Asymmetric Catalysis with "Planar-Chiral" Derivatives of 4-(Dimethylamino)pyridine

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ABSTRACT
Whereas chiral Lewis acid catalysis has been intensively investigated, chiral Lewis base (nucleophilic) catalysis has been comparatively neglected. We have developed "planar-chiral" derivatives of 4-(dimethylamino)pyridine (DMAP), a highly versatile nucleophilic catalyst, that are effective in a diverse array of processes, including the Staudinger synthesis of β-lactams, the acylation of silyl ketene acetals, and the kinetic resolution of amines.

Introduction

Nucleophiles have long been known to catalyze a wide array of transformations, but only recently has the development of enantioselective variants of these processes become the focus of significant interest.[1] Among nucleophilic catalysts, 4-(dimethylamino)pyridine (DMAP) is certainly one of the most versatile.[2] As described in a prior Account,[3] in 1995 we decided to explore the utility in asymmetric catalysis of "planar-chiral" derivatives of DMAP and related nitrogen heterocycles (e.g., **1**−**4**); at the time, there were no reports of effective chiral catalysts based on a DMAP framework. In that Account, we outlined the rationale for our catalyst design, and we described a few early applications of these complexes (Figure 1). In the interim, we have been pleased to discover that planar-chiral derivatives of DMAP catalyze a diverse array of asymmetric processes, and in this Account we provide an overview of these recent investigations.

Reactions of Ketenes

Couplings with Imines to Form β-Lactams.[4] We hypothesized that our catalytic enantioselective additions of alcohols to ketenes (Figure 1) proceed via chiral enolate **A** (Figure 2), which undergoes protonolysis to generate a new stereocenter.[5] We were curious as to whether we could intercept intermediate **A** with an electrophile more complex than a proton, specifically, an imine. This would transiently generate zwitterion **B** (Figure 3), which could cyclize to provide a β-lactam bearing up to two new stereocenters.

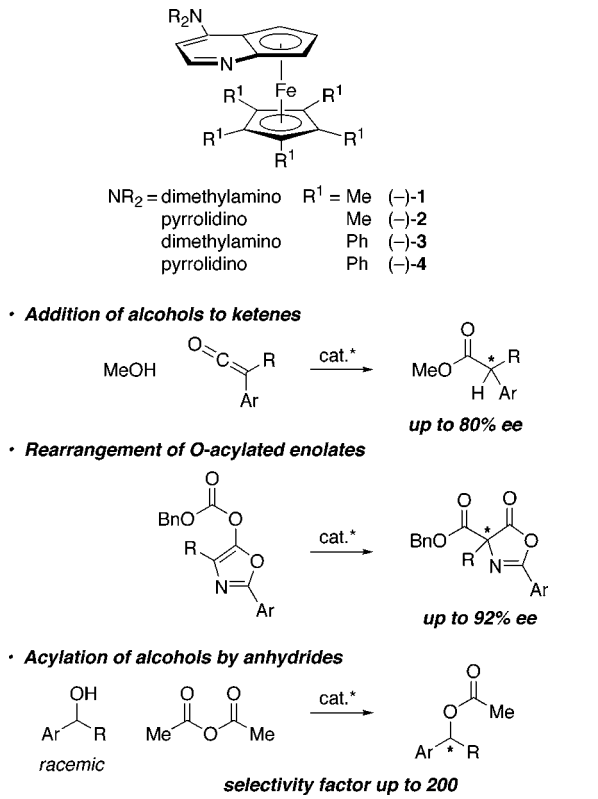


FIGURE 1. Early applications of planar-chiral heterocycles in asymmetric catalysis.

