Application of the Chiral Poisoning Strategy: Enantioselective Diels−Alder Catalysis with a Racemic Ru/BINAP-Monoxide Lewis Acid

J. W. Faller,* Adrien R. Lavoie, and Brian J. Grimmond

Department of Chemistry, Yale University, New Haven, Connecticut 06511

Received December 12, 2001

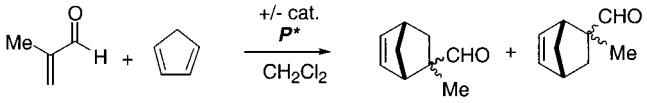
A chiral poisoning strategy has been applied to the [(±)-*p*-cymeneRuCl(BINPO)]SbF_6 (±**1**) catalyst system for the asymmetric Diels−Alder reaction between methacrolein and cyclopentadiene to produce enantioenriched *exo*-2-methylbicyclo[2.2.1]hept-5-ene-2-carboxaldehyde. When ±**1** was mixed with $AgSbF_6$, the dicationic Lewis acid [(±)-*p*-cymeneRu-(H_2O)(BINPO)]$(SbF_6)_2$ (±**2**) was generated. The additions of a number of chiral poisons (***P**** = enantiopure ligand) were found to deactivate one of the enantiomers of the catalyst with varied levels of selectivity. The most effective chiral poison was either L-proline or L-prolinamide. In catalytic trials with L-proline, an ee of up to 54% was observed. In the case where a stoichiometric amount of (±)-Ru/methacrolein reacted in the presence of L-prolinamide, the DA product was obtained with ee = 60% (*S*), de = 96% (exo), and 92% conversion.

Introduction

Owing to the difficulty and expense that must be employed to obtain effective and enantiopure chiral auxiliaries, alternative strategies in catalytic asymmetric synthesis and catalysis are highly desired. Such attempts have included the in situ resolution of racemic catalysts, wherein it was suggested that one enantiomer of the catalyst was deactivated.[1] The emergence[2a] of chiral poisoning marked the onset of an alternative economical strategy for use in catalytic asymmetric synthesis. In this approach, one enantiomer of a racemic catalyst is preferentially deactivated by the addition of a relatively inexpensive and readily available enantiomerically pure poison (***P**** = enantiopure ligand). In the ideal case, a 0.5 (***P****):1.0 (racemic catalyst) mixture would result in complete deactivation of one catalyst enantiomer while leaving the antipode free to catalyze an asymmetric reaction. On the basis of this premise, it would follow that enantioselective catalysis should be achieved with a racemic catalyst without the labor and expense involved with obtaining enantiopure ligands or catalysts.

Several successful examples of chiral poisoning have been reported for a variety of different asymmetric reactions, although this is, to our knowledge, the first account with Diels−Alder reactions. For example, variants of this strategy have been applied to the asymmetric hydrogenation of dimethyl itaconate by (±)-Rh(CHIRAPHOS), the asymmetric chloral-ene reaction by the Ti(O-*i*-Pr)$_2$Cl$_2$/(±)-BINOL/diisopropyl D-tartrate/Ti(O-*i*-Pr)$_2$Cl$_2$ catalyst system, the synthesis of homoallylic alcohols by Ti(O-*i*-Pr)$_4$/[(±)-BINOL], the kinetic resolution of 2-cyclohexenol with a racemic Ru(BINAP) catalyst, and more recently the asymmetric transfer hydrogenation of ketones by [(±)-$RuCl_2$(BINAP)$(dmf)_n$] in the presence of enantiopure diamines.[2] These successful examples have demonstrated that chiral poisoning is a feasible and effective strategy which can be applied to virtually any catalytic asymmetric reaction.

Scheme 1. Diels−Alder Condensation of Methacrolein with Cyclopentadiene

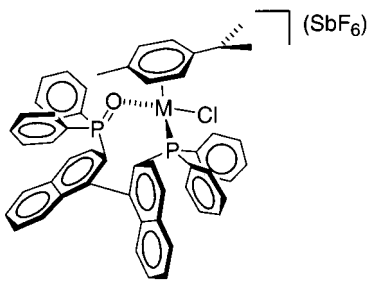


Recently, we reported that enantiomerically pure [(R_{Ru},*S*)-*p*-cymeneRuCl(BINPO)]SbF_6 was a highly enantioselective Lewis acid precatalyst for the asymmetric Diels−Alder reaction between methacrolein and cyclopentadiene (see Scheme 1 and Figure 1).[3a] In fact, when this reaction was carried out at −78 °C, (*S*)-(+)-*exo*-2-methylbicyclo[2.2.1]hept-5-ene-2-carboxaldehyde was obtained in high conversion with de = 93% and with ee = 99%. An analogous catalyst, containing an Os(II) metal center, was also found to effectively catalyze the same reaction with de = 99% and ee = 93%.[3d] Therefore, owing to the high level of diastereo- and enantioselectivity that was achieved with these enantiopure catalysts, we rationalized that, given the correct conditions, ±**1** would be an appropriate target for use with the chiral poisoning strategy.

