Tetrahedron Letters, Vol. 34, No. 46, pp. 7359-7362, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

Chiral Poisoning in the Kinetic Resolution of Allylic Alcohols

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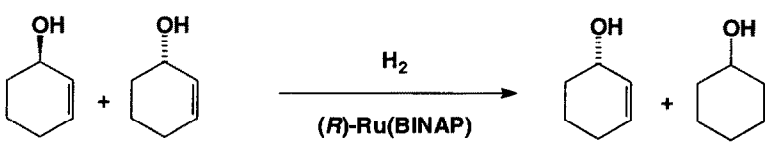
Abstract: Recently, hydrogenations of allylic alcohols using ruthenium catalysts with enantiomerically pure phosphines, such as (*R*)-BINAP were reported to be useful for the kinetic resolution of cyclic allylic alcohols. These kinetic resolutions can also be effected using *racemic* BINAP and preferentially deactivating one enantiomer of the catalyst with an enantiomerically pure chiral poison. Poisoning of racemic (BINAP)-$RuCl_2(dmf)_x$ with (1*R*,2*S*)-ephedrine provided (*R*)-2-cyclohexenol in 93% ee at 72% conversion.

Noyori and his coworkers[1] have shown that hydrogenation of allylic alcohols using ruthenium catalysts with enantiomerically pure phosphines, such as (*R*)-BINAP have proven effective for kinetic resolution of cyclic allylic alcohols. Since enantiomerically pure BINAP, 2,2'-bis(diphenylphosphino)-1-1'-binapthyl, is



obtained via a classical resolution,[2] the separation is time consuming and results in a rather high cost for a pure enantiomer. We have adopted a different aproach in which a *chiral poison* can deactivate one enantiomer of a racemic catalyst and so give high enantioselectivity in asymmetric reduction.[3] This sharply reduces the catalyst costs in situations where the cost of the ligands is high. There have also been several other reports of *in situ* resolutions,[4,5] where the deactivation of one hand of a catalyst has been proposed. We report here our findings that ephedrine, a relatively inexpensive and readily available enantiomerically pure amino alcohol, can effectively function to poison a ruthenium catalyst containing racemic BINAP. This provides a method complementary to Sharpless epoxidation. The Sharpless procedure is effective for flexible acyclic substrates, but does not always work well with cis olefins, particularly cyclic allylic alcohols.[6-8]

Using a racemic BINAP-ruthenium catalyst with (-)-(1*R*,2*S*)-ephedrine as a poison we have been able to prepare (*R*)-2-cyclohexenol in >95% ee. For ease in comparison of results we have used 0.3% catalyst loading and have observed 70-80% conversion in one hour. There appears to be no degradation in catalyst over moderate times.

The original studies of kinetic resolutions of cyclic allylic alcohols by asymmetric hydrogenation used [(*S*)-BINAP]Ru(acetate)$_2$.[1] *In situ* formation of (*R*)- or (*S*)-BINAP-ruthenium complexes, has become more popular since it eliminates the need to synthesize and handle the air-sensitive acetate.[9-14] We have used the racemic (BINAP)-$RuCl_2(dmf)_x$, **1** complex[12,14] for convenience in handling. Our results for a number of conditions are summarized in Table 1.[15] The enantiomeric purity of the remaining cycloalkenol was determined by conversion to the MTPA ester.[16]

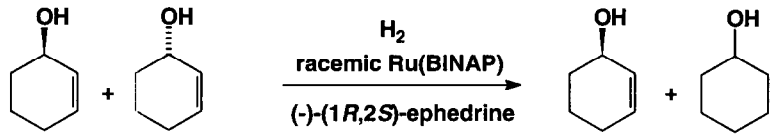


Table 1. Kinetic Resolution of 2-cyclohexenol by Chiral Poisoning of a Racemic Ru(BINAP) Catalyst

Poison	Eq poison	H_2 atm	rxn time min	convn %	ee %	config	k_f/k_s[b]
none, (*R*)-BINAPRu[b,c]	0	11	15	60	>95	(*S*)	>15
none, (±)BINAP	0	10	3	60	0		---
(1*R*,2*S*)-Ephedrine	10	2	720	66	53	(*R*)	2.8
(1*R*,2*S*)-Ephedrine	10	10	10	28	15	(*R*)	2.6
(1*R*,2*S*)-Ephedrine	10	10	40	57	58	(*R*)	4.4
(1*R*,2*S*)-Ephedrine	10	10	55	72	93	(*R*)	6.4
(1*R*,2*S*)-Ephedrine	10	10	60	77	>95	(*R*)	>6.4
(1*S*,2R)-Ephedrine	10	10	60	79	>95	(*S*)	>6.4
(1*R*,2*S*)-Ephedrine[d]	30	10	120	40	28	(*R*)	3.2
(1*R*,2*S*)-Ephedrine	10	100	7	57	44	(*R*)	3.0
(1*R*,2*S*)-N-methylephedrine	30	10	3	50	38	(*R*)	3.1
(1*S*,2R)-Norephedrine	5	10	130	44	7	(*S*)	1.3
(1*S*,2*S*)-Pseudoephedrine	10	10	60	49	20	(*S*)	1.8
Quinine	5	10	3	68	8	(*R*)	1.2
Quinidine	5	10	3	73	5	(*R*)	1.1

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a) The solvent was 2:1 CH_2Cl_2/MeOH with a substrate to catalyst ratio of 300. The amine was mixed with the solution of ruthenium catalyst two hours prior to pressurizing with hydrogen. The reactions were conducted at 21 ± 2°C.

b) The value of k_f/k_s if the reactions were first order in substrate. This is not the case for certain conditions.

c) First entry is for 100% ee BINAP-Ru catalyst; the other entries used 0% ee BINAP-Ru catalyst.

d) The substrate to catalyst ratio for this run was 900.

