Chiral Dialkylaminopyridine Catalysts in Asymmetric Synthesis

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Ryan Wurz obtained his bachelors of science degree in Chemistry in 1999 from the University of Victoria. In 2004, he received his Ph.D. degree at the Université de Montréal under the guidance of André B. Charette, focusing on the stereoselective synthesis of cyclopropane-α-amino acids. He then joined the group of Gregory C. Fu at Massachusetts Institute of Technology as a postdoctoral fellow. In 2006, he joined Small Molecule Drug Discovery at Amgen Inc. in Thousand Oaks, CA, where he currently resides.

1. Introduction

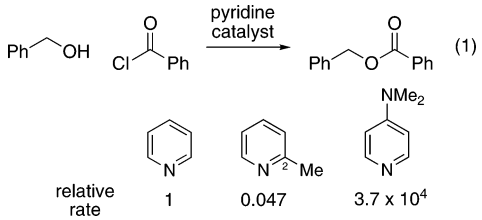
During the past decade, there has been a remarkable increase in interest in "organocatalytic" processes.[1] In part, this has been driven by the desire to develop environmentally friendly methods that obviate the need for potentially toxic metal-based catalysts. One particularly useful mode of reactivity of organocatalysts is as nucleophilic catalysts.

Among nucleophilic catalysts, 4-(dimethylamino)pyridine (DMAP) has proved to be particularly versatile. Its utility in organic chemistry was first described in two pioneering reports in the late 1960s. Thus, in 1967 Litvinenko and Kirichenko established that DMAP provides a 10^4-fold rate enhancement (versus pyridine) in the benzoylation of 3-chloroaniline.[2] Very soon thereafter, Steglich and Höfle described the use of DMAP as a catalyst for the acetylation of a sterically congested alcohol, 1-methylcyclohexanol.[3]

Since these initial studies, the breadth of applications of DMAP as a catalyst in organic synthesis has increased dramatically, and these developments have been the subject of a number of excellent reviews.[4,5] In view of the versatility of DMAP, a logical next step was to devise a chiral variant that would achieve asymmetric catalysis, and the first progress toward attaining this objective was reported by Vedejs in 1996.[6] Beginning with that seminal work, this review summarizes the exciting advances that have been described during the past decade in the design and development of chiral DMAP derivatives for use in enantioselective synthesis.[7]

2. Asymmetric Catalysis by Chiral DMAP Catalysts

Perhaps the most straightforward approach to the design of a chiral variant of DMAP would be to introduce the asymmetric environment by incorporating an appropriate substituent in the 2 position. However, as demonstrated in Litvinenko and Kirichenko's original study, the presence of even a small group (methyl) adjacent to the nitrogen markedly erodes the activity of pyridines as nucleophilic catalysts (eq 1).[8] In a nutshell, it is this sensitivity of pyridine-based nucleophilic catalysts to substitution at the 2 position that has provided the central challenge in the design of a chiral DMAP derivative: how can one best project an effective chiral environment without paying an unacceptable cost with respect to reactivity?



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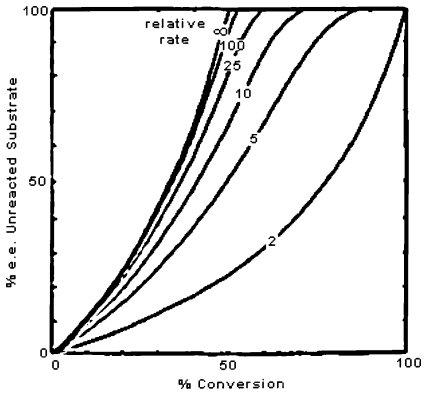


Figure 1. Dependence of enantiomeric excess on relative rate of reaction. [Reprinted with permission from ref 11. Copyright 1981 American Chemical Society.]

2.1. Kinetic Resolutions

2.1.1. Resolutions of Alcohols

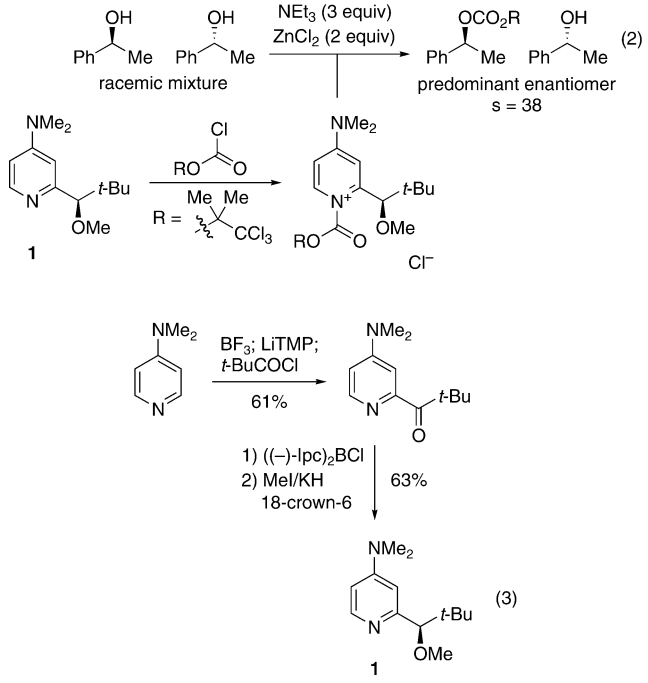
The kinetic resolution of racemic secondary alcohols has served as the primary testing ground for the design and development of chiral DMAP derivatives. Enantiopure secondary alcohols are important targets in organic chemistry (e.g., natural products, bioactive non-natural products, and chiral ligands), and a diverse array of approaches have been described for their synthesis.[9] Kinetic resolution via enzymatic acylation/deacylation is one widely used method, although this strategy can suffer from drawbacks such as low volumetric throughput, high cost, and poor generality.[10]