(1) (a) Alcock, N. W.; Brown, J. M.; Maddox, P. J. *J. Chem. Soc., Chem. Commun.* **1986**, 1532. (b) Brown, J. M.; Maddox, P. *Chirality* **1991**, *3*, 345. (c) Maruoka, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1989**, *111*, 789.

(2) (a) Faller, J. W.; Parr, J. *J. Am. Chem. Soc.* **1993**, *115*, 804. (b) Faller, J. W. Tokunaga, M. *Tetrahedron Lett.* **1993**, *34*, 7359. (c) Faller, J. W.; Mazzieri, M. M.; Nguyen, J. T.; Parr, J.; Tokunaga, M. *Pure Appl. Chem.* **1994**, *66*, 1463. (d) Faller, J. W.; Sams, D. W. I.; Liu, X. *J. Am. Chem. Soc.* **1996**, *118*, 1217. (e) Faller, J. W.; Liu, X. *Tetrahedron Lett.* **1996**, *37*, 3449. (f) Sablong, R.; Osborn, J. A.; Faller, J. W. *J. Organomet. Chem.* **1997**, *527*, 65. (g) Mikami, K.; Korenaga, T.; Ohkuma, T.; Noyori, R. *Angew. Chem., Int. Ed.* **2000**, *39*, 3707. (h) Noyori, R.; Ohkuma, T. *Angew. Chem., Int. Ed.* **2001**, *40*, 40−73 (this article reviews transfer hydrogenations and briefly summarizes chiral poisoning results).

10.1021/om011052f CCC: $22.00
Publication on Web 03/14/2002



M = Ru, Os

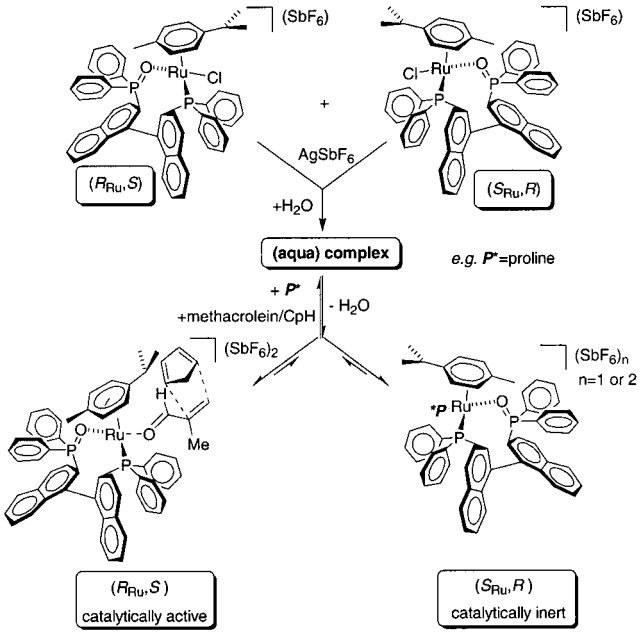
Figure 1. Enantiopure [*p*-CyRuCl(BINPO)]SbF_6 and [*p*-CyOsCl(BINPO)]SbF_6, effective catalyst precursors for the Diels–Alder reaction between methacrolein or ethylacrolein and CpH.

Results and Discussion

Treatment of ±**1** with 1 equiv of $AgSbF_6$ resulted in chloride abstraction and, thus, generation of a formally 16-electron Lewis acid. It is probable that this dication was ligated by water in the solvent to form [(±)-*p*-cymeneRu(H_2O)(BINPO)](SbF_6)$_2$ (±**2**). An analogous cationic aqua complex was found by Kurosawa et al. in [(η^6-benzene)Ru((*R*)-bpop)(H_2O)](BF_4)$_2$, where (*R*)-bpop = (*R*)-(+)-2,2′-isopropylidenebis(4-phenyl-2-oxazoline).[4] Subsequently, addition of the respective chiral poison established an equilibrium between the active aqua complexes (±**2**) and the poisoned adducts [(±)-*p*-cymeneRu(***P****)(BINPO)](SbF_6)$_2$ (±**2-*P****), as depicted in Scheme 2. It should be noted that, upon binding of ***P**** to each of the catalyst enantiomers, diastereomers were effectively produced. Owing to the relative stability of diastereomers, varying levels of enantioselectivity arise from the enantiomeric purity of the ruthenium catalyst which remains after the formation of the (+)-Ru-***P**** and the (−)-Ru-***P**** complexes. As a result, the enantiomer of [*p*-cymeneRu(H_2O)(BINPO)] with the largest equilibrium constant for Ru-***P**** formation would be expected to be the least effective during catalysis.