The first entry in Table 1 shows that the analogue of **1** prepared from pure (*R*)-BINAP is quite effective for the kinetic resolution of 2-cyclohexenol. Since the remaining (*S*)-2-cyclohexenol is obtained in >95% ee, this

indicates that the (*R*)-BINAP-Ru catalyst hydrogenates (*R*)-2-cyclohexenol much faster than (*S*)-2-cyclohexenol. When the reaction was carried out with racemic **1**, the observed rate was much faster owing to mutual kinetic resolution; i.e., in this case both enantiomers of the catalyst have the favored enantiomer of the substrate available to them.

Table 1 summarizes the effect of the number of equivalents of amine added per mole of Ru complex on the enantiomeric purity of the remaining 2-cyclohexenol as a function of % conversion to cyclohexanol. Addition of amine noticeably slows the reaction. The amine presumably interacts with and partially deactivates both the (*R*)- and (*S*)-BINAP-Ru catalysts, but it does so more selectively with one hand of the catalyst. A survey of a number of amines and amino alcohols showed that ephedrine was the most effective. Since the (*R*)-2-cyclohexenol is obtained in high ee with (1*R*,2*S*)-ephedrine, the poison is selectively deactivating the (*R*)-BINAP-Ru component of the racemic catalyst. This was confirmed by noting that the initial rate with the enantiomerically pure (*R*)-BINAP-Ru catalyst poisoned with (1*S*,2*R*)-ephedrine is 1.9 times faster than that poisoned with (1*R*,2*S*)-ephedrine.[17]

The results of kinetic resolution studies are normally analyzes by assuming that the reactions are first order in substrate. In these cases, a measurement of % ee at a particular % conversion allows the determination of the ratio of the rate constants for the faster and slower reacting enantiomers of the substrate. A relatively simple equation relates k_{fast}/k_{slow} to % ee and % conversion.[6] From this ratio one can predict the % conversion required to achieve a desired enantiomeric purity. These ratios are now generally reported in kinetic resolution studies and give a measure of the effectiveness of the kinetic resolution.

The calculated k_{fast}/k_{slow} values increase with % conversion for the studies with 10 eq of (1*R*,2*S*)-ephedrine and 10 atm H_2, which indicates that the reaction is not first order in substrate. Preliminary kinetics measurements of the (*R*)-BINAP complex poisoned with (1*S*,2*R*)-ephedrine confirmed that the reaction is not first order in substrate, but fractional or zero order. Thus the conventional equation[6] does not hold in this case for estimation of % ee as a function of % conversion. That equation leads to an underestimate of the effectiveness of the kinetic resolution if one extrapolates from % ee at low conversions.[18] We will report an more complete kinetic analysis in a future paper.

Preliminary results with 2-pentenol using similar conditions (10 atm H_2) and (1*R*,2*S*)-ephedrine showed 61% conversion after 30 minutes and a remaining substrate of 20% ee. After 120 min and 89% conversion, (*R*)-2-pentenol of 66% ee was obtained. It appears that this approach may be applicable to the kinetic resolution of other allylic alcohols. (*R*)-BINAP is much more expensive ($320/g, Aldrich Chemical Co.) than (1*R*,2*S*)-ephedrine ($0.50/g). Since racemic BINAP should be much less expensive, there is a significant economic motivation for using our chiral poisoning strategy.

Acknowledgement: We thank the National Science Foundation for support of this research.

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15. A typical reaction procedure follows. A dry 20 mL Schlenk tube was charged with (1*R*,2*S*)-ephedrine (16.5 mg, 0.1 mmol) and 1 mL of CH_2Cl_2 degassed by three freeze-thaw cycles, and then filled with N_2. $RuCl_2$[(±)-binap](dmf)$_x$, **1**, (9.0 mg, 0.01 mmol calculated with $x \approx 1.5$) was added to this solution under N_2 and the mixture allowed to stand for 2 h. A dry 80 mL Schlenk tube was charged with 2-cyclohexenol (300 mg, 3.06 mmmol), CH_2Cl_2 (1 mL) and MeOH (1mL) and degassed by three freeze-thaw cycles and then filled with N_2. This solution was added to the solution of catalyst via cannula using N_2 pressure. The reaction mixture was quickly transferred to a N_2-filled reaction vessel of a 75 mL Parr high pressure reactor under a stream of N_2. The reactor was flushed with 30 atm H_2 two times and then pressurized with 10 atm H_2 . After the desired time had passed, the H_2 pressure was released and the reaction mixture concentrated on a rotary evaporator. Percent conversion was determined by ^{1}H NMR . Conversion of the mixture of 2-cyclohexenol and cyclohexanol to the (*R*)-MTPA esters allowed analysis of enantiomeric purity.[16]
16. Enantiomeric purity was determined by ^{1}H NMR after conversion to the (*R*)-MTPA ester. One set of the olefinic protons are well separated and appear as multiplets in the diastereomers at δ 5.74 (*R,S*) and δ 5.83 (*R ,R*), ($CDCl_3$, 300 MHz).
17. Rates were determined by following changes in H_2 pressure.
18. The conventional equations[6] can take different form if the reactions are zero or fractional order. Under certain circumstances, such as the approach to saturation kinetics, the ability to accurately predict %ee as a function of % conversion can be complicated, but can lead to better results than expected on simple first order behavior. We are currently examining a broader profile of conditions to determine the appropriate equations for the kinetic resolution.

(Received in USA 27 August 1993; accepted 16 September 1993)