produce either enantiomer of the product in high ee. Kinetic resolution[2] can provide an alternative route to the other antipode. This approach exploits the favorable selectivity for a given reaction by proper manipulation of equilibrium conditions for a reversible reaction (See Figure 1). Given that a reaction

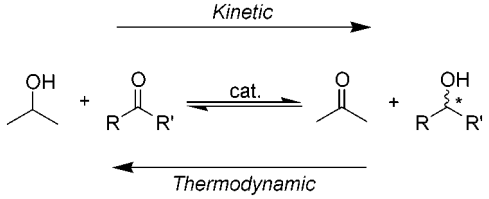


Figure 1. Equilibria between the kinetic and thermodynamic products for this investigation (R = aryl).

is thermodynamically favored and that the relative difference in rates (taken as a ratio = $k_{fast}/k_{slow} = k_{rel}$) is significant, then one enantiomer can selectively react with the chiral catalyst and induce an asymmetric transformation.[3,4] In an

(1) Palmer, M.; Walsgrove, T.; Wills, M. *J. Org. Chem.* **1997**, *62*, 5226.
(2) Reviews on chemical kinetic resolution: (a) Kagan, H. B.; Fiaud, J. C. *Top. Stereochem.* **1988**, *18*, 249. (b) Brown, J. M. *Chem. Ber.* **1989**, *25*, 276. (c) Noyori, R.; Tokunaga, M.; Kitamura, M. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 36.

10.1021/ol016641w CCC: $20.00
Published on Web 10/17/2001

ideal case, an ee = 100% can be obtained with a conversion of 50%. Thus, an asymmetric transfer hydrogenation catalyst should be capable of dehydrogenation, as well as hydrogenation, and should be able to be used in this manner. Asymmetric hydrogenations and dehydrogenations using different catalysts have been reported,[5,6] but Ru catalysts that have been reported by Noyori effect both reactions.[5a,6a] We report here that a different system developed by Palmer et al.[1] for hydrogenations that used Ru catalysts derived from amino alcohols can also be used for kinetic resolutions. Although both enantiomers of amino-2-indanol are available, our studies demonstrate the generally unappreciated notion that a single catalyst can provide a route to both antipodes of a product.

For our investigation, the system of choice involved the resolution of racemic α- and *β*-aryl alcohols because the oxidation of benzylic alcohols is thermodynamically favored over reduction relative to the oxidation of aliphatic alcohols (Figure 2).[4] This suggested to us that the kinetic resolution

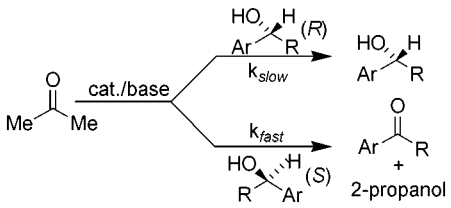


Figure 2. Net reaction for the kinetic resolution of (±)-aryl alcohols.

of aryl alcohols with a chiral Ru catalyst (shown by Palmer et al.[1] to reduce ketones to alcohols in high ee) could be effective. This catalyst (**1**), derived from the readily available *p*-cymene ruthenium complex, $(CyRuCl_2)_2$, and (1*R*,2*S*)-(+)-*cis*-1-amino-2-indanol, with addition of an appropriate base such as KOH or ^{t}BuOK was thus employed.[5−7] This hydrogenation catalyst often provides an excellent route to (*S*)-aryl alcohols from aryl ketones. Since there are numerous methods to reduce the ketones to the racemic alcohols, we sought to use it as a dehydrogenation catalyst in kinetic resolutions to prepare the (*R*)-aryl alcohols.