Following the addition of ***P**** to form ±**2-*P****, the solution was stirred for 10 min. Subsequently, methacrolein was added (generating σ-bound aldehyde complexes) and the solution was cooled to −24 °C for 30 min.[5] Presumably, the aldehyde coordination occurred to a greater extent with the least "poisoned" Ru complex. The reaction was initiated with the addition of freshly prepared CpH, which was precooled (−24 °C) and allowed to react for 16 h. After the reaction, an aliquot (1.0 mL) of the catalyst solution was added to a flask with pentane (5 mL), which resulted in precipitation and recovery of the catalyst. This mixture was filtered through Celite, and the filtrate was evaporated on a rotary evaporator to yield the product as a clear oil. The enantiomeric purity of the DA product was determined by addition of europium tris[3-(heptafluoropropylhydoxymethylene)-(+)-camphorate] to an aliquot in $CDCl_3$.

Scheme 2. Generation of a Lewis Acidic Catalyst and Competitive Equilibria[a]



[a] Initially, the chloride is abstracted with $AgSbF_6$ and the aqua complexes are generated from moisture in the solvent. Upon addition of the poison (*P**), which in this case is L-proline, the population of the poisoned S_{Ru},*R* catalyst is greater than that of the poisoned R_{Ru},*S* catalyst. As a result, the free R_{Ru},*S* enantiomer is free to coordinate and activate methacrolein for reaction. Note: the subscript (n = 1, 2) depends on whether the poison is bound as a neutral or anionic ligand.

In the most effective poisoning examples, both L-proline and L-prolinamide were found to produce (*S*)-(+)-*exo*-2-methylbicyclo[2.2.1]hept-5-ene-2-carboxaldehyde in approximately 60% ee when a stoichiometric amount of poisoned ±**2** was reacted with methacrolein and CpH (Table 1, entries 5 and 16). Since [(R_{Ru},*S*)-*p*-cymeneRu(BINPO)](SbF_6)$_2$ was previously found to preferentially produce the *S* enantiomer of the DA product,[3a] our initial hypothesis was that same ruthenium enantiomer was predominantly responsible for this catalytic activity.

Mode of Catalyst Deactivation. In general, the poisons that where investigated included enantiomerically pure molecules containing donor atoms (such as N, O, P, S) with the potential to bind at the Lewis acidic

(3) (a) Faller, J. W.; Grimmond, B. J.; D'Alliessi, D. G., *J. Am. Chem. Soc.* **2001**, *123*, 2525. For additional successful examples of enantioselective Diels–Alder catalysis, see: (b) Faller, J. W.; Lavoie, A. R. *J. Organomet. Chem.* **2001**, *630*, 17. (c) Faller, J. W.; Grimmond, B. J. *Organometallics* **2001**, *20*, 2454. (d) Faller, J. W.; Parr, J. *Organometallics* **2001**, *20*, 697. (e) Hall, J.; Lehn, J. M.; Decian, A.; Fischer, J. *Helv. Chim. Acta* **1991**, *74*, 1. (f) Corey, E. J.; Ishihara, K. *Tetrahedron Lett.* **1992**, *33*, 6807. (g) Corey, E. J.; Imai, N.; Zhang, H. Y.; *J. Am. Chem. Soc.* **1991**, *113*, 728. (h) Davies, I. W.; Gerena, L.; Cai, D. W.; Larsen, R. D.; Verhoeven, T. R.; Reider, P. J. *Tetrahedron Lett.* **1997**, *38*, 1145. (i) Davies, I. W.; Senanayake, C. H.; Larsen, R. D.; Verhoeven, T. R.; Reider, P. J. *Tetrahedron Lett.* **1996**, *37*, 1725. (j) Ghosh, A. K.; Mathivanan, P.; Cappiello, J. *Tetrahedron: Asymmetry* **1998**, *9*, 1. (k) Ghosh, A. K.; Cho, H.; Cappiello, J. *Tetrahedron: Asymmetry* **1998**, *9*, 3687.

(4) Asano, H.; Katayama, K.; Kurosawa, H. *Inorg. Chem.* **1996**, *35*, 5760.

