Enantioselective Nucleophilic Catalysis with "Planar-Chiral" Heterocycles

GREGORY C. FU

Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139

Received November 2, 1999

ABSTRACT

Although Lewis bases (e.g., tertiary phosphines, tertiary amines, and pyridines) serve as nucleophilic catalysts for a wide array of reactions, there have been relatively few reports of *enantioselective* nucleophilic catalysts. In this Account, we describe the design and synthesis of a new family of chiral nucleophilic catalysts, specifically, planar-chiral heterocycles. These complexes provide good levels of enantiomeric excess in the addition of alcohols to ketenes, the rearrangement of *O*-acylated azlactones, and the kinetic resolution of secondary alcohols.

Introduction

Nucleophilic Catalysis. Just as both Brønsted acids and Brønsted bases are capable of catalyzing chemical reactions, so, too, are Lewis acids and Lewis bases. Of these four modes of catalysis, Lewis base (nucleophilic) catalysis is the least well-appreciated.

A diverse array of Lewis bases (e.g., tertiary phosphines, tertiary amines, pyridines, and imidazoles) have been shown to serve as nucleophilic catalysts. These compounds accelerate a broad spectrum of processes, including the addition of alcohols to ketenes,[1] the rearrangement of *O*-acylated enolates,[2] and the acylation of alcohols by anhydrides[3] (Figure 1).

The acylation of alcohols by anhydrides, catalyzed by 4-(dimethylamino)pyridine (DMAP),[4] is perhaps the most frequently encountered example of nucleophilic catalysis. The mechanism by which DMAP accelerates this process furnishes an instructive illustration of how nucleophiles can catalyze chemical transformations (Figure 2). In the presence of DMAP, acylations typically occur several orders of magnitude more rapidly than in its absence.

DMAP is likely the most useful of all nucleophilic catalysts, and in view of this we found it surprising that when we initiated our program in 1995 there were no reports of successful chiral catalysts based on a DMAP framework.[5] Indeed, the study of chiral nucleophilic (Lewis base) catalysis has been neglected in general, relative to the tremendous attention that has been focused on the complementary mode of catalysis, chiral Lewis acid catalysis.

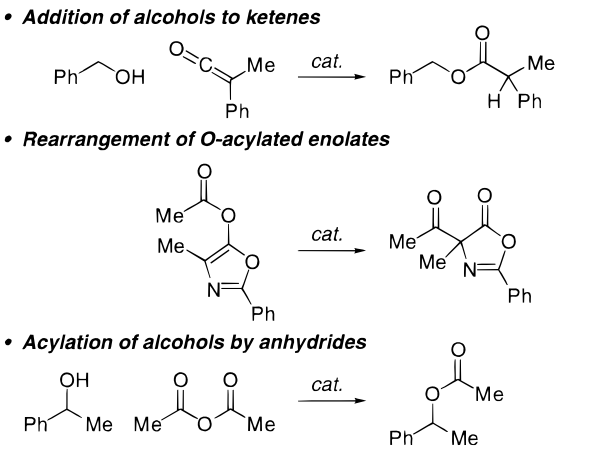


FIGURE 1. Examples of nucleophile-catalyzed reactions.

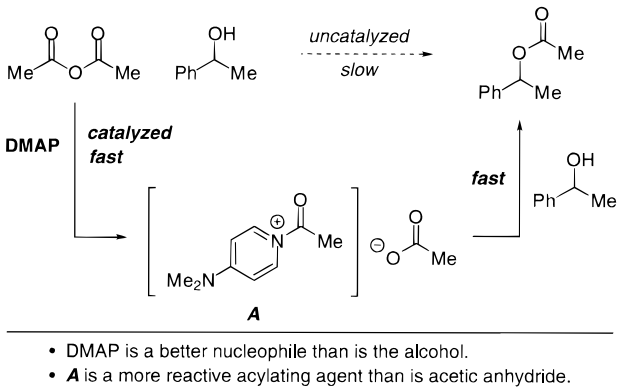


FIGURE 2. Mechanism for the DMAP-catalyzed acylation of alcohols.

Design of a Chiral Nucleophilic Catalyst. Because of its remarkable versatility, DMAP constitutes a particularly inviting starting point for the design of a chiral nucleophilic catalyst. Our approach evolved from recognition of a basic principle: a compound that possesses a mirror plane of symmetry is not chiral. Upon examining DMAP, one immediately identifies two mirror planes—a mirror plane in the plane of the pyridine ring and a perpendicular mirror plane that passes through the two nitrogens (Figure 3). We decided to develop a chiral derivative of DMAP by eliminating these two mirror planes in a stepwise fashion, namely, through π complexation of the pyridine ring to a metal (ML_n) and through incorporation of a substituent (R) in the 2-position of the pyridine ring (Figure 3). Chirality that results from π complexation to a metal is commonly referred to as "planar chirality".[6]

The design that is illustrated in Figure 3 (right-hand side) appears to provide a well-differentiated, "tunable" chiral environment in the vicinity of the nucleophilic nitrogen. Looking down the axis of the nitrogen lone pair, in terms of top-from-bottom differentiation, on top there

Gregory C. Fu received an S.B. degree from MIT in 1985, where he worked in the laboratory of Prof. Barry Sharpless. After earning a Ph.D. from Harvard in 1991 under the guidance of Prof. David Evans, he spent two years as a postdoctoral fellow with Prof. Robert Grubbs at Caltech. In 1993, he returned to MIT, where he is currently Professor of Chemistry. His research program has focused on the development of organotin chemistry, with a particular emphasis on transformations catalyzed by tin hydrides; exploration of the chemistry of borabenzenes; the development of palladium-catalyzed coupling reactions; and the application of "planar-chiral" heterocycles in asymmetric catalysis.

10.1021/ar990077w CCC: $19.00
Published on Web 03/18/2000

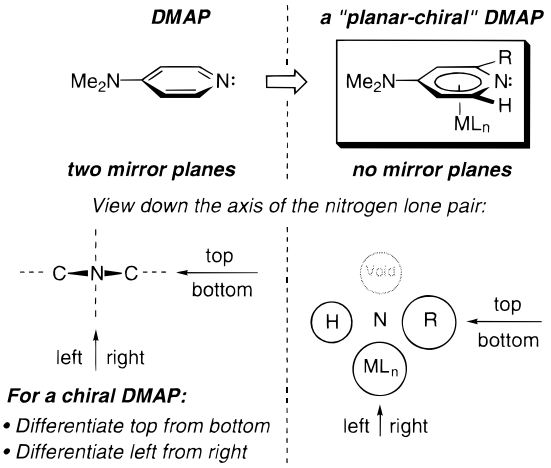


FIGURE 3. Design of a "planar-chiral" derivative of DMAP.

is nothing (the smallest "group" that is possible), and on bottom there is a metal fragment (ML_n), the steric demand of which can be modulated; a first-order analysis leads to the hypothesis that a large metal fragment might furnish a more effective chiral environment than a small one, since top-from-bottom differentiation decreases as the size of the metal fragment decreases. In terms of left-from-right differentiation, on the left there is a hydrogen (a rather small group), and on the right there is an alkyl group, the steric demand of which, again, can be modulated.