The selectivity factor (selectivity factor = s = [rate of fast-reacting enantiomer]/[rate of slow-reacting enantiomer]) provides a measure of the efficiency of a kinetic resolution.[9] For calibration, a kinetic resolution that proceeds with a selectivity factor greater than 10 furnishes unreacted starting material with >90% ee at 62% conversion. This value (s = 10) is often employed as the threshold for a synthetically useful kinetic resolution. Of course, even higher selectivity factors are desirable, e.g., a process with s > 50 affords starting material with >99% ee at 55% conversion (Figure 1).[11]

2.1.1.1. Catalysts with a Stereogenic Center. The first report of the development of an effective chiral DMAP derivative was provided by Vedejs and Chen in 1996.[6] In this pioneering study, a 2-substituted DMAP was employed as a *stoichiometric* chiral acylating agent for the kinetic resolution of racemic secondary alcohols (eq 2). In a typical experiment, enantiopure DMAP derivative **1** (for the synthesis of **1**, see eq 3[6]) was treated with 2,2,2-trichloro-1,1-dimethylethyl chloroformate, thereby generating an acylpyridinium salt (identified by ^{1}H NMR spectroscopy). This adduct did not react with typical secondary alcohols at room temperature. However, addition of a tertiary amine (Et_3N or 1,2,2,6,6-pentamethylpiperidine) and a Lewis acid (anhydrous $ZnCl_2$ or $MgBr_2$) led to the desired acyl transfer reaction.

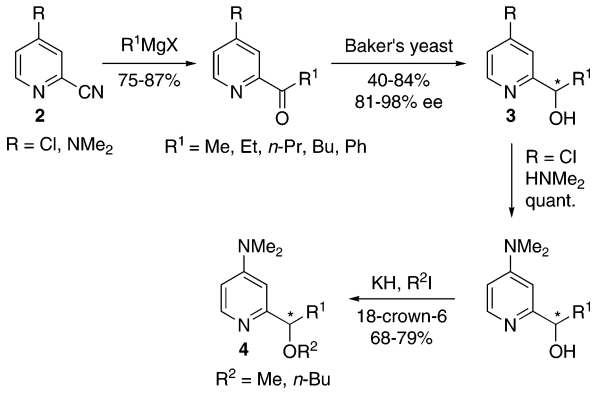
Kinetic resolutions of a broad range of arylalkylcarbinols (selectivity factors up to 53) as well as one allylic alcohol (s = 14) were described. Enantiopure DMAP derivative **1** that was recovered from the reactions after aqueous workup could be reused without any loss in selectivity.

Gotor reported an alternative synthesis of various analogues of DMAP derivative **1** (Scheme 1).[12] Thus, treatment of 2-cyanopyridine **2** with a Grignard reagent followed by Baker's yeast reduction of the resulting ketone furnished the corresponding secondary alcohols **3** in moderate to high ee's



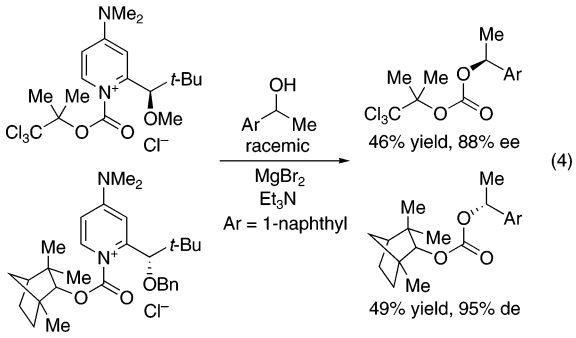
and yields. Displacement of the chloride with $HNMe_2$ and alkylation of the alcohols then furnished the chiral DMAP derivatives **4**.

Scheme 1



Under otherwise identical conditions to those reported by Vedejs and Chen, the catalysts prepared by Gotor were tested in the kinetic resolution of (±)-1-phenylethanol. Inferior levels of selectivity up to 10.1 (catalyst **4**, R^1 = Bu, R^2 = Me) were observed for the most selective analogue.