The results of kinetic resolutions of some chiral alcohols (as depicted in Figure 3) using catalyst **1** are shown in Table

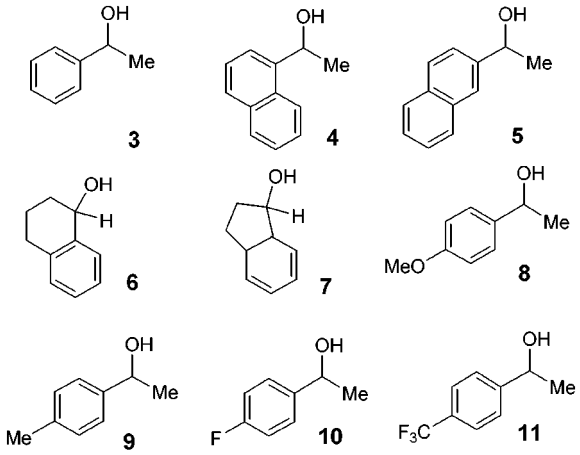


Figure 3. (±)-Aryl alcohols tested for kinetic resolution by dehydrogenation catalysis.

1. Notably, most of the examples[7] provide products with enantiomeric purities in excess of 90%. Furthermore, both tetralol, (±)-**6**, and indanol, (±)-**7**, were resolved to yield a single enantiomer in extremely high ee. For (±)-**7** the resolution was facile, thus producing the (*R*)-alcohol with 99% ee in 1 h (conv = 65%, +25 °C). A similar result was observed for the resolution of (±)-**6**, where the (*R*)-alcohol was produced with nearly ideal results (99% ee, conv = 51%).

Table 1. Data for Kinetic Resolution of (±)-Alcohols with Catalyst **1** That Yield (*R*)-Alcohols in Excess

substrate[a,7]	time (h)	°C	% conv	% ee	k_{rel}[b,c]
(±)-**3**	29	25	61	90	>10
(±)-**5**	19	25	69	87	>5
(±)-**6**	24	25	59	97	>20
(±)-**7**	1	25	65	99	>15
(±)-**3**[d]	360	0	54	90	>20
(±)-**6**	19	0	51	99	>100
(±)-**8**	18	25	61	89	>10
(±)-**9**	24	25	69	92	>7
(±)-**10**	18	25	57	81	~10
(±)-**11**	24	25	35	41	~11

[a] The substrate-to-metal ratio was 5.5:1.0, and all reactions used 2 mL of 0.1 M ^{t}BuOK/2-propanol. All reactions employed a $(CyRuCl_2)_2$/ligand mole ratio of 1.0:4.0.[1] [b] k_{rel} is defined by the ratio of the rate constants where $k_A/k_B = \ln[(1 - C)(1 - ee)]/\ln[(1 - C)(1 + ee)]$, where *C* is the fraction of consumption of racemate, ee is % ee/100, and A and B refer to the concentrations of the fast and slow reacting enantiomers, respectively. Sharpless et al. have noted that for practical purposes a $k_{rel} > 100$ is essentially the same as ∞.[3] [c] Determined from the final conversion and ee. [d] At 5.7 days, conv = 50% and ee = 88% (*R*).

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

(4) Keith, J. M.; Larrow, J. F.; Jacobsen, E. N. *Adv. Synth. Catal.* **2001**, *343*, 5.

(5) For Noyori's highly enantioselective example of kinetic resolution with ArRuClTsdpen, see: (a) Hashiguchi, S.; Fujii, A.; Haack, K.-J.; Matsumura, K.; Ikariya, T.; Noyori, R. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 288. For other selected kinetic resolution examples, see: (b) Nishibayashi, Y.; Takei, I.; Uemura, S.; Hidai, M. *Organometallics* **1999**, *18*, 2291. (c) Persson, B. A.; Larsson, A. L. E.; Le Ray, M.; Backvall, J.-E. *J. Am. Chem. Soc.* **1999**, *121*, 1645. (d) Kitamura, M.; Ohkuma, T.; Tokunaga, M.; Noyori, R. *Tetrahedron: Asymmetry* **1990**, *1*, 1. (e) Vedejs, E.; Mackay, J. A. *Org. Lett.* **2001**, *3*, 535.