With this basic design in hand, we next needed to address the choice of the metal fragment, ML_n. Some of the attributes that we deemed to be important were the following:

(i) it should be electron-rich, thereby enhancing the nucleophilicity of the catalyst;

(ii) its steric environment should be "tunable"; and

(iii) it should lead to robust planar-chiral complexes, for maximum versatility and for ease of handling.

On the basis of the first two criteria, the iron cyclopentadienyl group (FeCp′; Cp′ is a cyclopentadienyl-derived ligand) appeared to be a suitable choice for ML_n.[7] However, η^6-complexation of a pyridine ring to FeCp′ furnishes a 19-electron metal complex (Figure 4). Due to our requirement that our catalyst be robust (vide supra), it seemed more prudent to focus on 18-electron complexes. We therefore decided to explore two separate modifications of our original design.

One approach that we chose to pursue involved broadening our investigation to include the chemistry of π-bound *five*-membered nitrogen heterocycles. Specifically, we decided to study planar-chiral azaferrocenes, which are 18-electron metal complexes (Figure 4).[8−10] Since they share the feature of a nucleophilic nitrogen that is part of a five-membered aromatic ring, these azaferrocenes might be considered to be chiral analogues of imidazole, a well-known nucleophilic catalyst.

In the second approach, we chose to continue to focus on the development of a planar-chiral derivative of DMAP itself. We anticipated that we could generate a stable 18-electron complex by fusing a five-membered ring to the pyridine framework and binding this second ring to FeCp′ (Figure 4).[11] In this ferrocene derivative, the pyridine ring is bound η^2, rather than η^6, to FeCp′. Although this modification has the obvious consequence of moving the metal fragment away from the nucleophilic nitrogen, our hope was that the steric demand of the FeCp′ group might still furnish sufficient top-from-bottom differentiation to provide an effective chiral environment.

With respect to prior work, when we initiated our research program in 1995, there had been one report of an attempt to prepare a planar-chiral heterocycle in enantiopure form.[12] There were no reports at that time of applications of planar-chiral heterocycles in asymmetric catalysis.

Synthesis of Planar-Chiral Heterocycle Complexes and Their Activity as Nucleophilic Catalysts[13]

Our initial efforts were directed at the synthesis of planar-chiral azaferrocene complexes. Unfortunately, we discovered that with FeCp as the metal fragment, the resulting azaferrocenes are not sufficiently stable to be practical as catalysts. We therefore turned our attention to FeCp* complexes, and we synthesized achiral azaferrocene **1** and planar-chiral azaferrocene **2** from $FeCl_2$ through the sequences illustrated in Figure 5. We subsequently also produced planar-chiral pyridine derivative **3** and planar-chiral DMAP derivative **4** through this general pathway (Figure 5).[13]

With these four π-bound heterocycles in hand, we were in a position to determine if such complexes can, indeed, serve as nucleophilic catalysts. As test reactions, we chose to focus on three distinct processes that are known to be accelerated by nucleophiles, namely, the addition of alcohols to ketenes,[1] the cyanosilylation of carbonyl

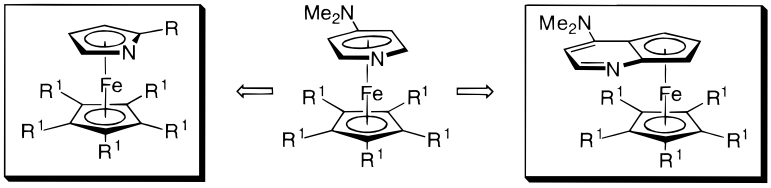


FIGURE 4. Eighteen-electron planar-chiral heterocycle complexes.

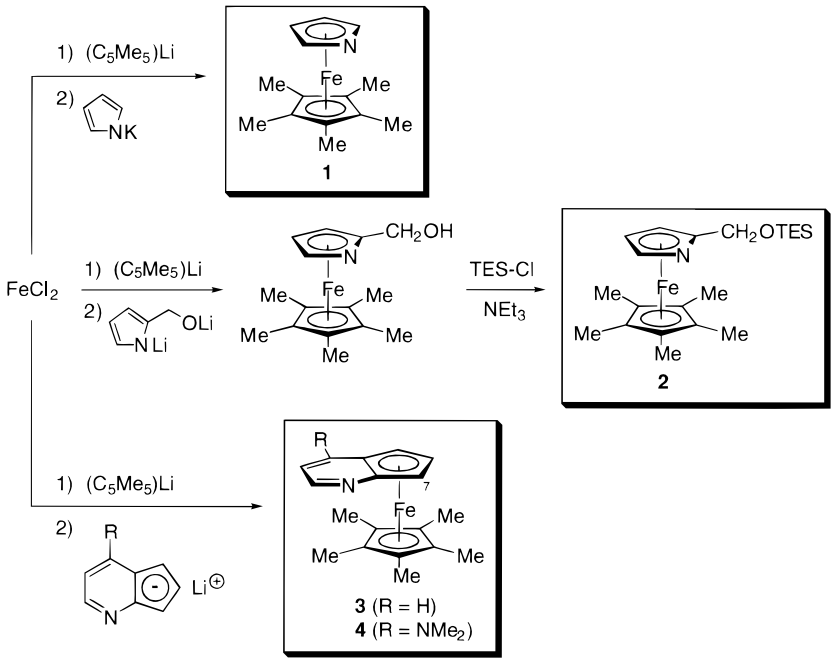
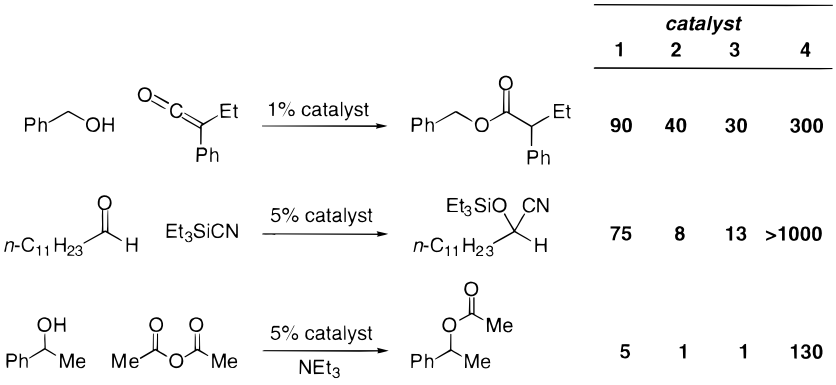