In 1997, Vedejs and Chen reported a resolution protocol wherein two stoichiometric chiral reagents were employed to achieve a parallel kinetic resolution (eq 4).[9a,13,14] Because the quasienantiomeric acylating agents prefer to acylate



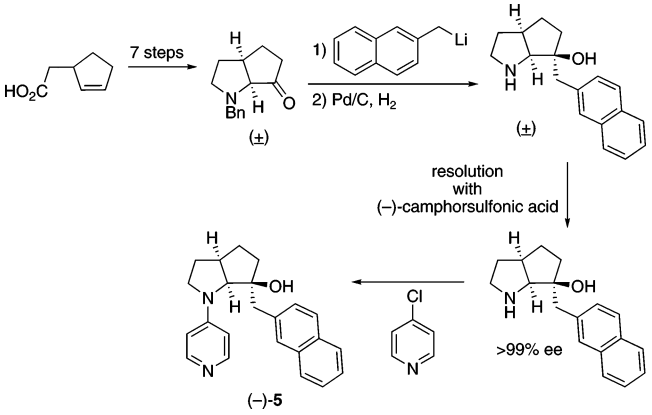


Figure 2. Synthesis of Fuji's chiral PPY derivative.

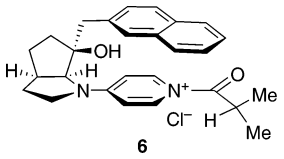


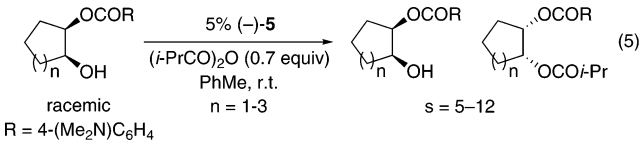
Figure 3. Proposed "closed-conformation" adopted by Fuji's catalyst.

different enantiomers of 1-phenylethanol, the racemic alcohol is resolved in very good yield and ee via separable carbonate derivatives.

Unfortunately, Vedejs was unable to employ any of his 2-substituted DMAP derivatives as chiral *catalysts*, presumably due to the steric demand of the substituent ortho to the pyridine nitrogen. Cognizant of the difficulty in retaining activity in the case of 2-substituted DMAPs, Fuji pursued an alternative approach to developing an asymmetric catalyst.[15] Specifically, he chose to synthesize a chiral PPY derivative (**5**; PPY = 4-pyrrolidinopyridine) in which the stereogenic centers are part of the 4-dialkylamino group (Figure 2).

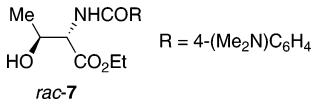
At first glance it may not be apparent that the asymmetric environment of the 4 substituent will be effectively conveyed to the vicinity of the nucleophilic nitrogen. On the basis of NOE studies Fuji proposed that, whereas pyridine **5** resides in an open (non-π-stacked) conformation, upon acylation the catalyst adopts a "closed-conformation" in which the naphthyl group and the pyridine ring are π stacked (**6**; Figure 3). This preferred conformation has the potential to furnish an effective chiral environment for asymmetric catalysis.

Fuji reported that catalyst **5** can kinetically resolve certain secondary alcohols, specifically, mono-acylated 1,2-diols (eq 5). He found that the choice of the acyl protecting group has a significant impact on the efficiency of the resolution. For example, in the case of benzoates, a more electron-rich aromatic ring leads to a higher selectivity factor. Fuji concluded that this trend supports the hypothesis that the catalyst adopts the "closed-conformation" (**6**) upon reaction with the acylating agent (isobutyric anhydride) and that $\pi-\pi$ interactions are important for selectivity. Interestingly, a pivaloate-protected 1,2-diol could also be kinetically resolved by catalyst **5** with good selectivity ($s = 8$).

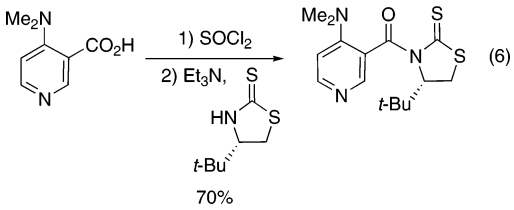


Kawabata and Fuji later demonstrated that catalyst **5** can also achieve kinetic resolutions of cyclic *cis*-1,2-aminoalcohols.[16] As observed for 1,2-diols, protection with the 4-(dimethylamino)benzoate group leads to the highest selectivity factors (Figure 4; 5% (+)-**5**, 0.7 equiv of $((i\text{-Pr})CO)_2O$, 1 equiv of collidine, rt).

Catalyst **5** is generally not effective for kinetic resolutions of acyclic 1,2-aminoalcohols, although Kawabata and Fuji determined that a particular *anti*-aminoalcohol (**7**) can be resolved with promising selectivity ($s = 7$). Under the same conditions, acylation of the syn diastereomer proceeds with no selectivity ($s = 1$).[16]



In 2005, Yamada described the design and utility of a family of chiral DMAP derivatives that are believed to operate by a "conformation-switch" mechanism related to that proposed by Fuji (**6**).[17] Specifically, Yamada synthesized compounds that bear pendant thiazolidine-2-thiones and related heterocycles from 4-aminonicotinic acid (eq 6).[18,19] This design was based on Yamada's 2002 study in which he showed via X-ray crystallography that upon *N*-alkylation a 3-substituted pyridine undergoes a conformational change that allows a pendant aromatic group to stabilize the pyridinium ion via a π-stacking interaction.[20]