(6) 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. (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. (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) Faller, J. W.; Lavoie, A. R. *Organometallics* **2001**, *20*, in press.

(7) Strem Chemicals has recently begun to market a CATHy catalyst system that is derived from $(Cp^*RhCl_2)_2$ and enantiopure *cis*-1-amino-2-indanol.

To expand the scope of this system, an investigation into the electronic effects of the substrates was undertaken. The highest level of enantioenrichment was observed for the substrates bearing electron-donating *para* substituents.[8] The results (Table 1, alcohols 3, 8−11) suggest that a strongly electron-withdrawing substituent (such as $-CF_3$) disfavors the oxidation of alcohols to ketones, whereas electron-donating substituents (such as −OMe and −Me) lead to high substrate conversion and thus higher ee. Such results are confirmed by the observation by our group and others[5a,6f] that (for the reduction of ketones to alcohols) electron-withdrawing substituents lead to lower ee's relative to electron-donating substituents.

While the reduction of ketones with **1** has been found to preferentially produce (*S*)-alcohols, the reverse process dehydrogenates (*S*)-alcohols and provides a route to the (*R*)-alcohols. *Therefore, it should be noted that both enantiomers can be obtained with high levels of enantioenrichment from a single enantiomer of the catalyst.* This methodology represents a highly efficient protocol that can be implemented into synthetic applications where precise control over the stereochemistry of alcohols is desired.

The observation of (*R*)-stereocenters in this series of kinetic resolutions (as opposed to the reduction of ketones) can be rationalized as a function of the complimentary stereochemistry of the (*S*)-alcohol with **1**. Since the catalyst produces the (*S*)-alcohol (from acetophenone), it is requisite that the chirality of the metal center is matched with that product. It is this "matched" interaction that leads to a preferred oxidation of the (*S*)-product to an achiral ketone.Where energetic considerations are concerned, the transition state energy for the diastereotopic interaction between **1** and the (*S*)-alcohol ($\Delta G^{\ddagger}_S$) is less than that for the interaction with the (*R*)-alcohol ($\Delta G^{\ddagger}_R$).[4] As such, the degree of enantioenrichment is directly proportional to the difference in transition state energies ($\Delta G^{\ddagger}$) between the two interactions.

Our optimization of reaction conditions also took into account the choice of base. We investigated 0.1 M solutions (in 2-propanol) of KOH, ^{t}BuOK, and NEt_3. While there were not large differences in activity when the catalyst was activated with KOH or ^{t}BuOK, it was determined that ^{t}BuOK was slightly advantageous (at 25 °C) as determined by comparison of the k_{rel} values.[9] Inferior results were obtained upon use of NEt_3 with <1% conversion of (±)-1-phenyl-ethanol to acetophenone. Furthermore, it should be noted that the attempted kinetic resolution of (±)-1-(1′-naphthyl)-ethanol was particularly sluggish.[9,10]

The source of the transferred hydrogen atom in similar systems has been attributed to a metal-centered hydride. Perhaps the most widely accepted theory is that a nitrogen atom as well as the metal is intimately involved in the hydride transfer process. Noyori and co-workers[11] have suggested that the transferred hydride originates from an intimate Ru−N−H interaction. These authors have referred to the important Ru−N−H moiety as an example of metal−ligand bifunctional catalysis. Others have expanded upon Noyori's work and have provided mass spectrometry evidence for a proposed active catalyst with a metal-centered hydride.[11b] Both of these proposals suggest that a N−H moiety could be a prerequisite for an effective catalyst in asymmetric transfer hydrogenation reactions. Although this is frequently the case, it should be noted that various aprotic sp^2 nitrogen ligands have also been employed.[12]