(5) The driving force for binding via the carbonyl functionality (as opposed to the double bond) has previously been documented and is suggested to be a function of the metal's preference for the "hard" donor. For examples of σ-bound aldehyde complexes, see: (a) Faller, J. W.; Patel, B. P.; Albrizzio, M. A.; Curtis, M. *Organometallics* **1999**, *18*, 3096. (b) Faller, J. W.; Parr, J. *Organometallics* **2000**, *19*, 3556. (c) Faller, J. W.; Liu, X.; Parr, J. *Chirality* **2000**, *12*, 325. (d) Garner, C. M.; Mendez, N. Q.; Kowalczyk, J. J.; Fernandez, J. M.; Emerson, K.; Larsen, R. D.; Gladysz, J. A. *J. Am. Chem. Soc.* **1990**, *112*, 5146. (e) Mendez, N. Q.; Arif, A. M.; Gladysz, J. A. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 1473. (f) Carmona, D.; Cativiela, C.; Elipe, S.; Lahoz, F. J.; Lamata, M. P.; Pilar, M.; de Viu, L. R.; Oro, L. A.; Vega, C.; Viguri, F. *Chem. Commun.* **1997**, 2351.

Table 1. Selected Catalytic Results for the Diels−Alder Reaction of Methacrolein and Cyclopentadiene with the Catalyst Derived from [(±)-CyRuCl(BINPO)]SbF_6 in the Presence of Chiral Poisons Including and Derived from L-Proline

entry	***P****	(±)-cat. loading (%)	***P**** loading ((mol of ***P****): (mol of ±-Ru))	temp (°C)	time (h)	conversn (%)	de[a] (exo:endo)	ee[b] (confign)
1	L-proline (control)[c]	0	5.0:0.0	−24	16	0		
2	L-proline[d]	10	0.5:1.0	−24	16	76	98	8[e] (*S*)
3	L-proline[d]	10	1.0:1.0	−24	140	28	95	54[e] (*S*)
4	L-proline[d]	30[f]	5.0:3.0	−24	110	53	95	51[e] (*S*)
5	L-proline[d]	100[f]	5.0:1.0	−24	120	35	95	59[e] (*S*)
6	L-proline[d]	100	2.0:1.0	−24	16	39	84	47[e] (*S*)
7	L-proline[d]	10	5.0:1.0	−24	16	16	87	43[e] (*S*)
8	L-proline[d]	10	5.0:1.0	0	16	46	87	36[e] (*S*)
9	L-proline[d]	10	5.0:1.0	+25	16	62	83	25[e] (*S*)
10	L-proline[d]/2,6-lutidine[g]	100	2.0:1.0	−24	16	29	88	35[e] (*S*)
11	L-proline methyl ester·HCl[d]	10	0.5:1.0	−24	16	92	97	2[e] (*S*)
12	L-prolinamide	10	0.5:1.0	−24	40	82	96	43[e] (*S*)
13	L-prolinamide	10	0.5:1.0	−24	16	90	96	42[e] (*S*)
14	L-prolinamide	10	0.7:1.0	−78	30	16	94	42[e] (*S*)
15	L-prolinamide	10	0.5:1.0	−78	16	48	95	30[e] (*S*)
16	L-prolinamide	100[f]	0.8:1.0	−78	140	92	96	60[e] (*S*)

[a] The de was determined by ^{1}H NMR spectroscopy. [b] The ee was determined by ^{1}H NMR spectroscopy with (+)-Eu(hfc)$_3$ as a chiral shift reagent. [c] Control experiment that was carried out in order to ensure that the catalytic activity was not due to ***P****. [d] The poison was not fully dissolved, as determined by visual inspection. It should be noted that excess L-proline was added simply to ensure that saturation of the dicationic Ru acids had occurred. [e] The downfield aldehyde resonance resulting from the chiral shift experiment had a greater intensity. [f] The catalyst loading was increased 3-fold with respect to the general experimental protocol. [g] The 2,6-lutidine was added to scavenge H^+ (potentially generated upon ionization of ***P****) that could catalyze the cyclo condensation in a nonenantioselective manner. Note: see the Supporting Information for complete poisoning results (50 entries).

Table 2. Selected Catalytic Results for the Diels−Alder Reaction of Methacrolein and Cyclopentadiene with the Catalyst Derived from [(±)-CyRuCl(BINPO)]SbF_6 in the Presence of Various Chiral Poisons

entry	***P****	(±)-cat. loading (%)	***P**** loading ((mol of ***P****): (mol of ±-Ru))	temp (°C)	time (h)	conversn (%)	de[a] (exo:endo)	ee[b] (confign)
1	(+)-INDABOX[c]	10	0.5:1.0	−24	16	15	92	13[d] (*S*)
2	(*R*)-methyl *p*-tolyl sulfoxide	10	0.5:1.0	−24	16	94	99	9[e] (*R*)
3	(*R*)-methyl *p*-tolyl sulfoxide	10	5.0:1.0	−24	16	90	98	12[e] (*R*)
4	(1*R*)-(−)-myrtenal	20	0.2:1.0	−24	16	30	96	10[e] (*R*)
5	(TADDOL)PPh[f]	10	0.5:1.0	−24	16	95	96	20[e] (*R*)