Yamada hypothesized that upon acylation of a chiral DMAP derivative an attractive interaction between the thiocarbonyl and the pyridinium subunit[21] would bring the asymmetric environment of the 3-substituent close to the acyl group, thereby allowing effective kinetic resolution.[22] Indeed, Yamada was able to establish that the illustrated chiral DMAP derivative can achieve resolutions of a range of secondary alcohols with interesting levels of selectivity

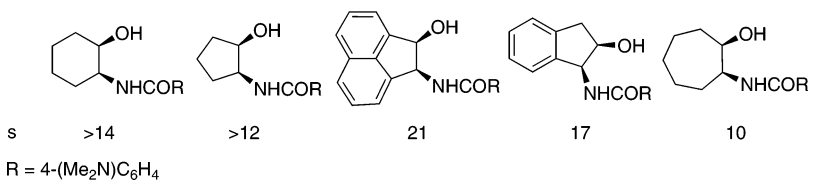


Figure 4. Kinetic resolutions of racemic 1,2-aminoalcohols by the Fuji/Kawabata catalyst ((+)-**5**).

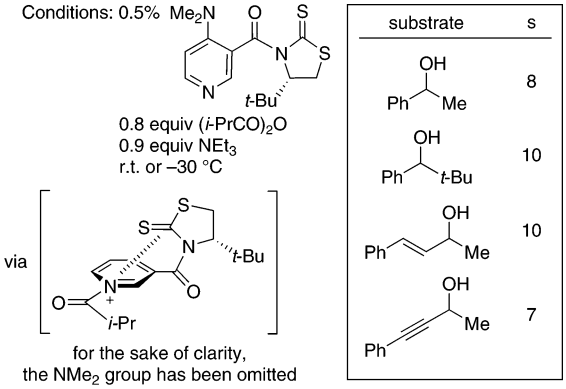


Figure 5. Yamada's design of a chiral derivative of DMAP: application to the kinetic resolution of secondary alcohols.

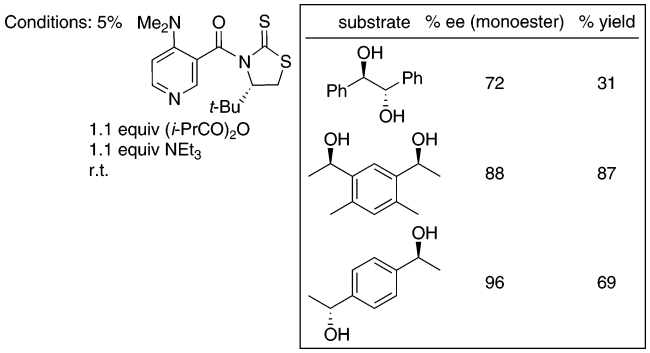


Figure 6. Yamada's chiral DMAP derivative: application to the desymmetrization of *meso*-diols.

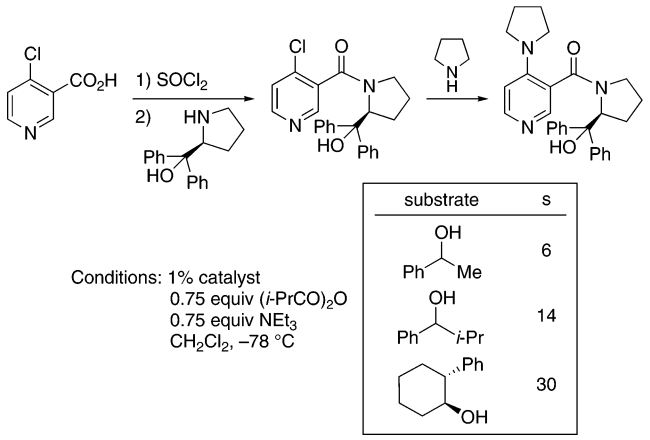


Figure 7. Connon's chiral PPY derivative: application to the kinetic resolution of secondary alcohols.

(Figure 5).[17] The feasibility of these stacking interactions has been further explored by Zipse in a recent computational study.[23]

In a follow up study, Yamada applied this catalyst to the desymmetrization of various *meso*-diols (Figure 6).[19] The resulting monoesters could be isolated in moderate to high ee's and yields.

In 2005, also building upon the 2002 Yamada study, Connon described the synthesis and utility of a 3-substituted chiral PPY derivative with a pendant aromatic group (Figure 7).[24] The selectivity factors were generally moderate for arylalkylcarbinols. One dialkyl carbinol, *trans*-2-phenylcyclohexanol, was resolved with very good selectivity (s = 30). In a subsequent study, it was shown that modest improvements in selectivity were possible when electron-deficient aryl groups were incorporated into this catalyst.[25]