FIGURE 5. Synthesis of planar-chiral heterocycle complexes.



	catalyst 1	2	3	4
	90	40	30	300
	75	8	13	>1000
	5	1	1	130

FIGURE 6. Rates of reaction in the presence of π-bound heterocycle complexes **1**−**4**, relative to the background reaction.

groups,[14] and the acylation of alcohols by anhydrides[3] (Figure 6). On the basis of the data that we accumulated, the following conclusions can be drawn:

(i) π-bound heterocycles can function as nucleophilic catalysts;

(ii) steric effects are important in determining catalyst activity (**1** vs **2**);

(iii) electronic effects are important in determining catalyst activity (**3** vs **4**); and

(iv) planar-chiral DMAP derivative **4** is the most active catalyst among complexes **1**−**4**.

Asymmetric Catalysis

Having established that planar-chiral heterocycles can serve as nucleophilic catalysts, we were ready to pursue asymmetric catalysis. The routes to racemic **2** and **4** that are outlined in Figure 5 were adequate for our reactivity studies, but we now needed enantiopure complexes. Initially, we solved this problem through a strategy of separation of diastereomeric precursors (Figure 7).[15]

More recently, we have concluded that chiral HPLC is the method of choice for resolving our planar-chiral heterocycles, at least during the catalyst-development stage of the program, since the enantiomers of most of the complexes that we have synthesized are separable by this technique. Figure 8 provides an HPLC trace of racemic **4**, which illustrates the quality of separation that is possible.

Catalytic Enantioselective Addition of Alcohols to Ketenes.[16] As suggested by the data in Figure 6, azaferrocene **2** is generally a less active catalyst than DMAP derivative **4**. Because catalyst **2** furnishes substantial acceleration in the addition of alcohols to ketenes, we decided to explore asymmetric catalysis of this process. When we initiated our study, the only report of effective asymmetric catalysis of this reaction was the pioneering work of Pracejus, who investigated the addition of metha-

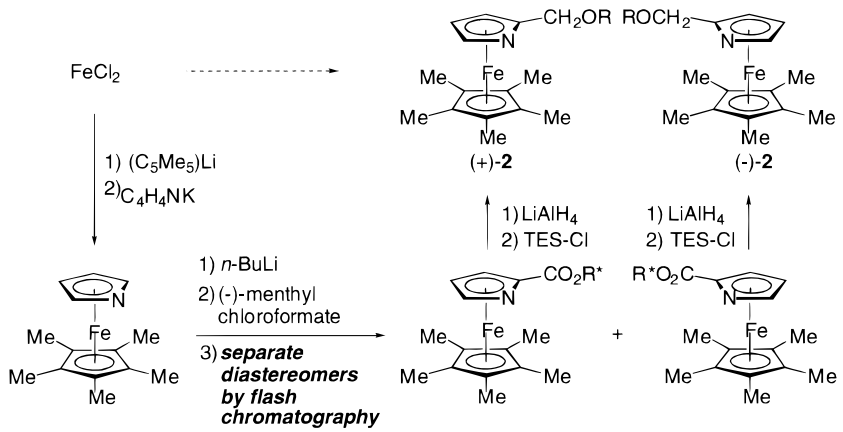


FIGURE 7. Preparation of enantiopure (+)-**2** and (−)-**2** via the separation of diastereomeric precursors.

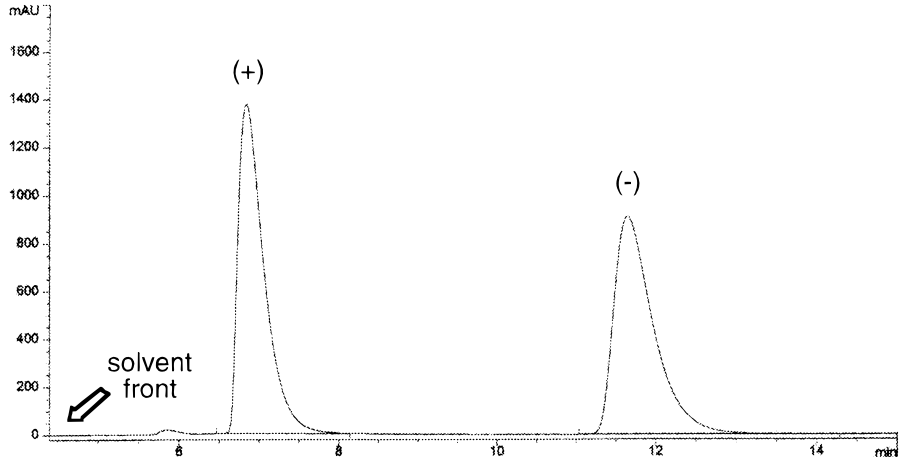
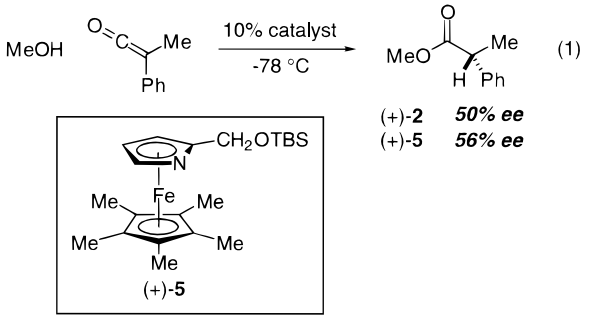


FIGURE 8. Chiral HPLC trace of racemic **4** (Chiralcel OD).

nol to two ketenes, phenylmethylketene (76% ee) and phenyl-α-*o*-trimethyleneketene (40% ee).[17]

In an initial study, we discovered that in the presence of (+)-**2**, MeOH adds to phenylmethylketene with moderate enantioselection (50% ee; eq 1). Use of the more sterically demanding azaferrocene **5** provides somewhat higher selectivity (56% ee).