[a] The de was determined by ^{1}H NMR spectroscopy. [b] The ee was determined by ^{1}H NMR spectroscopy with (+)-Eu(hfc)$_3$ as a chiral shift reagent. [c] (+)-INDABOX = [3a*R*-[2(3′a*R**,8′a*S**),3′aβ,8′aβ]]-(+)-2,2′-methylenebis[3a,8a-dihydro-8*H*-indeno[1,2-*d*]-oxazole]. [d] The downfield aldehyde resonance resulting from the chiral shift experiment had a greater intensity. [e] The upfield aldehyde resonance resulting from the chiral shift experiment had a greater intensity. [f] (TADDOL)-PPh = (1*R*,7*R*)-9,9-dimethyl-2,2,4,6,6-pentaphenyl-3,5,8,10-tetraoxa-4-phosphabicyclo[5.3.0]decane (Seebach, D.; Hayakawa, M.; Sakaki, J., Schweizer, W. B. *Tetrahedron* **1993**, 49, 1711−1724). Note: see the Supporting Information for complete poisoning results.

coordination sites (Table 2). Upon binding to ±**2**, the poison may have partially or completely deactivated one of the enantiomers of the catalyst. This deactivation may have proceeded by several different modes. The most general mode is displacement of water to yield [*p*-cymeneRu(BINPO)(***P****)]$^{(2-n)+}$ diastereomers ($n = 0$ if ligand is neutral; $n = 1$ if ligand is an anion) in which either the +**2**-***P**** or −**2**-***P**** diastereomer is formed to a greater extent. In such a case, the selectivity probably results from steric interactions involving the BINPO ligand and its repulsions with the enantiopure chiral poison. In some situations electrostatic interactions via ionization of the chiral poison are also a possibility, and this may have led to favorable ion pairing between a dicationic ruthenium center and the anionic poison. Furthermore, an anionic poison may be bound to ±**2**, producing a monocation. As a third mode, the poison may have led to the selective displacement of BINPO from one enantiomer of the catalyst.

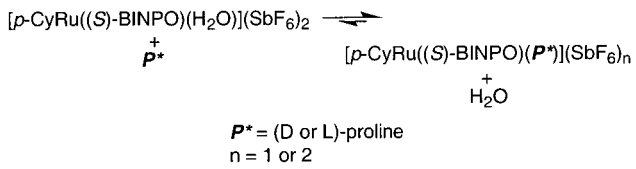
Confirmation of Chiral Poisoning/Mechanistic Considerations. The discussion above assumes that the origin of enantioselection is chiral poisoning. It is possible that either the "poison" or a catalyst derived from the "poison" actually gives rise to the observed enantiomeric excess. Reactions leading to C−C bond formation via organo catalysis have been reported.[6] Among these include the use of amino acids and their derivatives as catalysts for asymmetric Diels−Alder reactions.[6] In particular, Ahrendt and MacMillan have reported that substituted prolines (as the HCl adducts) are capable of enantioselectively catalyzing Diels−Alder reactions. In light of this, we undertook an investigation to probe for the ability of L-proline·HCl or L-prolinamide·HCl to enantioselectively catalyze the Diels−Alder reaction under our conditions.

In our hands, a 10 mol % mixture of either HCl adduct *did not* catalyze the reaction (in CH_2Cl_2) within 20 h at −24 °C. However, when separate and identical reactions were run at +25 °C, the condensation reactions proceeded smoothly. In the case with L-proline·HCl, 55% conversion was observed at 22 h (de = 85% exo, racemic), while with L-prolinamide·HCl, 70% conversion was observed at 20 h (de = 82% exo, ee = 1% *R*). Finally, we investigated the role of added water (10% v/v), although nearly identical results were obtained.[7] These

(6) (a) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2001**, *40*, 3726. (b) Riant, O.; Kagan, H. B. *Tetrahedron Lett.* **1989**, *30*, 7403. (c) Riant, O.; Kagan, H. B. *Tetrahedron* **1994**, *50*, 4543. (d) Koerner, M.; Rickborn, B. *J. Org. Chem.* **1990**, *55*, 2662. (e) Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 4243.

data suggest that the observation of optical activity in our "poisoned" experiments was not due to catalysis by L-proline or L-prolinamide adducts.

