J|A|C|S
COMMUNICATIONS

Asymmetric Catalysis of Hetero-Ene Reactions with Tridentate Schiff Base Chromium(III) Complexes

Rebecca T. Ruck and Eric N. Jacobsen*

Harvard University, Department of Chemistry and Chemical Biology, Cambridge, Massachusetts 02138

Received January 14, 2002

Reactions between weakly nucleophilic and electrophilic partners constitute interesting targets for asymmetric catalysis, particularly in the context of synthetically valuable carbon−carbon bond-forming processes. In this context, we discovered recently that chiral tridentate Schiff base chromium(III) complexes catalyze highly enantioselective and diastereoselective hetero-Diels−Alder (HDA) reactions between simple aldehydes and only mildly nucleophilic dienes.[1] Mechanistic studies performed on this reaction indicate that the role of the catalyst is simply that of Lewis acid activation of aldehydes through single-point binding.[2] This observation raises the possibility of a spectrum of other enantioselective reactions of weak nucleophiles with aldehydes catalyzed by chiral Cr^{III} complexes. In this contribution, we describe the first evidence of the generality of these catalysts, with the observation of highly selective ene reactions between alkoxy- and silyloxyalkenes and aromatic aldehydes.[3,4] The β-hydroxyenol ether products formed in these reactions are valuable chiral building blocks, useful as nucleophilic partners in subsequent reactions or as direct precursors to β-hydroxyketone and β-hydroxyester derivatives (Scheme 1).

Systematic optimization of the tridentate ligand framework and counterion of the (Schiff base)Cr(III) complex led to the identification of **1** as a highly enantioselective catalyst for the model ene reaction between 2-methoxypropene and 2-bromobenzaldehyde.[5] Catalyst **1** is prepared easily from commercially available components, by condensation of 3,5-di-*tert*-butylsalicylaldehyde with *cis*-1,2-aminoindanol, followed by reaction with $CrCl_2$.[6] The ene reaction was found to proceed with highest enantioselectivities and fastest rates in the presence of acetone or ethyl acetate as solvent and added barium oxide as desiccant.[7] Aging the catalyst for 5 h at room temperature with desiccant prior to addition of 2-methoxypropene and aldehyde at 4 °C led to a measurable improvement in ee (up to 8% increase in the case of reactions with benzaldehyde).

With the optimized conditions outlined above in hand, a variety of substituted benzaldehyde derivatives (**2a**−**r**) were examined in asymmetric ene reactions with 2-methoxypropene (Table 1). β-Hydroxyenol ether products **3a**−**r** were obtained in 75−97% isolated yield and 70−96% ee, with >85% ee obtained in the majority of cases. The scope of this reaction was found not to be limited to aromatic aldehyde derivatives, as *n*-hexanal underwent conversion to the corresponding enol ether in 84% ee and 54% yield. In all cases examined, crude product could be obtained in nearly quantitative yield by filtration of the reaction mixtures through a small pad of Celite. Material thus isolated was contaminated with catalyst, but could be used nonetheless in subsequent reactions without deleterious effect (vide infra). Separation of catalyst was accomplished by silica gel chromatography, leading to the product yields listed in the table.[8]

Scheme 1

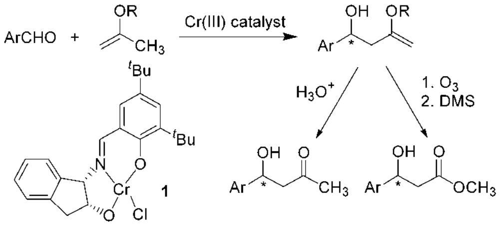
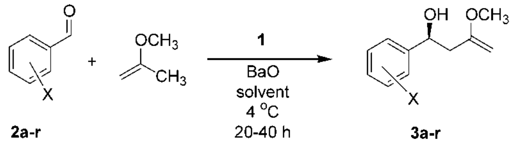