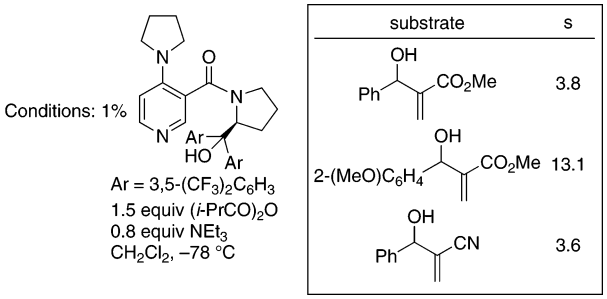
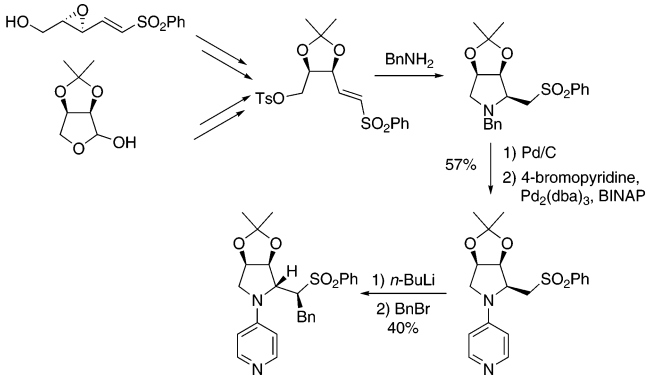


Figure 8. Connon's chiral PPY derivative: application to the kinetic resolution of Baylis–Hillman adducts.

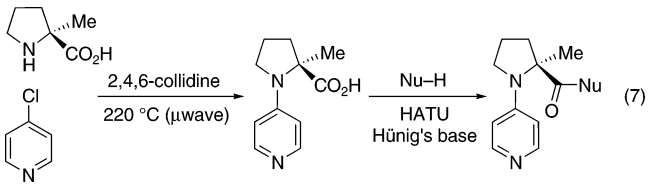
Scheme 2



In addition, Connon successfully expanded the scope of the kinetic resolutions to include secondary alcohols of Baylis–Hillman adducts (Figure 8).[25]

Díez pursued another strategy in order to benefit from the pendant attractive interaction exploited by Yamada. Thus, a series of chiral PPY catalysts containing a sulfone tethered to a pyrrolidine ring was prepared (Scheme 2).[26] Unfortunately, selectivities in the kinetic resolution of (±)-1-phenylethanol were low (<2).

Stimulated by the Fuji/Kawabata investigations, Campbell studied a group of catalysts based on 4-(α-methyl)proline derivatives of DMAP (eq 7; Figure 9).[27] Use of α-methylproline avoided the possibility of racemization of the catalyst, which had sometimes been observed during the preparation of analogues derived from proline itself.[28] Campbell included compounds in his catalyst library that could exploit the "induced-fit" mechanism proposed by Fuji and Kawabata (e.g., aromatic substituents) as well as those that could not.



Campbell examined the efficiency of his catalysts (Figure 9) for the kinetic resolution of a cyclic diol that had been explored by Fuji and Kawabata (eq 5). Although some catalysts that include an aromatic group are effective, so too are catalysts that lack such a substituent. PPY derivatives in which the side chain was a secondary amide were relatively effective (s = 8–13), whereas if a tertiary amide or an ester were present, a poor selectivity factor was observed (s < 2). Campbell suggested that hydrogen bonding to the N–H was likely a key component for good selectivity since the best substrates for kinetic resolution contained a carbonyl

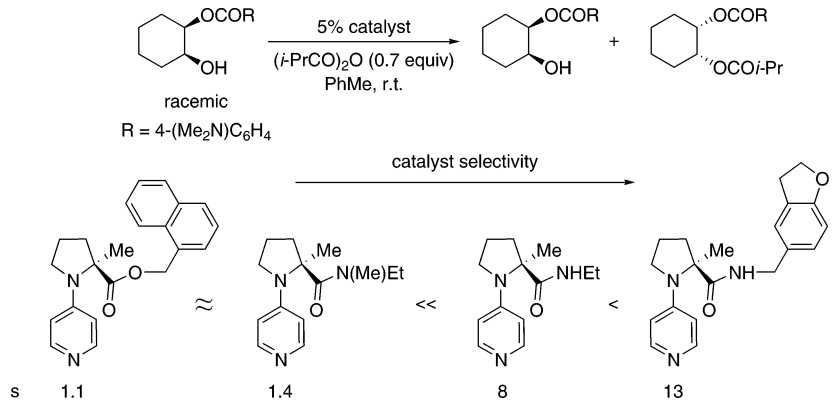
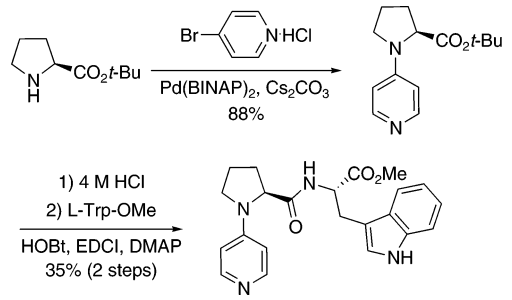


Figure 9. Selectivity trends in kinetic resolutions of monoprotected 1,2-cyclohexanediol in Campbell's DMAP catalysts.

Scheme 3



group in proximity to the hydroxyl group being acylated, which may serve as a point of hydrogen bonding.[29,30]

Campbell immobilized derivatives of these catalysts on a solid support, enabling the successful recovery and recycling of the catalyst, although with slightly diminished levels of selectivity when compared to the parent compound.[31] This represents one of the few reports of a polymer-bound chiral DMAP derivative.