A working hypothesis for the mechanism of this process is illustrated in Figure 9. It occurred to us that if step 2 is stereochemistry-determining, then the enantioselectivity might be affected by the addition of an alternate (to ROH) proton source. Through a survey of Brønsted acids, we found that the presence of a very bulky proton donor, 2,6-

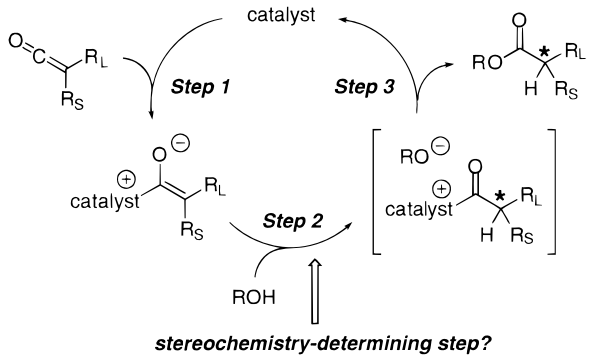
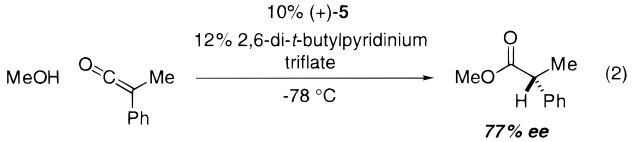


FIGURE 9. Possible pathway for the azaferrocene-catalyzed addition of an alcohol to a ketene.

di-*tert*-butylpyridinium triflate (12 mol %), appreciably enhances the enantioselection of this reaction (eq 2; cf. eq 1).



We have established that under these conditions we can effect the catalytic enantioselective addition of MeOH

Table 1. Enantioselective Addition of MeOH to Ketenes, Catalyzed by Planar-Chiral Azaferrocene 5

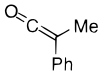
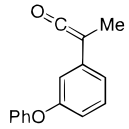
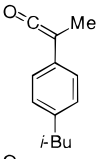
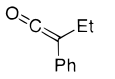
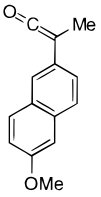
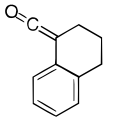
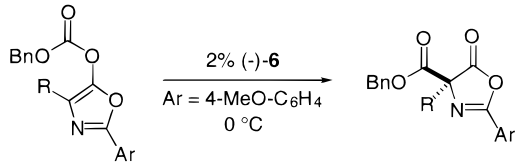
Entry	Substrate	% ee	% Yield	Entry	Substrate	% ee	% Yield
1		77	87	4		74	96
2		77	88	5		68	92
3		75	80	6		80	97

Table 2. Enantioselective Rearrangement of *O*-Acylated Azlactones, Catalyzed by Planar-Chiral PPY Derivative 6

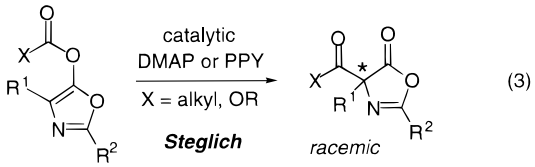


Entry	R	% ee	% Yield
1	Me	91	94
2	Et	90	93
3	CH_2Ph	90	93
4	allyl	91	93
5	CH_2CHMe_2	92	95
6	CH_2CH_2SMe	88	94

to an array of arylalkylketenes (Table 1). The electronic nature of the aromatic group appears to have little effect on stereoselectivity; thus, the methyl esters of ibuprofen, naproxen, and fenoprofen are produced with good enantiomeric excess (74−77% ee; entries 2−4). The steric demand of the alkyl group, on the other hand, seems to have a significant impact on stereoselectivity, with a larger alkyl group leading to lower ee (entry 1 vs entry 5). In the addition of MeOH to phenyl-α-*o*-trimethyleneketene, a substrate also explored by Pracejus, we obtain 80% ee with azaferrocene **5** (entry 6).

In preliminary mechanistic studies of the reaction of methanol with phenylmethylketene, we have determined that the ee of the product varies linearly with the ee of the catalyst, an observation consistent with the presence of one azaferrocene molecule in the stereochemistry-determining step of the process. In addition, we have measured a deuterium kinetic isotope effect of 3.2, which is consistent with proton transfer in the rate-determining step.

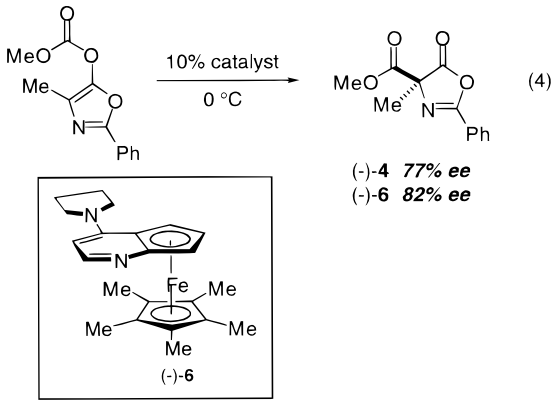
Catalytic Enantioselective Rearrangement of *O*-Acylated Azlactones.[18] Steglich and Höfle reported in 1970 that DMAP and 4-(pyrrolidino)pyridine (PPY) serve as catalysts for the rearrangement of *O*-acylated azlactones to their *C*-acylated isomers,[2] a process that furnishes both a new carbon−carbon bond and a new quaternary stereocenter[19] (eq 3). These rearrangement products can be



(3)

converted to α-alkylated α-amino acid derivatives,[20] an important family of chiral building blocks, through ring-opening of the azlactone by nucleophiles. There have been no reports of either diastereo- or enantioselective variants of the Steglich rearrangement reaction.

In early work, we established that planar-chiral DMAP derivative **4** functions as an effective asymmetric catalyst for this reaction (77% ee; eq 4). During the interval since our initial reactivity studies, we had developed a synthesis of planar-chiral PPY derivative **6**, and we were pleased to discover that this catalyst is even more selective than **4** (82% ee; eq 4).



(4)

Optimization studies revealed that the stereoselectivity is dependent on the 2-substituent (the nitrogen protecting group in the ring-opened product) and on the migrating acyl group. Among the substituents that we have examined thus far, the ones that have proved to be best are the 4-methoxyphenyl group and the benzyl carbonate, respectively. With this framework, planar-chiral PPY derivative **6** catalyzes the rearrangement of a variety of 4-substituted *O*-acylated azlactones with very good enantioselection and in excellent yield (88−92% ee; Table 2). Examples of uses of the rearrangement products are provided in Figure 10.[21]

A likely mechanism for this nucleophile-catalyzed rearrangement process is illustrated in Figure 11. Preliminary kinetic studies show that the rate of the rearrangement is zero-order in substrate and independent of concentration, which is consistent with the ion pair being the resting state of the system and step B being turnover-limiting; our ^{1}H NMR spectroscopic data corroborate this conclusion. To further probe the mechanism, we have conducted the double-labeling/crossover experiment outlined in Figure 12. Our observation of scrambling both in

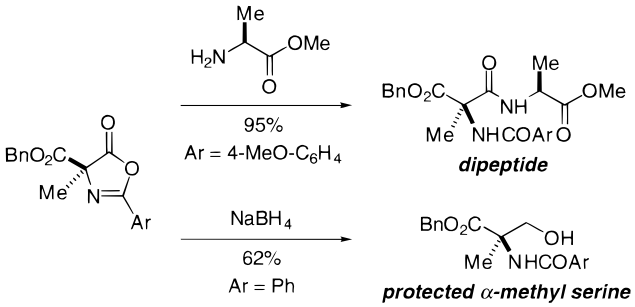


FIGURE 10. Examples of uses of the rearrangement products.