To confirm that there is preferential diastereomer formation, the ratio of formation constants, K_{fS}/K_{fR}, for the generation of (S_{Ru},*R*)- and (R_{Ru},*S*)-[*p*-cymeneRu-(BINPO)-***P****](SbF$_6$)$_n$ complexes (where n = 1, 2 and ***P**** = L-proline) was estimated (see eq 1).[9] This ratio would



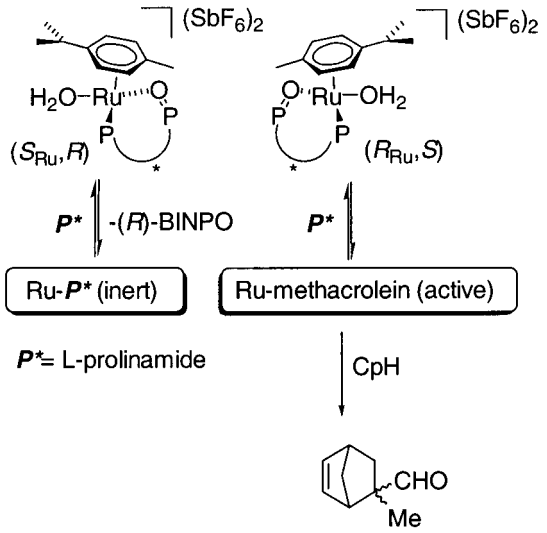
be expected to be similar for other achiral donors, such as methacrolein, being displaced by ***P****. The ratio of formation constants, K_{fS}/K_{fR} was ∼3.3, showing that [(S_{Ru},*R*)-*p*-cymeneRu(BINPO)-L-proline](SbF$_6$)$_n$ is formed preferentially at −24 °C. Thus, it can be inferred that, during a catalytic reaction, the S_{Ru},*R* catalyst was preferentially sequestered by L-proline, leaving the excess R_{Ru},*S* catalyst free to catalyze the reaction.

Some free proline remains when it is added to a stoichiometric amount of catalyst ($K_f \sim 1$). However, when stoichiometric amounts of L-prolinamide were combined (separately) with both Ru enantiomers, the ^{31}P NMR indicated that no free catalyst could be detected (suggesting $K_f \gg 1$) for both formation constants). These results are in agreement with those observed during "poisoned" catalytic trials in which the reactions were completely suppressed when the poison was used in *greater than or equal to* stoichiometric amounts with respect to the catalyst. A competition equilibrium experiment was carried out in which a mole ratio of 1:2 of L-prolinamide to (±)-**2** was investigated. The ^{31}P NMR showed a ratio of diastereomeric complexes that indicated a ratio of formation constants for (S_{Ru},*R*)-***P**** to (R_{Ru},*S*)-***P**** of ∼8. This translates to a ratio of (R_{Ru},*S*)-**2** to (S_{Ru},*R*)-**2** remaining of ∼3:1 with 0.004 M solutions.[10]

Although L-prolinamide was found to be a highly effective poison, inspection of the post-catalytic solutions indicated the presence of the free BINPO ligand (see Scheme 3). ^{1}H NMR inspection of the precipitated solid catalyst indicated that at least two Ru−prolinamide complexes were formed (although pure samples could not be obtained), thus bringing the identity of the true catalyst into question. Further, ^{31}P{^{1}H} NMR spectroscopy of the post-catalytic solutions indicated that L-prolinamide displaced BINPO for both catalyst enantiomers, as shown in Table 3.[9,11] In this case the R_{Ru},*S* enantiomer lost BINPO to the extent of 10%,while for the S_{Ru},*R* enantiomer the extent was 58% in 16 h. This suggests that the ee's for reactions with ±**1**/L-prolinamide may have been due to selective displacement (via dissociation of the *R*-BINPO ligand), leading to a greater population of the R_{Ru},*S* catalyst.

The possibility of a catalytically active Ru−prolinamide complex was ruled out following a series of competition experiments (see Scheme 4). We rationalized that if a given Ru−prolinamide catalyst was kinetically competent, then it would be expected to produce either an increasing effect on ee (both Ru−BINPO and Ru-prolinamide generate the same product enantiomer) or a diminishing effect on ee (the Ru complexes generate opposite enantiomers) in the presence of an enantiopure Ru−BINPO catalyst. However, if a Ru−prolinamide complex was inactive,[11] then it should not alter the product ee (although decreased

Scheme 3[a]



[a] Upon addition of L-prolinamide to a solution of ±**2**, the BINPO ligand in the S_{Ru},*R* enantiomer of the catalyst was preferentially displaced. As a result, the increased population of the R_{Ru},*S* enantiomer was responsible for the observed enantiomeric excess of the DA product.