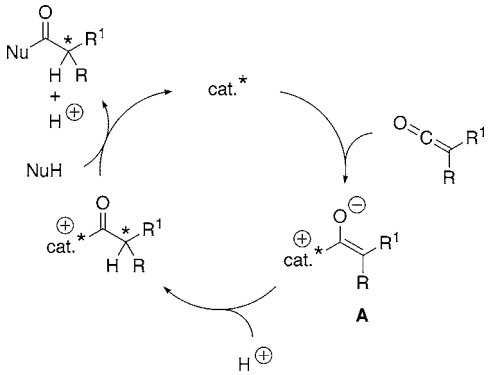
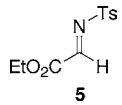


FIGURE 2. Possible pathway for catalytic enantioselective additions to ketenes.

To the best of our knowledge, at the time that we initiated our investigation there were no examples of such a nucleophile-catalyzed [2 + 2] cycloaddition to produce β-lactams. However, soon after we began our studies, Lectka reported that a quinine-derived catalyst can in fact achieve couplings of a variety of monosubstituted ketenes (and diphenyl ketene) with imine **5**, with excellent stereoselectivity.[6]



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Our own work focused on nucleophile-catalyzed Staudinger reactions of *di*substituted ketenes. We were

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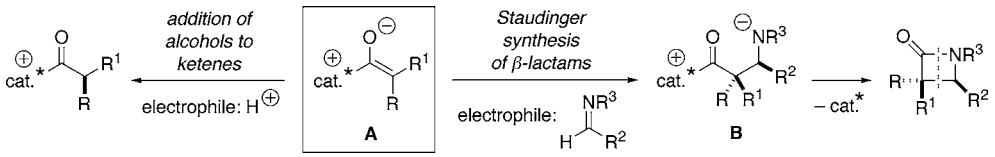
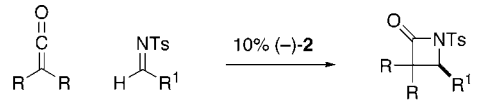


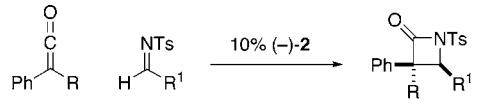
FIGURE 3. Nucleophile-catalyzed reactions of ketenes: Interception of chiral enolate **A** with electrophiles.

Table 1. Catalytic Asymmetric Staudinger Reactions of Symmetrical Ketenes



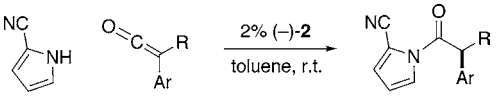
entry	R	R^1	ee (%)	yield (%)
1	$-(CH_2)_6-$	Ph	81	84
2	Et	2-furyl	92	93
3	Et		92	83
4	$-(CH_2)_6-$	cyclopropyl	94	89
5	$-(CH_2)_6-$	cyclohexyl	94	76

Table 2. Catalytic Asymmetric Staudinger Reactions of Unsymmetrical Ketenes



entry	R	R^1	dr	ee (%)	yield (%)
1	*i*-Bu	Ph	8:1	98	88
2	*i*-Bu	2-furyl	11:1	98	97
3	*i*-Bu		10:1	98	95
4	*i*-Bu	cyclopropyl	15:1	89	88
5	Et	2-furyl	9:1	95	97
6	Et	cyclopropyl	10:1	98	98

Table 3. Catalytic Asymmetric Additions of 2-Cyanopyrrole to Ketenes



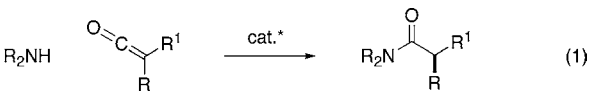
entry	Ar	R	ee (%)	yield (%)
1	Ph	Me	81	91
2	Ph	Et	90	93
3	Ph	*i*-Pr	95	96
4[a]	Ph	*t*-Bu	81	90
5	*o*-tol	Et	98	95
6	*o*-anisyl	Me	94	94
7	3-(*N*-methylindolyl)	Bn	86	80

[a] 5% catalyst was used.

pleased to discover that planar-chiral DMAP and PPY [PPY = 4-(pyrrolidino)pyridine] derivatives that bear an FeCp* group (complexes **1** and **2**, respectively) are efficient, enantioselective catalysts for a wide range of couplings. In the case of symmetrical disubstituted ketenes, we obtain good ee with a broad spectrum of imines (aryl-, heteroaryl-, alkenyl-, and alkyl-substituted; Table 1).