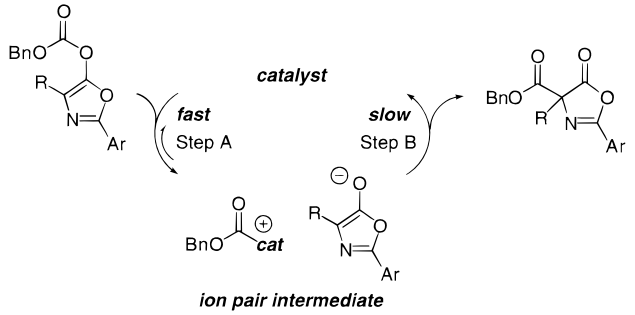


FIGURE 11. Likely mechanism for the catalytic rearrangement of *O*-acylated azlactones.

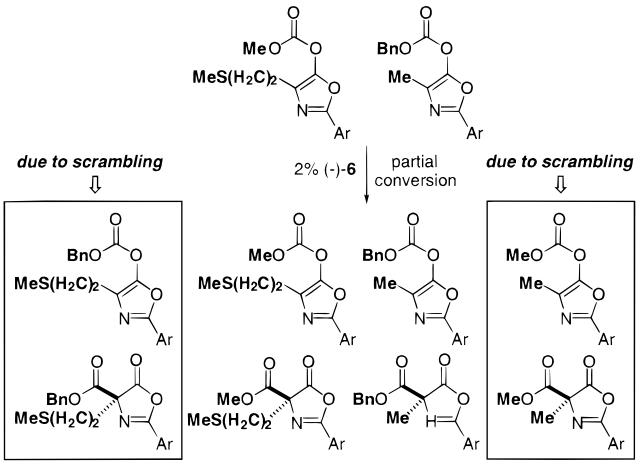


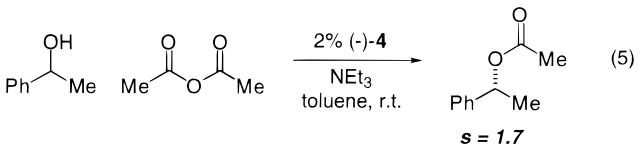
FIGURE 12. Double-labeling/crossover study of the rearrangement of *O*-acylated azlactones.

the rearrangement products and in the recovered *O*-acylated azlactones is consistent with exchange of ions between ion pairs and with step A being reversible. Finally, we have determined that step B is irreversible by demonstrating that the rearrangement products are configurationally stable under the reaction conditions.

Kinetic Resolution of Secondary Alcohols.[22] As noted earlier, the DMAP-catalyzed acylation of alcohols with anhydrides is perhaps the most familiar example of nucleophilic catalysis. For this process, an obvious potential application of a chiral derivative of DMAP is the kinetic resolution of a racemic mixture of secondary alcohols.

In a kinetic resolution, the key parameter is the selectivity factor, *s*, which measures the relative rate of reaction of the two enantiomers.[23] Under most circumstances, a selectivity factor greater than 10 is required in order for a kinetic resolution to be synthetically useful. When we initiated our studies in 1995, there were no examples of nonenzymatic acylation catalysts that furnish this level of selectivity, but in the interim, Vedejs et al.,[24] Oriyama et al.,[25] Kawabata et al.,[26] and Miller et al.[27] have described catalysts that achieve this objective, with varying levels of generality.

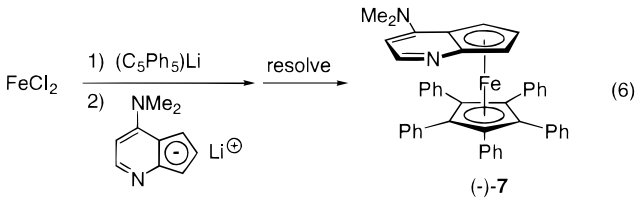
In our initial reactivity studies, we had established that planar-chiral DMAP derivative **4** is an efficient catalyst for the acylation of 1-phenylethanol with acetic anhydride (Figure 6). Unfortunately, our attempt to effect kinetic resolution with enantiopure **4** proved to be disappointing, providing a selectivity factor of only 1.7 (eq 5). The "glass-



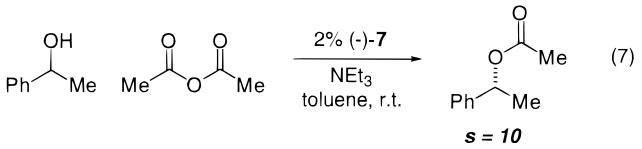
(5)

half-full" view of this result is that, because the selectivity factor is not 1.0, there must be some stereochemical communication between the catalyst and the alcohol in the stereochemistry-determining step of the acylation. Based on this optimistic assessment of the data, we decided to tune the chiral environment of our DMAP catalyst by exploring derivatives that have greater left-from-right and top-from-bottom differentiation (Figure 3).

Unfortunately, modification directed at increased left-from-right differentiation, through incorporation of a methyl substituent in the 7-position of catalyst **4**, led to a loss in activity. On the other hand, modification directed at increased top-from-bottom differentiation furnished the hoped-for enhancement in stereoselection. Thus, catalyst **7**, in which the Cp* group of **4** has been replaced with the bulkier C_5Ph_5 group (eq 6; C_5Ph_5H is available from Aldrich), effects the kinetic resolution of (±)-1-phenylethanol with a selectivity factor of 10 (eq 7; cf. eq 5).