Table 3. ^{31}P{^{1}H} NMR Chemical Shifts for Complexes of (R_{Ru},*S*)- and (S_{Ru},*R*) Complexes with Chiral Poisons (*P) To Generate Diastereomers**

entry	enantiopure cat.	***P****	temp (°C)	^{31}P{^{1}H} NMR chem shift (ppm)	ligand displacemt (%; 16 h)
1	R_{Ru},*S*	D-proline	−24	53.1; 48.5	5
2	R_{Ru},*S*	L-proline	−24	52.9; 48.5	5
3	R_{Ru},*S*	L-prolinamide	−24	53.3; 45.0	10
4	S_{Ru},*R*[a]	L-prolinamide	−24	52.9; 44.8	58

[a] Because D-prolinamide is not currently commercially available, the opposite enantiomer of the catalyst (S_{Ru},*R*) was synthesized and employed with L-prolinamide. This interaction is expected to be analogous to using D-prolinamide with the R_{Ru},*S* enantiomer.

(7) Ahrendt and MacMillan have reported that addition of water increased rates and enantioselectivities for similar reactions.[6e]

(8) This is substantiated by the lack of catalytic activity at −24 °C and the production of racemic material at +25 °C.

(9) (a) Determined by integration of the appropriate catalyst/proline resonances in addition to resonances at $\delta \sim 30.5$ (singlet), which corresponded to the dissociated (and subsequently oxidized) ligand.

(10) The ratio K_S/K_R = [(*S*)-**P***][*R*]/[*S*][(*R*)-**P***] involves both the concentrations of free and bound forms of the catalyst. With 50% poison added and $K \gg 1$, [(*S*)-**P***]/[(*R*)-**P***] = $(K_S/K_R)^{1/2}$ as found for prolinamide. A comparison of the extent of complexation of R_{Ru},*S* catalyst by L-proline (29% complexed:71% free) and by D-proline (51% (complexed): 49% (free)) in 0.008 M solutions of complex and proline illustrates the selectivity. Since accurate determination of concentrations of bound and free water was not practical, we have not evaluated K_{eq} but have determined ratios of formation constants in which all quantities can be measured with reasonable accuracy.

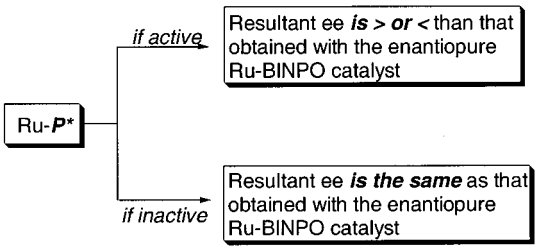
(11) cymeneRuCl(N−O$^-$) (where N−O$^-$ = carboxylate derived from L-proline) was synthesized (Ohta, T.; Nakahara, S.; Shigemura, Y.; Hattori, K.; Furukawa, I. *Chem. Lett.* **1998**, 491) in an attempt to determine the nature of the generated Ru−(***P****) complex. Upon addition of AgSbF$_6$ to this complex in CH$_2$Cl$_2$, AgCl was generated but the cationic ruthenium complex was not a catalyst for the DA reaction. (See also Hoffmuller, W.; Polborn, K.; Knizek, J.; Beck, W. *Z. Anorg. Allg. Chem.* **1997**, *623*, 1903.)

Table 4. Catalytic Results for the Diels−Alder Reaction of Methacrolein and Cyclopentadiene with Enantiopure Catalysts in the Presence of Chiral Poisons (P*$_S$)

entry	enantiopure cat.	*P** loading ((mol of *P**): (mol of ±-Ru))	temp (°C)	time (h)	conversn (%)	de[a] (exo:endo)	ee[b] (confign)
1	R_{Ru},S	none	−24	16	100	95	89 (*S*)
2	S_{Ru},R	none	−24	16	95	96	89 (*R*)
3	R_{Ru},S	D-proline (1.0:1.0)	−24	16	93	95	89 (*S*)
4	R_{Ru},S	L-proline (1.0:1.0)	−24	16	95	96	89 (*S*)
5	S_{Ru},R	L-prolinamide (0.5:1.0)	−24	16	81	95	90 (*R*)
6	R_{Ru},S	L-prolinamide (0.5:1.0)	−24	16	93	97	88 (*S*)

[a] The de was determined by ^{1}H NMR spectroscopy. [b] The ee was determined by ^{1}H NMR spectroscopy with (+)-Eu(hfc)$_3$ as a chiral shift reagent.

Scheme 4. Rationale Used in Competition Experiments between "Poisoned"/Enantiopure Ru−BINPO Catalysts vs Ru−Prolinamide Complexes[a]



[a] The results (Table 4) indicate that catalysis was not due to a Ru−prolinamide complex.

conversion would be expected, owing to lowered catalyst concentration by *P** deactivation).