Catalyst **2** is also effective for Staudinger reactions of *un*symmetrical disubstituted ketenes with an array of imines (Table 2), thereby efficiently generating two contiguous stereocenters (one tertiary and one quaternary). These highly substituted β-lactams can be converted into other useful building blocks, such as γ-amino amides or γ-amino alcohols, via reaction with amines or $LiAlH_4$. Furthermore, catalyst **2**, which is commercially available, can be recovered in good yield (~80%).

Additions of Amines to Form Amides.[7] Having established that our planar-chiral heterocycles can catalyze enantioselective reactions of ketenes with alcohols and with imines, we turned our attention to couplings of ketenes with amines (eq 1). As far as we were aware, there had been no reports of asymmetric catalysis of this transformation.



(1)

Undoubtedly, this lack of success is due in part to the high nucleophilicity of many amines, which leads to a relatively rapid uncatalyzed addition reaction that, of course, is not enantioselective. We investigated a variety of amines, and we determined that commercially available 2-cyanopyrrole has sufficiently attenuated nucleophilicity that it does not directly add to a disubstitututed ketene at room temperature. However, in the presence of catalyst **2**, the desired *N*-acylpyrrole is produced, generally with very good ee (Table 3). The method tolerates hindered aryl, as well as heteroaryl, substituents on the ketene, as well as a wide range of alkyl groups (Me → *t*-Bu). The *N*-acylpyrroles can be converted in one step to an array of useful compounds (e.g., acids, esters, amides, aldehydes, and alcohols) with essentially no erosion in enantiomeric excess (≤2%; Figure 4).

Initially, we assumed that these catalytic asymmetric additions of 2-cyanopyrrole, like the reactions of ketenes with alcohols and with imines, proceed via enolate **A** (Figure 3). However, relative to the latter processes, the pyrrole additions displayed puzzling differences in stereoselectivity and in reactivity. As a consequence of these dichotomies, we embarked on a mechanistic investigation of the reaction of 2-cyanopyrrole with ketenes, and we made the following observations:

(1) Treatment of 2-cyanopyrrole with **2** leads to deprotonation of the pyrrole and formation of an ion pair; this ion pair, not **2** itself, is the resting state of the catalyst during the reaction.

(2) The rate of the reaction has a first-order dependence on ketene and on **2** and a zero-order dependence on 2-cyanopyrrole.

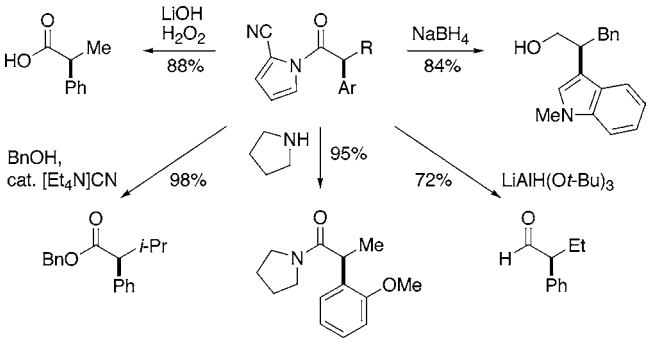


FIGURE 4. Transformations of *N*-acylpyrroles.