(6)



(7)

Although the ferrocene framework is a common component of chiral catalysts,[28] to the best of our knowledge this study was the first to demonstrate that an increase in the steric demand of a remote cyclopentadienyl ring can lead to a significant improvement in enantioselectivity.[29]

Subsequent optimization experiments established that acylations catalyzed by **7** are solvent-dependent, with *tert*-amyl alcohol being the solvent of choice from the standpoints of both selectivity factor and reaction rate. For the

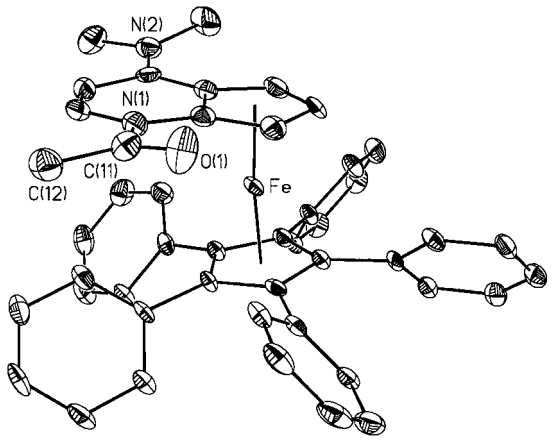
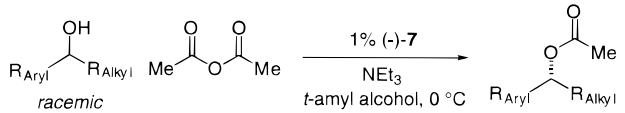
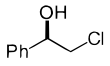
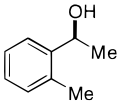
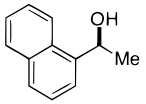
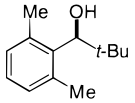


FIGURE 13. ORTEP illustration, with thermal ellipsoids drawn at the 35% probability level, of acetylated **7**. The SbF_6 counterion and two solvent molecules (THF) have been omitted for clarity.

Table 3. Kinetic Resolution of Arylalkylcarbinols Catalyzed by Planar-Chiral DMAP Derivative 7



Entry	Unreacted alcohol, major enantiomer	s	% ee (% conversion)
1	R = Me	*43*	99 (55)
2	Et	*59*	99 (54)
3	*i*-Pr	*87*	97 (52)
4	*t*-Bu	*95*	96 (51)
5		*32*	98 (56)
6		*71*	99 (53)
7		*65*	95 (52)
8		*>200*	99 (51)

kinetic resolution of (±)-1-phenylethanol in *tert*-amyl alcohol, we obtain a selectivity factor of 29 at room temperature and 43 at 0 °C (Table 3, entry 1).

As illustrated in Table 3, under these conditions a wide array of arylalkylcarbinols are resolved by catalyst **7** with excellent stereoselection. For phenylalkylcarbinols, the selectivity factor increases as the steric demand of the alkyl group increases (entries 1−4). These kinetic resolutions are not sensitive to small amounts of oxygen, moisture, or adventitious impurities—reactions run exposed to air with unpurified reagents provide rates and selectivities identical to those observed for reactions run under an inert atmosphere with purified reagents. Furthermore, the catalyst can be recovered quantitatively (>98%) at the end of the acylations. Others, including Harmata and Kahraman[30] and Stork,[31] have employed catalyst **7** to effect kinetic resolutions of arylalkylcarbinols.[32]

Treatment of **7** with 1 equiv of acetyl chloride leads to quantitative formation of the acylpyridinium salt. Although we were not able to obtain X-ray quality crystals with chloride as the counterion, we found that crystallization of the SbF_6 salt, produced through reaction of the chloride salt with $AgSbF_6$, was straightforward (Figure 13). To the best of our knowledge, this is the first structural characterization of the acylated form of a chiral, nonenzymatic acylation catalyst.

In the crystal, the NMe_2 group, the pyridine ring, and the acetyl group of the acylpyridinium ion lie essentially in a single plane, a conformation consistent with extended conjugation (Figure 13). The changes in bond lengths of the (dimethylamino)pyridine fragment that are observed upon acylation are consistent with a substantial contribution by resonance structure **B** (Figure 14). Further support for significant conjugation is provided by the increased rotational barrier about the Me_2N-C bond in the acetylated catalyst ($\Delta G^{\ddagger}$ >21 kcal/mol) as compared to that in the parent compound ($\Delta G^{\ddagger} \approx 10$ kcal/mol).

Of the two possible rotamers of the acetyl group (about the N(1)−C(11) bond; Figure 13), the one observed in the crystal structure is consistent with minimization of steric interactions with the fused five-membered ring (the oxygen of the acetyl is smaller than the methyl).[33] Finally, it is interesting to note that the two cyclopentadienyl rings deviate from coplanarity by about 8°, perhaps due to repulsion between the pyridine ring and the phenyl substituents of the C_5Ph_5 group; of course, sterically blocking one face of the pyridine ring is critical to the asymmetry of these planar-chiral catalysts.[34]

Summary

Asymmetric nucleophilic catalysis is a relatively unexplored area of research. In 1995, we decided to pursue the possibility that planar-chiral heterocycles might be

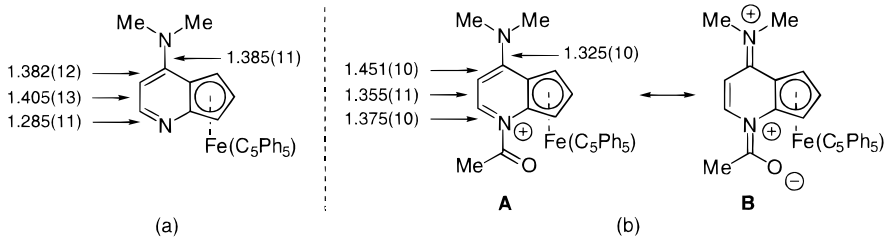


FIGURE 14. Bond distances (Å) for the (dimethylamino)pyridine fragment of (a) complex **7** and (b) acetylated complex **7**.

effective as asymmetric nucleophilic catalysts. During the past several years, we have designed, synthesized, and developed applications of two families of planar-chiral heterocycles. As described in this Account, these complexes have proved to be useful for enantioselective catalysis of the addition of alcohols to ketenes, the rearrangement of *O*-acylated azlactones, and the kinetic resolution of secondary alcohols. Current efforts are directed at developing additional applications of planar-chiral heterocycles as asymmetric nucleophilic catalysts, as well as exploring the utility of these intriguing molecules in a range of other, mechanistically distinct roles (e.g., as chiral Brønsted acid/base catalysts and as chiral ligands for transition metals).

I am very grateful to my co-workers for their experimental and their intellectual contributions to this program. Support is currently provided by the National Institutes of Health (National Institute of General Medical Sciences, R01-GM57034).

References

(1) Tidwell, T. T. *Ketenes*; Wiley: New York, 1995.

(2) Steglich, W.; Höfle, G. Hypernucleophilic Acylation Catalysts. II. Simple Preparation of Acyl-5-oxazolinones from 5-Acyloxyoxazoles. *Tetrahedron Lett.* **1970**, 4727−4730.