As such, DA reactions were carried out with enantiopure catalysts in the presence of 0.5 molar equiv of L-prolinamide. As shown in Table 4, a decrease in ee was not observed for any of the cases. These data suggest that the generated Ru−prolinamide complexes were inactive during catalysis and, in particular, that L-prolinamide selectively displaced BINPO in the (S_{Ru},*R*)-Ru catalyst, thus leaving the (R_{Ru},*S*)-Ru enantiomer free to catalyze the reaction. These results support our previous hypothesis and are consistent with our observation that a solution of ±**2**/L-prolinamide produced an excess of the (*S*)-DA product (refer to Table 1).

This same methodology was then extended to examination of the enantiopure D- and L-proline poisons in combination with the enantiopure R_{Ru},*S* catalyst (these are diastereomeric interactions that are equivalent to using opposite Ru−BINPO enantiomers with enantiopure *P**). These experiments also proceeded without decreased product ee, as shown in Table 4.

Conclusions

The combination of ±**2** with various enantiopure chiral poisons has been found to produce optically active Diels−Alder products for the condensation of methacrolein with CpH. The most successful poisons, L-proline and L-prolinamide, are believed to preferentially deactivate the S_{Ru},*R* catalyst, thus allowing for predominant catalysis by the R_{Ru},*S* enantiomer for each reaction. These results have illustrated that chiral poisoning may be an effective alternative to the use of enantiopure auxiliaries that are difficult to synthesize, are unavailable, or are expensive. We are currently investigating an extension of this chiral poisoning strategy to involve related Ru−bisphosphine monoxide catalysts that have not been successfully resolved.

Experimental Section

All synthetic manipulations were carried out using standard Schlenk techniques under an inert atmosphere. Reagent grade dichloromethane was distilled over CaH_2 prior to use, and pentane was used without further purification. Methacrolein (95%, Aldrich), $AgSbF_6$ (Strem), and ±BINAP (Strem) were all used without further purification. ±**1**, ±-, (*R*)-, and (*S*)-BINPO, and (*p*-cymene$RuCl_2$)$_2$ were synthesized according to previously published procedures.[3a,12,13] Enantiomeric excesses were determined by addition of the chiral shift reagent europium tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorate] to an aliquot of the Diels−Alder product in $CDCl_3$. This gave rise to a splitting of the aldehyde resonance in which the most downfield resonance had the highest intensity. Integration and peak fitting was performed using NUTS (NMR Utility Transform Software for Windows 95/NT) and the Jandel PeakFit program Version 4 for Win32. ^{1}H NMR spectra were recorded on a Bruker 500 MHz or Bruker 400 MHz spectrometer, and chemical shifts are reported in ppm relative to residual solvent peaks (^{1}H). Optical rotations were measured on a Perkin-Elmer Model 341 polarimeter at 589 nm and 25.0 °C, using a 1 dm path length.

Protocol for Chiral Poisoning with ±1. A centrifuge tube was charged with ±**1** (32 mg, 0.02 mmol) and $AgSbF_6$ (7 mg, 0.02 mmol). To this was added CH_2Cl_2 (3 mL), and the tube was agitated in order to rinse the walls of the tube. Within 10 min, a precipitate developed (presumably AgCl) and the tube was centrifuged in order to pelletize the solid. The clear solution was removed by pipet and was added to a vial which had been previously charged with the desired chiral poison and a small stir bar. The solution was stirred at ambient temperature for 10 min, after which it was added to a separate vial which had been previously charged with methacrolein (15 mg, 0.21 mmol). This solution was cooled to −24 °C for 30 min followed by the addition of precooled CpH (0.17 g, 2.1 mmol) via syringe. The resultant mixture was stored at −24 °C for 16 h. After this time, an aliquot of the reaction mixture (~1 mL) was added to a flask of pentane (5 mL), which resulted in precipitation and recovery of the catalyst. This solution was filtered through Celite, and the filtrate was evaporated on a rotary evaporator to yield the product as a clear oil.

Acknowledgment. A.R.L. thanks Darlene D'Alliessi for providing entry 5 in Table 2 and entry 45 in the Supporting Information. We thank the National Science Foundation (Grant No. CHE0092222) for support of this research.

Supporting Information Available: A complete table of chiral poisoning results containing 50 entries. This material is available free of charge via the Internet at http://pubs.acs.org.

OM011052F

(12) Grushin, V. V. *J. Am. Chem. Soc.* **1999**, *121*, 5831.
(13) Bennett, M. A.; Huang, T.-N.; Maitlis, T. W.; Smith, A. K. *Inorg. Synth.* **1981**, *21*, 74.