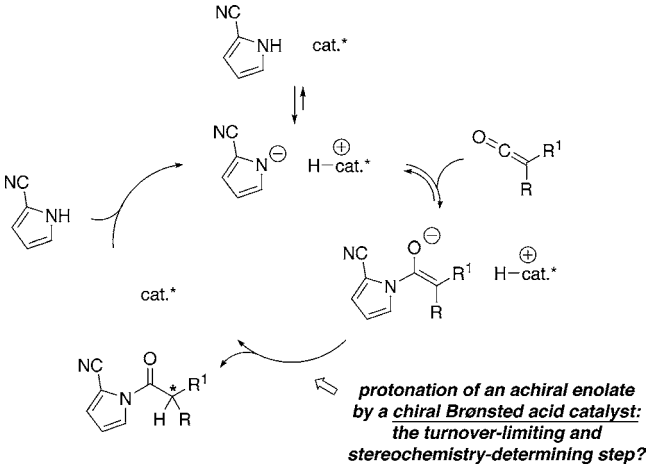


FIGURE 5. Proposed pathway for enantioselective additions of 2-cyanopyrrole to ketenes catalyzed by **2**.

(3) The rate of the reaction is approximately 5 times faster with 1-*H*-2-cyanopyrrole than with 1-*D*-2-cyanopyrrole.

(4) The ee of the product decreases as the concentration of the reaction mixture increases.

(5) The ee of the product varies linearly with the ee of **2**.[8]

On the basis of these data, we postulate that additions of pyrroles to ketenes that are catalyzed by **2** proceed through the pathway illustrated in Figure 5. According to this mechanism, the role of **2** is to serve, in protonated form, as a *chiral Brønsted acid catalyst*.[9] This discovery of a new, highly enantioselective mode of reactivity for planar-chiral heterocycles adds an exciting dimension to their utility in asymmetric catalysis.

C-Acylations to Form 1,3-Dicarbonyls

Intramolecular Processes.[10] In an early study, we showed that planar-chiral complexes **1** and **2** effectively catalyze the enantioselective rearrangement of O-acylated azlactones (Figure 1).[11] Because a diverse array of indole alkaloids and benzofuran-derived natural products bear quaternary stereocenters in the 3-position of the heterocycle, we decided to pursue the possibility of accessing such compounds via rearrangement processes. We were pleased to determine that complex **4** furnishes very good

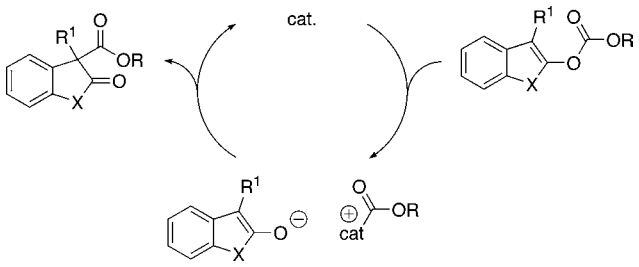
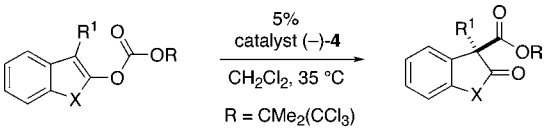


FIGURE 6. Proposed pathway for nucleophile-catalyzed rearrangements of O-acylated enolates.

Table 4. Catalytic Asymmetric Rearrangements of O-Acylated Oxindoles and Benzofuranones

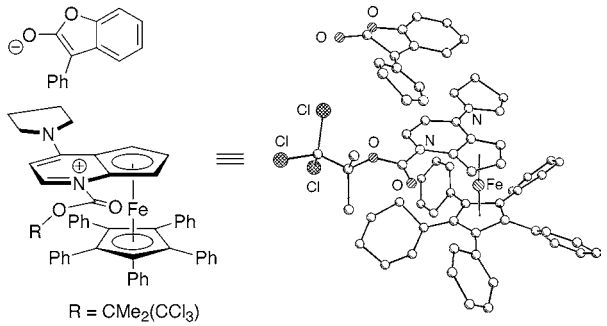


entry	R^1	X	ee (%)	yield (%)
1	Ph	NMe	99	91
2	2-thienyl	NMe	95	81
3[a]	benzyl	NMe	94	82
4[a]	Me	NMe	93	72
5	Ph	NBn	98	88
6	Ph	O	97	81
7	Bn	O	88	95

[a] 10% catalyst was used.

enantioselectivity for reactions of both O-acylated oxindoles and benzofuranones (Table 4).