Additionally, the catalyst generated in-situ from $(CyOsCl_2)_2$, (1*R*,2*S*)-(+)-*cis*-1-amino-2-indanol, and ^{t}BuOK was screened for the asymmetric transfer hydrogenation of ketones. As shown in Table 2 the catalyst was highly enantioselective, yielding ee's that were generally >90%. It should be noted that for the reduction of 1′-tetralone and 1′-indanone, the corresponding alcohols were obtained with ee's = 97% and 98% (*S*), respectively. However, when the osmium catalyst was applied to reactions with higher substrate loadings (over longer time periods), the ee's were slightly diminished.[9]

Table 2. Asymmetric Transfer Hydrogenation Results for Various Ketones with the Catalyst System Prepared in Situ from $(CyOsCl_2)_2$ and (1*R*,2*S*)-(+)-*cis*-1-Amino-2-indanol (Catalyst **2**)[a]

substrate[b]	base	°C	time (h)	% conv	% ee
(±)-**3**	KOH	−24	24	87	91
(±)-**3**	^{t}BuOK	−24	24	86	92
(±)-**4**	^{t}BuOK	−24	48	80	94
(±)-**5**	^{t}BuOK	−24	48	77	89
(±)-**6**	^{t}BuOK	+25	12	84	97
(±)-**7**	^{t}BuOK	−24	48	37	98

[a] The substrate to metal ratio was 100:1, and all reactions used 2 mL of 0.1 M base/2-propanol. All configurations were (*S*). [b] All reactions employed a $(CyOsCl_2)_2$/ligand mole ratio of 1.0:4.0.

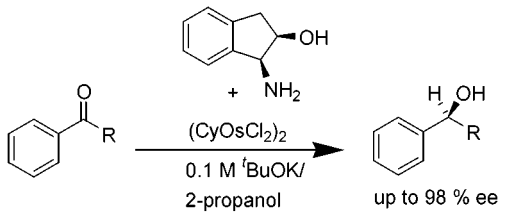


Figure 4. The generation of catalyst **2** (in situ) for the asymmetric hydrogenation of ketones.

In conclusion, we have expanded the scope of catalyst **1** to include the highly effective kinetic resolution of (±)-aryl

(8) One measure of the electronic effects is the Hammett σ constant: OMe, −0.268; Me, −0.170; H, 0.000; F, +0.062; CF_3, +0.54. McDaniel, D. H.; Brown, H. C., *J. Org. Chem.* **1958**, *23*, 420.

(9) See Supporting Information.

(10) Conversion = 15%, ee = 14% (*R*) at 3 days. Conversion = 25%, ee = 33% (*R*) at 20 days.

(11) (a) Haack, K.-J.; Hashiguchi, S.; Fujii, A.; Ikariya, T.; Noyori, R. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 285. (b) Kenny, J. A.; Versluis, K.; Heck, A. J. R.; Walsgrove, T.; Wills, M. *Chem. Commun.* **2000**, 99−100.

(12) Corey, E. J.; Helal, C. J. *Tetrahedron Lett.* **1995**, *36*, 9153.

alcohols. In most cases, ee's > 90% have been obtained with ee's of 99% in some cases. When the same catalyst was applied to the kinetic resolution of para substituted (±)-aryl alcohols, a trend was observed in which the electron-withdrawing substituents led to reduced ee's in comparison to electron-donating groups. In addition, the asymmetric transfer hydrogenation of ketones with $(CyOsCl_2)_2$, (1*R*,2*S*)-(+)-*cis*-1-amino-2-indanol, and ^{t}BuOK was investigated, yielding ee's of up to 98%.

Acknowledgment. This work was financially supported by the National Science Foundation (Grant No. CHE0092222). A.L. would like to thank Dr. Jonathan Parr for helpful discussions in addition to the generous gift of $(CyOsCl_2)_2$.

Supporting Information Available: Experimental methods, determination of ee's, results for the determination of optimization conditions, and additional asymmetric osmium hydrogenation results. This material is available free of charge via the Internet at http://pubs.acs.org.

OL016641W