Table 1. Ene Reaction of 2-methoxypropene with Aldehydes **2a**−**r**



product	X	method[a]	ee (%)	yield (%)[e]	time (h)
3a	H	B	88[b]	82	40
3b	2-Br	A	96[b]	97	20
3c	3-Br	A	86[b]	94	36
3d	4-Br	B	87[b]	78	40
3e	2-CH_3	B	94[b]	41	40
3f	3-CH_3	B	90[b]	50	40
3g	4-CH_3	B	89[b]	26	40
3h	2-Cl	A	96[b]	98	20
3i	3-Cl	A	84[b]	97	36
3j	4-Cl	B	85[c]	78	40
3k	2-OCH_3	B	95[c]	75	40
3l	3-CN	A	86[d]	80	36
3m	4-CN	A	84[b]	92	40
3n	2-NO_2	A	96[b]	89	20
3o	3-NO_2	A	90[d]	85	36
3p	4-NO_2	A	70[d]	88	36
3q	2,4-Cl	A	92[b]	96	20
3r	2,6-Cl	A	86[b]	82	20

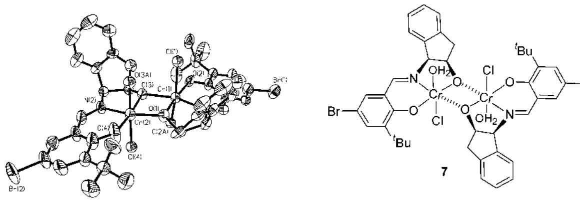
[a] Reactions were carried out with 1.0 mmol of aldehyde and 2.09 mmol (200 μL) 2-methoxypropene at 4 °C. Conditions A: 5 mol % catalyst, 5 h pre-stir with 90% BaO (650 mg) and acetone (400 μL) at rt. B: 7.5 mol % catalyst, 5 h pre-stir with 97% BaO (975 mg) and ethyl acetate (400 μL). [b] Ee determined by chiral GC on a Cyclodex-β column. [c] Ee determined by chiral HPLC after hydrolysis to the hydroxyketone on a (*R*,*R*)-Whelk-01 column. [d] Ee determined by chiral HPLC after ozonolysis to the ester on a Chiralcel OD or Chiralpak AS column. [e] Isolated yield after silica gel chromatography. [f] Absolute stereochemistry determined by hydrolysis of **3a** to the hydroxyketone and comparison of optical rotation to known literature value (ref 9).

The identity and position of the substitution on the benzaldehyde ring is observed to have a significant impact on both the rate and enantioselectivity of the reaction. Electron-deficient benzaldehydes reacted smoothly within 40 h to provide the desired β-hydroxyenol ether products. In contrast, electron-rich substrates such as *o*-, *m*-, and *p*-tolualdehyde (Table 1, entries 3e−g) underwent reaction more slowly, achieving 40−60% conversion during the same reaction time. Ortho-substituted benzaldehyde derivatives displayed par-

---

* To whom correspondence may be sent. E-mail: jacobsen@chemistry.harvard.edu.

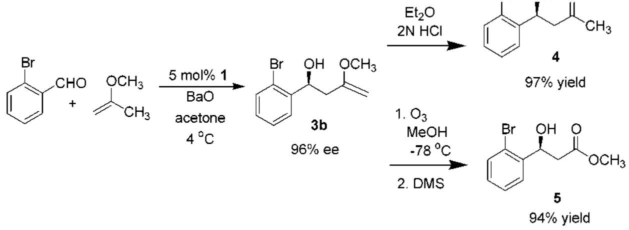
10.1021/ja025588j CCC: $22.00



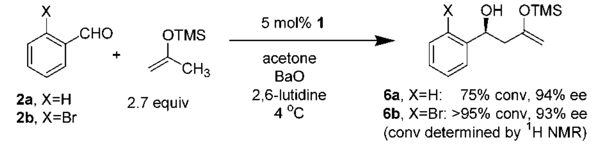
7

Figure 1. X-ray crystal structure of catalyst **7**.