Our data and the observations of Black and coworkers[12] are consistent with these nucleophile-catalyzed rearrangements proceeding through the pathway illustrated in Figure 6. Indeed, we have been able to obtain a low-resolution crystal structure of the ion pair (**6**) derived from the reaction of catalyst **4** with an O-acylated benzofuranone.



6

Intermolecular Processes.[13] Most recently, we have been pursuing *inter*molecular C-acylations to form 1,3-dicarbonyls. In the absence of a catalyst, silyl ketene acetals do not generally react with anhydrides. We anticipated that a nucleophilic catalyst might accelerate this process via the pathway outlined in Figure 7.

We have determined that complexes **1**−**4** can in fact catalyze the C-acylation of silyl ketene acetals by anhydrides. Although C_5Me_5-substituted **1** and **2** furnish only modest enantioselectivity, C_5Ph_5-bearing **4** (as well as **3**)

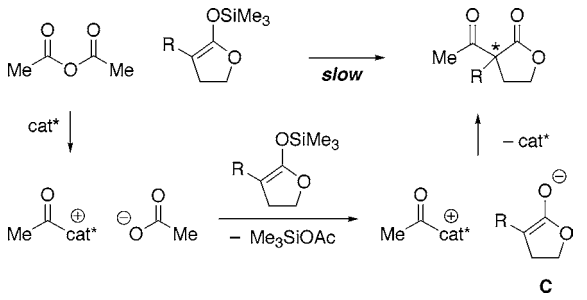
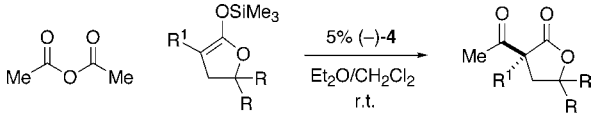


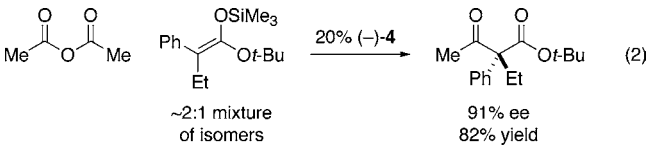
FIGURE 7. Possible pathway for nucleophile-catalyzed C-acylations of silyl ketene acetals.

Table 5. Catalytic Asymmetric Intermolecular Acylations of Silyl Ketene Acetals



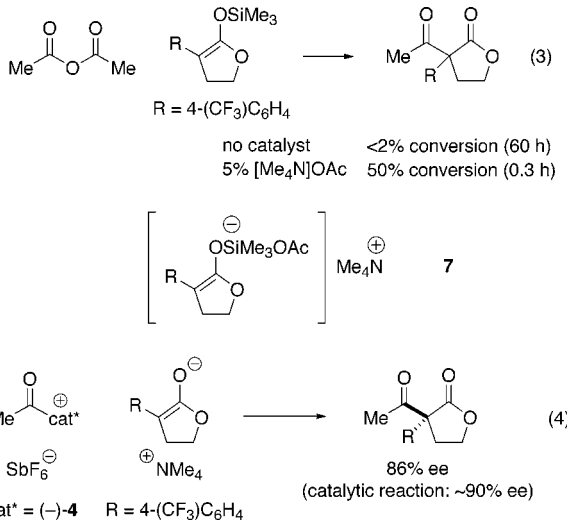
entry	R^1	R	ee (%)	yield (%)
1	Ph	Me	90	80
2	4-$(CF_3)C_6H_4$	H	90	84
3	1-naphthyl	Me	99	82
4	3-thienyl	H	80	73
5	3-(*N*-methylindolyl)	Me	94	92

provides good to excellent ee (Table 5). As illustrated in eq 2, we can also apply this method for catalytic asymmetric intermolecular C-acylation to reactions of *a*cyclic silyl ketene acetals; interestingly, we observe high ee even when we employ an isomeric mixture of substrates. Currently, the scope of these processes is limited to silyl ketene acetals that bear an α-aryl substituent.