(3) (a) Pyridine: Verley, A.; Bölsing, F. Ueber Quantitative Esterbildung und Bestimmung von Alkoholen resp. Phenolen. *Ber. Dtsch. Chem. Ges.* **1901**, *34*, 3354-3358. (b) 4-Dimethylaminopyridine: *N,N*-Dimethyl-4-pyridinamine, A Very Effective Acylation Catalyst. Steglich, W.; Höfle, G. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 981. See also: Litvinenko, L. M.; Kirichenko, A. I. Basicity and Stereospecificity in Nucleophilic Catalysis by Tertiary Amines. *Dokl. Akad. Nauk SSSR Ser. Khim.* **1967**, *176*, 97−100.

(4) For reviews, see: (a) Scriven, E. F. V. 4-Dialkylaminopyridines: Super Acylation and Alkylation Catalysts. *Chem. Soc. Rev.* **1983**, *12*, 129−161. (b) Hassner, A.; Krepski, L. R.; Alexanian, V. Aminopyridines as Acylation Catalysts for Tertiary Alcohols. *Tetrahedron* **1978**, *34*, 2069-2076. (c) Höfle, G.; Steglich, W.; Vorbrüggen, H. 4-Dialkylaminopyridines as Highly Active Acylation Catalysts. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 569−583.

(5) For a chiral derivative of DMAP that has been used as a very effective stoichiometric chiral acylating reagent, see: Vedejs, E.; Chen, X. Kinetic Resolution of Secondary Alcohols. Enantioselective Acylation Mediated by a Chiral (Dimethylamino)pyridine Derivative. *J. Am. Chem. Soc.* **1996**, *118*, 1809−1810.

(6) (a) Schlögl, K. Planar Chiral Molecular Structures. *Top. Curr. Chem.* 1984, 125, 29−62. (b) Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*; Wiley Interscience: New York, 1994.

(7) For a study of the corresponding RuCp′ complexes, see: Garrett, C. E.; Lo, M. M.-C.; Fu, G. C. Nucleophilic Catalysis with π-Bound Nitrogen Heterocycles: Synthesis of the First Ruthenium Catalysts and Comparison of the Reactivity and the Enantioselectivity of Ruthenium and Iron Complexes. *J. Am. Chem. Soc.* **1998**, *120*, 7479−7483.

(8) For early work on azaferrocenes, see: (a) King, R. B.; Bisnette, M. B. Organometallic Chemistry of the Transition Metals. VIII. π-Cyclopentadienyl−π−pyrrolyliron and π-Cyclopentadienyl−π−indenyliron. *Inorg. Chem.* **1964**, *3*, 796−800. (b) Joshi, K. K.; Pauson, P. L.; Qazi, A. R.; Stubbs, W. H. Metal Complexes of Heterocycles. I. The Preparation of Pyrrolyl Manganese and Iron Derivatives. *J. Organomet. Chem.* **1964**, *1*, 471−475. The pK_a of azaferrocene (aqueous ethanol) is 4.5.

(9) For reviews that include overviews of azaferrocene chemistry, see: (a) Sadimenko, A. P.; Garnovskii, A. D.; Retta, N. Organometallic Complexes of Heterocycles. I. σ,π-Complexes of Five−membered Monoheterocycles. *Coord. Chem. Rev.* **1993**, *126*, 237−318. (b) Zakrzewski, J. Reactions of the η5−Pyrrolyl Ligand: A New Challenge in the Chemistry of Pyrroles. *Heterocycles* **1990**, *31*, 383−396. (c) Kuhn, N. Pyrroles and Related Systems as π-Ligands in Coordination Chemistry. *Bull. Soc. Chim. Belg.* **1990**, *99*, 707−715.

(10) (a) For a report of *N*-alkylation of azaferrocene with methyl iodide, see ref 8b. (b) For a report of *N*-acylation of 2,3,4,5-tetramethylazaferrocene with acetyl chloride, see: Kuhn, N.; Schulten, M.; Zauder, E.; Augart, N.; Boese, R. Heterocycles as Ligands. V. Synthesis and Characterization of 2,3,4,5-Tetramethyl-1-azaferrocene. *Chem. Ber.* **1989**, *122*, 1891−1896.

(11) We are aware of one previous report of a pyrindinyl-metal complex: Ji, L.-N.; Kershner, D. L.; Rerek, M. E.; Basolo, F. Syntheses and Carbon Monoxide Substitution Reactions of η^5-*N*-Heterocycle Manganese Tricarbonyls. *J. Organomet. Chem.* **1985**, *296*, 83−94.

(12) Optically active 2-methylazaferrocene has been prepared through classical resolution (the level of enantiomeric purity was not determined): Bauer, K.; Falk, H.; Schlögl, K. Optically Active 2-Methylazaferrocene. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 135.

(13) Ruble, J. C.; Fu, G. C. Chiral π-Complexes of Heterocycles with Transition Metals: A Versatile New Family of Nucleophilic Catalysts. *J. Org. Chem.* **1996**, *61*, 7230−7231.

(14) (a) Evans, D. A.; Wong, R. Y. Synthesis of Antibacterial *p*-Quinols from Marine Sponges. Synthetic Applications of "Masked" Quinones. *J. Org. Chem.* **1977**, *42*, 350−352. (b) Kobayashi, S.; Tsuchiya, Y.; Mukaiyama, T. A Facile Synthesis of Cyanohydrin Trimethylsilyl Ethers by the Addition Reaction of Trimethylsilyl Cyanide with Aldehydes Under Basic Condition. *Chem. Lett.* **1991**, 537−540.

(15) Ruble, J. C. Ph. D. thesis, Massachusetts Institute of Technology, 1999.

(16) Hodous, B. L.; Ruble, J. C.; Fu, G. C. Enantioselective Addition of Alcohols to Ketenes Catalyzed by a Planar-Chiral Azaferrocene: Catalytic Asymmetric Synthesis of Arylpropionic Acids. *J. Am. Chem. Soc.* **1999**, *121*, 2637−2638.

(17) (a) Pracejus, H. Asymmetrische Synthesen mit Ketenen. I. Alkaloidkatalysierte Asymmetrische Synthesen von α-Phenyl-propionsäureestern. *Justus Liebigs Ann. Chem.* **1960**, *634*, 9−22. (b) Pracejus, H. Asymmetrische Synthesen mit Ketenen. II. Stereospezifische Addition von α-Phenyl-äthylamin an Phenyl-methyl-keten. *Justus Liebigs Ann. Chem.* **1960**, *634*, 23−29. (c) Pracejus, H.; Tille, A. Über den Lösungsmitteleinfluss auf den Sterischen Ablauf Zweier Asymmetrischer Amidsynthesen. *Chem. Ber.* **1963**, *96*, 854−865. (d) Pracejus, H.; Mätje, H. Zusammenhänge Zwischen dem Räumlichen Bau Einiger Alkaloidartiger Katalysatoren und Ihren Stereospezifischen Wirkungen bei Asymmetrischen Estersynthesen. *J. Prakt. Chem.* **1964**, *24*, 195-205. (e) For polymer-bound variants of the Pracejus catalyst, see: Yamashita, T.; Yasueda, H.; Nakamura, N. Asymmetric Reactions. IV. Asymmetric, Catalytic Activity of Poly(2-quinuclidinylmethyl Acrylate). *Bull. Chem. Soc. Jpn.* **1979**, *52*, 2165−2166.