Scheme 2



Scheme 3



ticularly good reactivity and enantioselectivity relative to other substituted derivatives (e.g., entry 3k, and comparison of entries 3b vs 3c or 3d and 3e vs 3f or 3 g). It is apparent that ortho substituents serve to help define a particularly reactive Cr^{III}•aldehyde complex wherein enantiofacial discrimination is enhanced, although the bases for these effects are as yet not known.

The enantioenriched β-hydroxyenol ether products formed in the ene reaction are easily transformed into aldol derivatives (Scheme 2). For example, the crude reaction mixture containing enol ether **3b** was diluted with ether and filtered to remove the BaO. Hydrolysis of **3b** was performed by treatment with 2 N HCl, affording β-hydroxyketone **4** in 97% isolated yield and with no measurable racemization.[10] Alternatively, the filtered reaction solution containing **3b** was diluted with methanol and subjected to ozonolysis at −78 °C. The resultant ozonide was quenched with dimethyl sulfide, and β-hydroxyester **5** was obtained in 94% isolated yield.[11]

The scope of the ene methodology was extended successfully to the use of silyl enol ethers.[12] Reaction of 2-trimethylsilyloxypropene with either benzaldehyde (**2a**) or 2-bromobenzaldehyde (**2b**) proceeded smoothly to generate β-hydroxysilylenol ethers **6a** and **6b**, respectively, with no observable silyl transfer (Scheme 3).[13] A small volume of 2,6-lutidine was added to each of these reactions to serve as an acid scavenger, and no pre-stir was necessary to achieve the optimal enantioselectivity. The β-hydroxysilylenol ether products of these reactions are interesting chiral building blocks for subsequent aldol-type reactions.

A crystal structure of catalyst **7** (Figure 1), prepared from 3-*tert*-butyl-5-bromosalicyladehyde and aminoindanol, provides valuable information to begin mechanistic analysis of the ene reaction.[14] The X-ray data reveal a dimeric structure bearing two ligands and two Cr^{III} centers bridged through the indane-bound oxygens. Each molecule of chromium also is bound to an axially positioned chloride ion and water molecule.[15] We propose that the role of the pre-stir is to remove one molecule of bound water from the catalyst dimer, thus providing an open coordination site for binding of aldehyde.[16]

We have shown that tridentate Schiff base chromium(III) complex **1** efficiently catalyzes the asymmetric ene reaction between aryl aldehydes and both 2-methoxypropene and 2-trimethylsilyloxypropene. Studies are currently underway to elucidate the mechanism and scope of this new reaction.

Acknowledgment. This work was supported by the NIH (GM-59316) and by a predoctoral fellowship from the National Science Foundation and an ACS Division of Organic Chemistry Graduate Fellowship sponsored by Albany Molecular Research, Inc. to R.T.R. The X-ray crystal structure was solved by Dr. Richard Staples (Harvard University).

Supporting Information Available: Complete experimental procedures, chiral chromatographic analyses of racemic and enantiomerically enriched products, and crystallographic data for **7** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Dosseter, A. G.; Jamison, T. F.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **1999**, *38*, 2398−2400.

(2) The HDA reaction exhibits a first-order kinetic dependence on catalyst and on diene, and saturation kinetics with respect to aldehyde. Ruck, R. T.; Jacobsen, E. N., *manuscript in preparation*.

(3) For examples of asymmetric catalytic ene reactions of glyoxylate derivatives, wherein two-point substrate binding is implicated, see: Mikami, K.; Terada, M. *Comprehensive Asymmetric Catalysis*, Vol. III.; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds. Springer-Verlag: Heidelberg, 1999; Chapter 32.

(4) Carreira has described asymmetric titanium-catalyzed ene reactions between 2-methoxypropene and propargylic aldehydes as well as certain aliphatic aldehydes. However, unsatisfactory results were described for benzaldehyde derivatives. Carreira, E. M.; Lee, W.; Singer, R. A. *J. Am. Chem. Soc.* **1995**, *117*, 3649−3650.