The α-methylprolinyl amide-derived catalysts reported by Campbell in 2003 fared better in the kinetic resolution of certain amino alcohols with selectivities ranging from $s = 9$ to 19.[27] Crucial to success in these resolutions was again the presence of the 4-(dimethylamino)benzoate protecting group on the amine. Since strongly acidic conditions (6 N HCl) are required for cleavage of this protecting group,[32] other protecting groups were also examined. To this end, the trifluoroacetyl protecting group was found to be best with selectivity factors ranging from 5 to 10.[32] The polymer-supported catalyst again gave slightly poorer selectivities in this resolution, but it has the advantage of being easy to recycle and reuse.

Around the same time Kawabata and Fuji reported a class of catalysts structurally related to those developed by

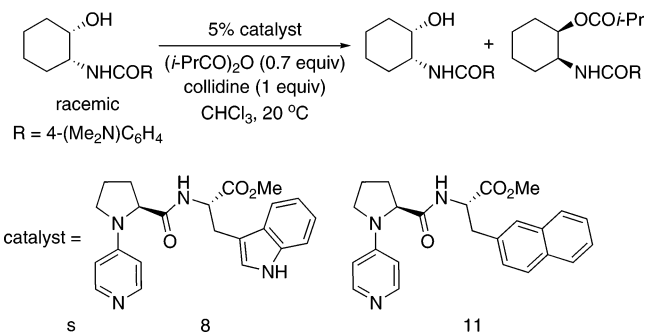


Figure 10. Proline-derived DMAP analogues reported by Kawabata and Fuji.

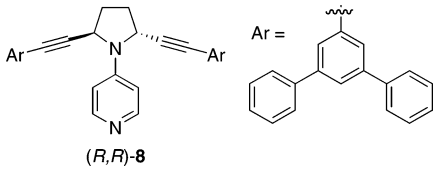
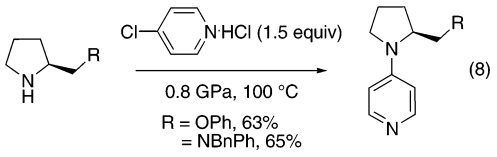


Figure 11. Inanaga's C_2-symmetric 4-(pyrrolidino)pyridine catalyst.

Campbell. The source of chirality in these catalysts is from a proline-derived dipeptide.[33] These DMAP analogues were prepared with greater ease than Campbell due to the absence of the α-chiral quaternary center (for the synthesis, see Scheme 3).

For the resolution of *cis*-amino alcohols, the most selective catalysts again had amide N−H bonds present. Two of the most selective catalysts are depicted in Figure 10.[33]

Kotsuki also reported the synthesis of two proline-derived DMAP derivatives using high pressure (0.8 GPa) in 63−65% yields (eq 8).[34] These catalysts were briefly examined in the kinetic resolution of (±)-1-phenylethanol, affording disappointing levels of selectivity (up to 20% ee at 12% conversion).

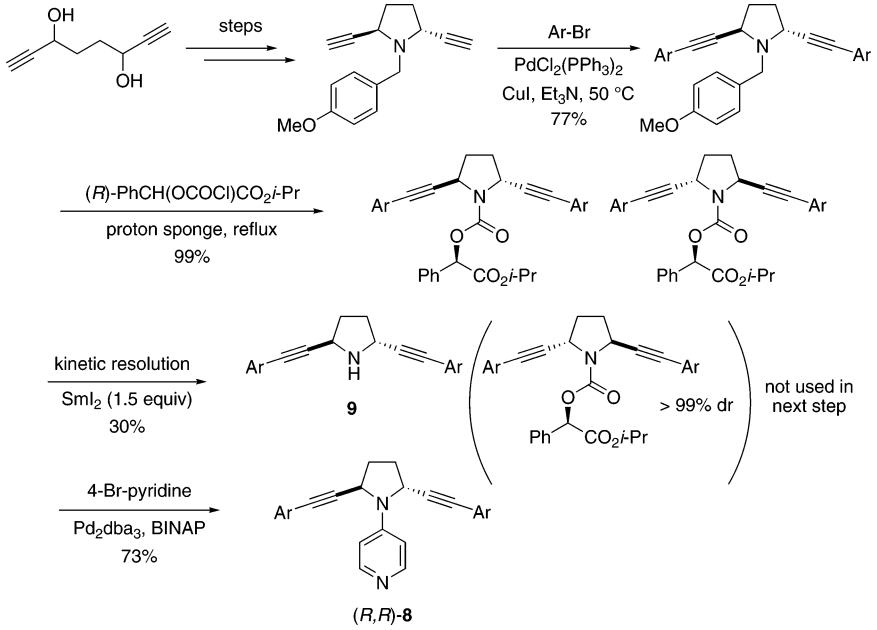


In 2000, Inanaga reported the first C_2-symmetric 4-(pyrrolidino)pyridine derivative in enantiomerically pure form (**8**; Figure 11).[35] This catalyst used a terphenyl group to effectively project a chiral environment from the remote stereocenter to the reaction site.