(18) Ruble, J. C.; Fu, G. C. Enantioselective Construction of Quaternary Stereocenters: Rearrangements of *O*-Acylated Azlactones Catalyzed by a Planar-Chiral Derivative of 4-(Pyrrolidino)pyridine. *J. Am. Chem. Soc.* **1998**, *120*, 11532−11533.

(19) For a recent review of asymmetric synthesis of quaternary stereocenters, see: Corey, E. J.; Guzman-Perez, A. The Catalytic Enantioselective Construction of Molecules with Quaternary Carbon Stereocenters. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 388−401. See also: Fuji, K. Asymmetric Creation of Quaternary Carbon Centers. *Chem. Rev.* **1993**, *93*, 2037−2066.

(20) For a brief overview of the synthesis and the significance of α-alkylated α-amino acids, see: Wirth, T. New Strategies to α-Alkylated α-Amino Acids. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 225−227 and references therein.

(21) For a discussion of the synthesis and the significance of α-methylserine, see: Moon, S.-H.; Ohfune, Y. Efficient Syntheses of the Four Enantiomers and Diastereomers of α-Methylthreonine and Both Enantiomers of α-Methylserine. *J. Am. Chem. Soc.* **1994**, *116*, 7405−7406.

(22) (a) Ruble, J. C.; Latham, H. A.; Fu, G. C. Effective Kinetic Resolution of Secondary Alcohols with a Planar-Chiral Analogue of DMAP. Use of the Fe(C_5Ph_5) Group in Asymmetric Catalysis. *J. Am. Chem. Soc.* **1997**, *119*, 1492−1493. (b) Ruble, J. C.; Tweddell, J.; Fu, G. C. Kinetic Resolution of Aryl Alkyl Carbinols Catalyzed by a Planar-Chiral Derivative of DMAP: A New Benchmark for Non-Enzymatic Acylation. *J. Org. Chem.* **1998**, *63*, 2794−2795. (c) Tao, B.; Ruble, J. C.; Hoic, D. A.; Fu, G. C. Non-Enzymatic Kinetic Resolution of Propargylic Alcohols by a Planar−Chiral DMAP Derivative; Crystallographic Characterization of the Acylated Catalyst. *J. Am. Chem. Soc.* **1999**, *121*, 5091−5092.

(23) For a review of kinetic resolution, see: Kagan, H. B.; Fiaud, J. C. Kinetic Resolution. *Top. Stereochem.* **1988**, *18*, 249−330.

(24) (a) Vedejs, E.; Daugulis, O.; Diver, S. T. Enantioselective Acylations Catalyzed by Chiral Phosphines. *J. Org. Chem.* **1996**, *61*, 430-431. (b) Vedejs, E.; Daugulis, O. 2-Aryl-4,4,8-trimethyl-2−phosphabicyclo-[3.3.0]octanes: Reactive Chiral Phosphine Catalysts for Enantioselective Acylation. *J. Am. Chem. Soc.* **1999**, *121*, 5813−5814.

(25) (a) Oriyama, T.; Hori, Y.; Imai, K.; Sasaki, R. Nonenzymic Enantioselective Acylation of Racemic Secondary Alcohols Catalyzed by a SnX_2-Chiral Diamine Complex. *Tetrahedron Lett.* **1996**, *37*, 8543−8546. (b) Sano, T.; Imai, K.; Ohashi, K.; Oriyama, T. Catalytic Asymmetric Acylation of Racemic Secondary Alcohols with Benzoyl Chloride in the Presence of a Chiral Diamine. *Chem. Lett.* **1999**, 265−266.
(26) Kawabata, T.; Nagato, M.; Takasu, K.; Fuji, K. Nonenzymic Kinetic Resolution of Racemic Alcohols through an "Induced Fit" Process. *J. Am. Chem. Soc.* **1997**, *119*, 3169−3170.
(27) (a) Miller, S. J.; Copeland, G. T.; Papaioannou, N.; Horstmann, T. E.; Ruel, E. M. Kinetic Resolution of Alcohols Catalyzed by Tripeptides Containing the *N*-Alkylimidazole Substructure. *J. Am. Chem. Soc.* **1998**, *110*, 1629-1630. (b) Copeland, G. T.; Jarvo, E. R.; Miller, S. J. Minimal Acylase-Like Peptides. Conformational Control of Absolute Stereospecificity. *J. Org. Chem.* **1998**, *63*, 6784−6785.
(28) (a) *Ferrocenes*; Togni, A., Hayashi, T., Eds.; VCH: New York, 1995. (b) Togni, A. Planar−chiral Ferrocenes: Synthetic Methods and Applications. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1475−1477.
(29) *Decreased* enantioselectivity upon substitution of an η^5-C_5H_5 group with a bulkier η^5-C_5Me_5 group has been reported: Abbenhuis, H. C. L.; Burckhardt, U.; Gramlich, V.; Martelletti, A.; Spencer, J.; Steiner, I.; Togni, A. Comparing Chiral Ferrocenyl and Ruthenocenyl Ligands: How Subtle Structural Changes Influence Their Performance in Asymmetric Catalysis. *Organometallics* **1996**, *15*, 1614−1621.
(30) Harmata, M.; Kahraman, M. Preparation of 2,8-Dihydroxy-5,6,-11,12-tetrahydro-5,11-epoxydibenzo[a,e]cyclooctene, An Analog of Kagan's Ether. *J. Org. Chem.* **1999**, *64*, 4949−4952.
(31) Stork, G. Progress and Problems in Stereocontrolled Synthesis. *Abstracts of Papers*, 218th National Meeting of the American Chemical Society, New Orleans, LA, Aug 22−26, 1999; American Chemical Society: Washington, DC, 1999: ORGN 1.
(32) Catalyst **7** can also kinetically resolve certain propargylic alcohols: ref 22c.
(33) NMR studies (presaturation difference NOE experiments in CD_2Cl_2) indicate that this rotamer is also the only detectable rotamer in solution.
(34) For catalyst **4**, which is the Cp* analogue of catalyst **7**, the corresponding angle is 2°.

AR990077W