(5) Ligands derived from a series of chiral β-amino alcohols and various 3,5-disubstituted salicylaldehyde derivatives were evaluated. The 3-adamantyl substituted catalyst identified as optimal for the HDA reaction (ref 1) afforded 2−5% lower ee than **1** for a range of substrates. Catalysts bearing noncoordinating counterions such as SbF_6- afforded substantially lower enantioselectivity than the corresponding chloride complexes, in contrast to that which was observed in HDA reactions. Chiral (salen)CrCl complexes were also found to be catalytically active in the ene reaction; however poor (<30%) ee's were obtained.

(6) Complete experimental details are provided as Supporting Information.

(7) Reactions employing ethyl acetate as solvent afforded slightly lower enantioselectivities (1−4%) than those carried out in acetone. However, ethyl acetate proved preferable for electron-rich aldehydes, as these underwent side reactions with acetone. The role of BaO as a desiccant rather than as an acid scavenger is supported by the observation that added bases such as 2,6-lutidine bore no effect on the reaction outcome.

(8) Lower-than-quantitative isolated yields result from partial decomposition of β-hydroxyenol ether products upon exposure to silica gel. For certain reactions, (e.g. leading to **3e-3 g** via "Conditions B") the modest yields reflect incomplete conversion of the starting aldehyde.

(9) Rho, H. S. *Synth. Commun.* **1997**, *27*, 3887−3893.

(10) This ene reaction-hydrolysis sequence is equivalent to a direct aldol reaction between an aldehyde and acetone. For examples of acetone direct aldol reactions, see: (a) Trost, B. M.; Silcoff, E. R.; Ito, H. *Org. Lett.* **2001**, *3*, 2587−2590. (b) List, B.; Lerner, R. A.; Barbas, C. A., III *J. Am. Chem. Soc.* **2000**, *122*, 2395−2396. (c) Yoshikawa, N.; Yamada, Y. M. A.; Das, J.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1999**, *121*, 4168−4178.

(11) This ene reaction-ozonolysis sequence is equivalent to a traditional Mukaiyama aldol reaction between an aldehyde and the silylketene acetal of methyl acetate. For examples, see: Carreira, E. M. *Comprehensive Asymmetric Catalysis III*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds. Springer-Verlag: Heidelberg, 1999; Chapter 29.1.

(12) (a) Mikami, K. et al. *Tetrahedron Lett.* **1997**, *38*, 579−582. (b) Mikami, K.; Matsukawa, S. *J. Am. Chem. Soc.* **1993**, *115*, 7039−7040.

(13) Failure to observe silyl transfer with trimethylsilyloxy-substituted ene reactants is consistent with a concerted pathway for this reaction. Shoda, H.; Nakamura, T.; Tanino, K.; Kuwajima, I. *Tetrahedron Lett.* **1993**, *34*, 6281−6284.

(14) Cr^{III} complex **7** is also catalytically active in the ene reaction, but it displays slightly lower enantioselectivity than **1**.

(15) Full crystallographic data are provided as Supporting Information.

(16) The removal of water from the catalyst is an energetically difficult process as a result of the strong driving force for Cr^{III} to maintain a hexacoordinate ligand environment (Huheey, J. E.; Keiter, E. A.; Keiter, R. L. *Inorganic Chemistry*; Harper Collins College Publishers: New York, 1993.) The mildly Lewis basic solvents employed in this reaction presumably assist in the displacement of water from the catalyst. Use of less polar, noncoordinating solvents such as CH_2Cl_2 result in poorer reactivity and enantioselectivity in the ene reaction. Ene reactions with 2-trimethylsilyloxypropene do not require aging of catalyst with drying agent, the likely result of catalyst-bound water reacting rapidly with excess starting silyl enol ether.

JA025588J