Key to the synthesis of the Inanaga catalyst was the preparation of *trans*-bis(arylethylnyl)pyrrolidine **9**, which was accomplished in four steps from *N*-methoxybenzyl-2,5-diethynylpyrrolidine (Scheme 4). Introduction of the *m*-terphenyl blocking groups to the terminal acetylenes using a Sonogashira coupling proceeded in 77% yield. Kinetic discrimination of the diastereomers, formed from *rac*-**9** and (*R*)-(chloroformyloxy)phenylacetate, with SmI_2 afforded enantiopure **9** in 30% yield. Buchwald−Hartwig coupling of **9** with 4-bromopyridine furnished Inanaga's catalyst (**8**) in 73% yield.[35]

The C_2-symmetric 4-(pyrrolidino)pyridine catalyst **8** can successfully resolve secondary alcohols with selectivity factors ranging from $s = 2$ to 14 (Figure 12).[35]

Scheme 4



Structurally related C_2-symmetric catalysts reported by Spivey were prepared from a dimesylate (Scheme 5), which is available from D-mannitol (5 steps, 42% overall yield).[36] Hydrogenolysis of the benzyl ethers afforded the corresponding diol in 94% yield, from which a variety of aryl ethers were introduced via Mitsunobu reactions in yields ranging from 81% to 88%.[36] The C_2-symmetric catalysts reported by Spivey resulted in dramatically lower selectivity factors for the kinetic resolution of (±)-1-phenylethanol. It appears that there is ineffective transfer of chirality from the more flexible C_2-symmetric catalysts as selectivities of only 1.1−1.8 were obtained.[36]

Jeong designed chiral DMAP derivatives based on Kemp's triacid and a binaphthyl framework.[37] The chiral binaphthyl unit is tethered to the 3 position of DMAP to avoid interference with its catalytic activity. In the calculated minimized conformation, the 4-dimethylamino group of the DMAP is positioned away from the neighboring binaphthyl unit in order to avoid otherwise severe steric repulsion between the two groups. Consequently, the pyridine nitrogen atom is in close proximity to the dissymmetric binaphthyl moiety.

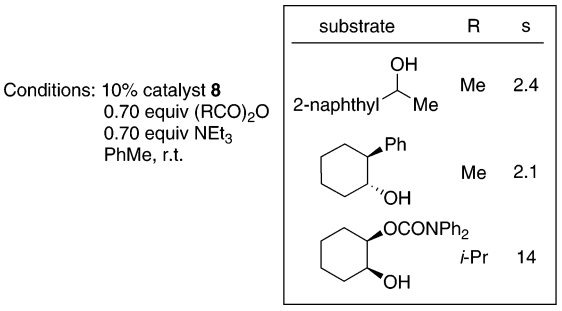
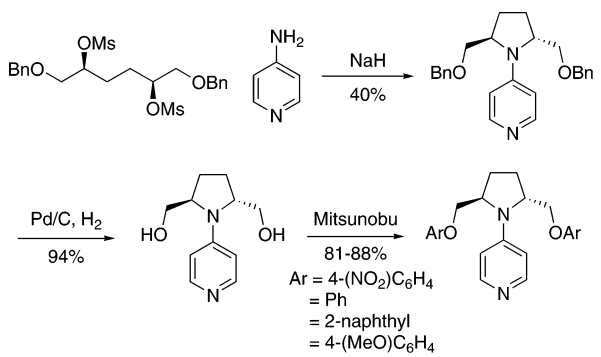
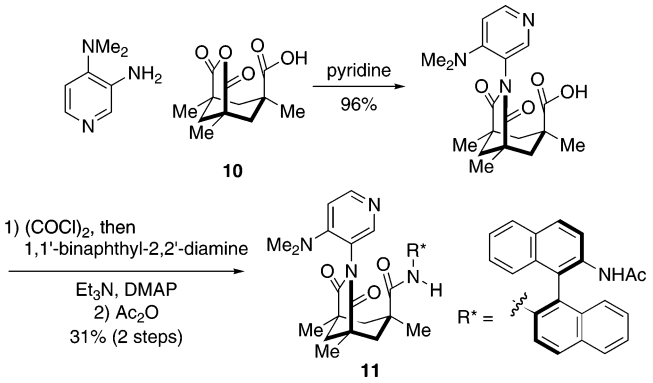


Figure 12. Resolution of secondary alcohols using Inanaga's C_2-symmetric 4-(pyrrolidino)pyridine catalyst.

Scheme 5



Scheme 6



The synthesis of Jeong's catalyst is relatively straightforward. 3-Amino-DMAP and anhydride acid **10** were heated at reflux in pyridine to give the imide acid in 96% yield (Scheme 6). After activation of the imide acid with oxalyl chloride, coupling with (*S*)-1,1′-dinaphthyl-2,2′-diamine (47%), followed by acetylation with Ac_2O (67%), furnished Jeong's catalyst **11**.[37]

Catalyst **11** gave modest to good levels of selectivity for the resolution of racemic secondary alcohols in the absence of additional base (s = 4−21, Figure 13).[37] It was found that the s value increased as the steric bulk of the alkyl group of the alcohol increased. The best result was obtained for the acylation of racemic *trans*-2-phenylcyclohexanol, which proceeded with s = 21.