(2)

Our mechanistic data are consistent with the pathway outlined in Figure 7. In the second step of the catalytic cycle, we believe that the acetate anion activates the silyl ketene acetal via desilylation to generate enolate **C**. To provide support for this hypothesis, we examined the acylation depicted in eq 3. In the absence of a catalyst, this silyl ketene acetal does not react with Ac_2O; on the other hand, the addition of 5% $[Me_4N]OAc$ leads to rapid C-acylation. These observations are readily explained by attack of the acetate at silicon to generate either hypervalent silicate **7** or enolate **C**. Other data suggest that the enolate, not the silicate, is the reactive species. For example, a change in the substituents on silicon [e.g., $SiMe_3 \rightarrow SiMe_2Ph \rightarrow Si(i\text{-}Pr)_3$] does not affect the ee of the catalytic asymmetric process, and independently generated acylpyridinium and enolate ions react to furnish the C-acylated product with enantioselectivity comparable to that obtained in the catalytic reaction (eq 4).[14] Thus, our studies support the hypothesis that the asymmetric acylations illustrated in Table 5 and eq 2 capitalize on *dual* activation of the electrophile and the nucleophile: the catalyst generates a more reactive (and chiral) acylating agent (acetic anhydride → acylpyridinium ion) as well as a more reactive nucleophile (silyl ketene acetal → enolate).



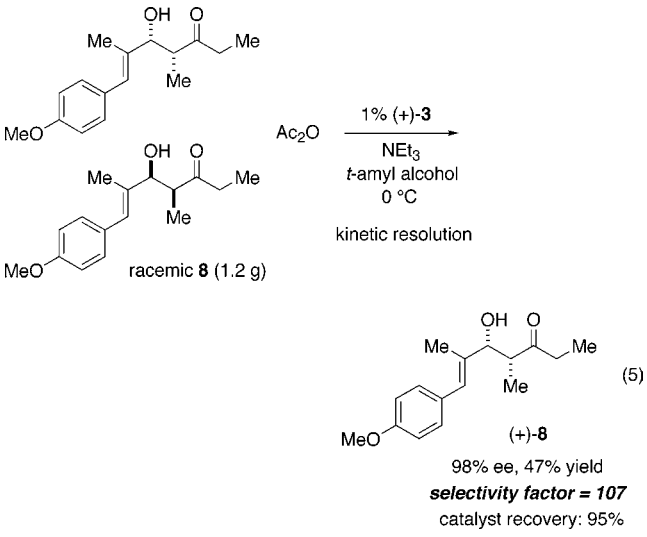
(3)

(4)

Kinetic Resolutions

Alcohols.[15] In early studies, we established that catalyst **3** can kinetically resolve a variety of arylalkylcarbinols,[16] as well as certain propargylic alcohols.[17] More recently, we have determined that **3** is also effective for a range of allylic alcohols (Table 6).

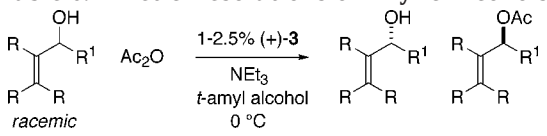
We have applied catalyst **3** to the kinetic resolution of an allylic alcohol (**8**) that has served as an intermediate in a synthesis of the potent anti-cancer agent epothilone A.[18] In their study, Sinha and Lerner employed a catalytic antibody to achieve the desired kinetic resolution (selectivity factor ~17); with catalyst **3**, the reaction also proceeds with excellent selectivity (eq 5).

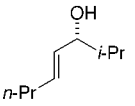
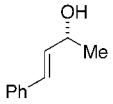
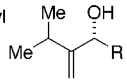
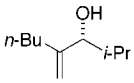
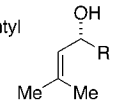
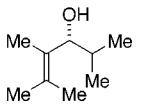


(5)

Amines.[19] Although we and others have recently reported progress in the development of nonenzymatic acylation catalysts for the kinetic resolution of alcohols,[20] corresponding advances for reactions of amines have not

Table 6. Kinetic Resolutions of Allylic Alcohols



entry	unreacted alcohol, major enantiomer	selectivity factor; ee of unreacted alcohol
1		**5.4** 92% ee @ 75% conv.
2		**64** 99% ee @ 54% conv.
3	R = *n*-pentyl 	**4.7** 90% ee @ 77% conv.
4	R = *i*-Pr	**10** 92% ee @ 63% conv.
5		**25** 94% ee @ 55% conv.
6	R = *n*-pentyl 	**12** 97% ee @ 66% conv.
7	R = *i*-Pr	**18** 97% ee @ 60% conv.
8		**29** 99% ee @ 59% conv.

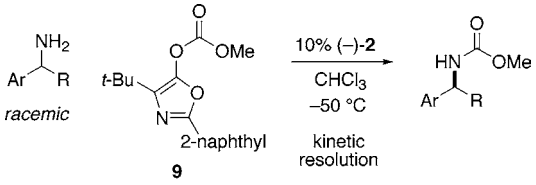
been described. Indeed, when we attempted to apply complexes **1**−**4** to the kinetic resolution of 1-phenylethylamine, for a variety of acylating agents (e.g., anhydrides, acid chlorides, and chloroformates), we observed essentially no selectivity. Control experiments indicated that the likely culprit is direct reaction of the amine with the acylating agent.

Fortunately, as a consequence of our studies of catalytic asymmetric rearrangement processes (Figure 1), we discovered an acylating agent (**9**) that reacts with our chiral DMAP derivatives much more rapidly than with primary amines. By employing this O-acylated azlactone, we can resolve an array of primary benzylic amines with useful selectivity (Table 7). An increase in the steric demand of the aryl or alkyl group leads to a moderate enhancement in the selectivity factor (entries 1−4), whereas electronic alterations have essentially no effect (entries 1, 5, and 6).

Conclusion

During the past several years, we have established that planar-chiral DMAP derivatives **1**−**4** serve as effective enantioselective catalysts for an array of processes (e.g., the synthesis of β-lactams, *N*-acylpyrroles, and α,α-disubstituted β-ketoesters). During the course of these studies, we have uncovered an unanticipated mode of catalysis for these complexes (in protonated form)—as chiral Brønsted acids. This discovery adds an interesting

Table 7. Kinetic Resolutions of Amines



entry	Ar	R	selectivity factor
1	Ph	Me	12
2	*o*-tol	Me	16
3	1-naphthyl	Me	27
4	Ph	Et	16
5	4-(OMe)C_6H_4	Me	11
6	4-(CF_3)C_6H_4	Me	13

new dimension to future investigations of applications of planar-chiral derivatives of DMAP in asymmetric catalysis.

For the studies described in this Account, I am deeply indebted to a highly talented group of co-workers. Support for this program is currently provided by the National Institutes of Health (National Institute of General Medical Sciences, R01-GM57034) and by Novartis.

References

(1) For some recent overviews, see (a) France, S.; Guerin, D. J.; Miller, S. J.; Lectka, T. Nucleophilic Chiral Amines as Catalysts in Asymmetric Synthesis. *Chem. Rev.* **2003**, *103*, 2985−3012. (b) Denmark, S. E.; Fu, J. Catalytic Enantioselective Allylation with Chiral Lewis Bases. *Chem. Commun.* **2003**, 167−170. (c) Vedejs, E.; Daugulis, O.; MacKay, J. A.; Rozners, E. Enantioselective Acyl Transfer Using Chiral Phosphine Catalysts. *Synlett* **2001**, 1499−1505.

(2) For a recent review, see Murugan, R.; Scriven, E. F. V. Applications of Dialkylaminopyridine (DMAP) Catalysts in Organic Synthesis. *Aldrichim. Acta* **2003**, *36*, 21−27.

(3) Fu, G. C. Enantioselective Nucleophilic Catalysis with "Planar-Chiral" Heterocycles. *Acc. Chem. Res.* **2000**, *33*, 412−420.

(4) Hodous, B. L.; Fu, G. C. Enantioselective Staudinger Synthesis of β-Lactams Catalyzed by a Planar-Chiral Nucleophile. *J. Am. Chem. Soc.* **2002**, *124*, 1578−1579.

(5) 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.

(6) Taggi, A. E.; Hafez, A. M.; Wack, H.; Young, B.; Drury, W. J., III; Lectka, T. Catalytic, Asymmetric Synthesis of β-Lactams. *J. Am. Chem. Soc.* **2000**, *122*, 7831−7832.

(7) Hodous, B. L.; Fu, G. C. Enantioselective Addition of Amines to Ketenes Catalyzed by a Planar-Chiral Derivative of PPY: Possible Intervention of Chiral Brønsted-Acid Catalysis. *J. Am. Chem. Soc.* **2002**, *124*, 10006−10007.

(8) For a review of nonlinear effects in asymmetric catalysis, see Kagan, H. B.; Luukas, T. O. Non-Linear Effects and Autocatalysis. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: New York, 1999; Chapt. 4.1.

(9) For example, see: Yanagisawa, A.; Yamamoto, H. Protonation of Enolates. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: New York, 1999; Chapt. 34.2.

(10) Hills, I. D.; Fu, G. C. Catalytic Enantioselective Synthesis of Oxindoles and Benzofuranones that Bear a Quaternary Stereocenter. *Angew. Chem., Int. Ed.* **2003**, *42*, 3921−3924.

(11) 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.

(12) (a) Black, T. H.; Arrivo, S. M.; Schumm, J. S.; Knobeloch, J. M. A Novel Oxygen-to-Carbon Ester Migration Catalyzed by 4-(Dimethylamino)pyridine in the Benzofuranone Ring System. *J. Chem. Soc., Chem. Commun.* **1986**, 1524−1525. (b) Black, T. H.; Arrivo, S. M.; Schumm, J. S.; Knobeloch, J. M. 4-(Dimethylamino)-pyridine as a Catalyst for Carbon Acylation. 2. Control of Carbon vs Oxygen Acylation in Benzofuranones. *J. Org. Chem.* **1987**, *52*, 5425−5430.

(13) Mermerian, A. H.; Fu, G. C. Catalytic Enantioselective Synthesis of Quaternary Stereocenters via Intermolecular C-Acylation of Silyl Ketene Acetals: Dual Activation of the Electrophile and the Nucleophile. *J. Am. Chem. Soc.* **2003**, *125*, 4050−4051.
(14) The silyl ketene acetal does not react with the acylpyridinium ion at room temperature.
(15) Bellemin-Laponnaz, S.; Tweddell, J.; Ruble, J. C.; Breitling, F. M.; Fu, G. C. The Kinetic Resolution of Allylic Alcohols by a Non-Enzymatic Acylation Catalyst; Application to Natural Product Synthesis. *Chem. Commun.* **2000**, 1009−1010.
(16) (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.
(17) 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.
(18) Sinha, S. C.; Barbas, C. F., III; Lerner, R. A. The Antibody Catalysis Route to the Total Synthesis of Epothilones. *Proc. Natl. Acad. Sci. U.S.A.* **1998**, *95*, 14603−14608.
(19) Arai, S.; Bellemin-Laponnaz, S.; Fu, G. C. Kinetic Resolution of Amines by a Non-Enzymatic Acylation Catalyst. *Angew. Chem., Int. Ed.* **2001**, *40*, 234−236.
(20) For an overview of the early breakthroughs, see Somfai, P. Non-Enzymatic Kinetic Resolution of Secondary Alcohols. In *Organic Synthesis Highlights IV*; Schmalz, H.-G., Ed.; Wiley−VCH: New York, 2000; pp 175−181.

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