In 2005, Levacher reported the synthesis of a chiral DMAP catalyst bearing a chiral sulfoxide as a chiral inducer (eq 9; Figure 14).[38] The catalyst was readily prepared from 3-bromo-DMAP via metal−halogen exchange with *i*-PrMgCl followed by addition of a chiral sulfoxide, furnishing catalyst

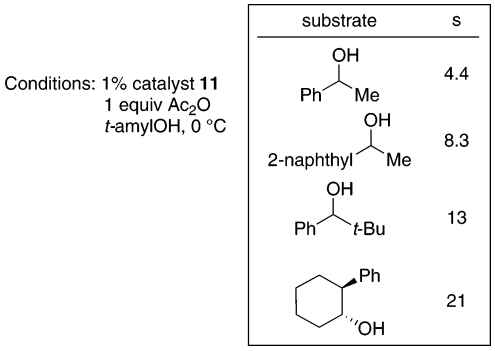


Figure 13. Kinetic resolution of secondary alcohols with Jeong's catalyst.

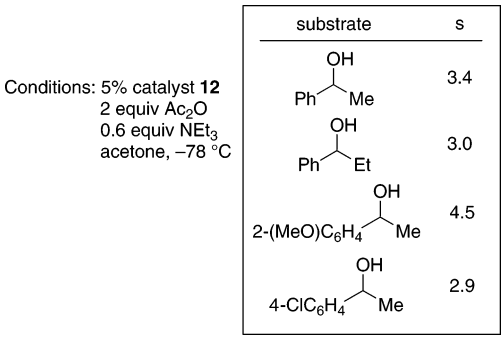
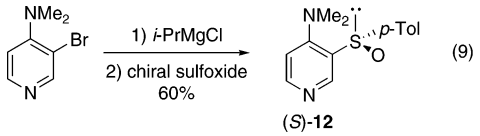


Figure 14. Kinetic resolution of secondary alcohols with Levacher's catalyst.

12 in 60% yield. Catalyst **12** gave modest levels of selectivity ($s \leq 4.5$) in the resolution of arylalkylcarbinols in acetone at −78 °C.



(9)

2.1.1.2. Catalysts with a Chiral Axis. In 1998, Spivey introduced the first members of a novel family of chiral DMAP-based nucleophilic catalysts[39] inspired by axially chiral biaryls such as BINOL. In this case, the asymmetry stems from restricted rotation about an aryl−aryl bond appended to the 3 position. These catalysts show activity comparable to DMAP in the acylation reaction of 1-methylcyclohexanol by acetic anhydride.[39]

Since the first report by Spivey, an extensive series of analogues of these atropisomeric biaryl 4-aminopyridines has been prepared due to their success in kinetic resolutions of alcohols (Figure 15).[40] In order to prevent thermal racemization of the biaryls, both the 4-amino group and the placement of substituents on the naphthyl ring were varied.[40a] Attempts to improve upon the ease of synthesis and performance of these catalysts led to derivative **16**, which has a more sterically demanding substituent in the 2′ position for a more effective chiral environment.[40b]

In 2001, Spivey undertook an extensive evaluation, both experimentally and computationally, of a variety of analogues of their catalysts to determine the barriers of rotation leading to racemization.[41] Surprisingly, they found that the barriers of rotation in derivatives based on the 5-azaindoline core (catalysts **13**, **14**, **16**) were lower than those in the corresponding derivatives based on the 4-(diethylamino)pyridine core (catalyst **15**).

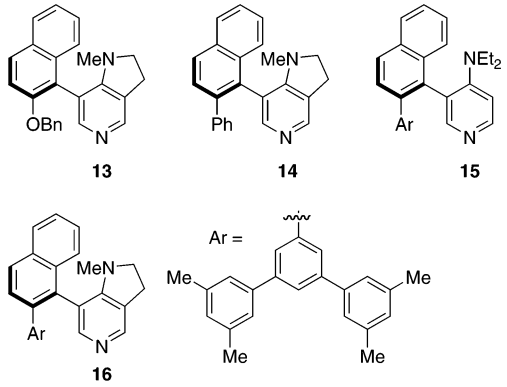
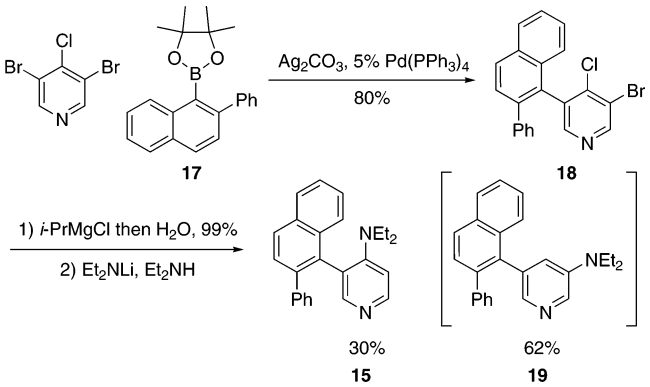


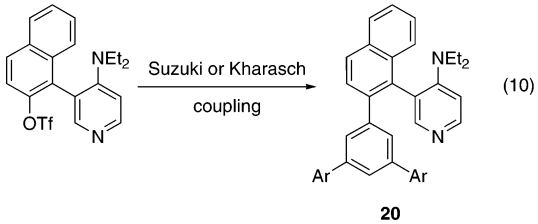
Figure 15. Spivey's biaryl analogues of DMAP.

Scheme 7



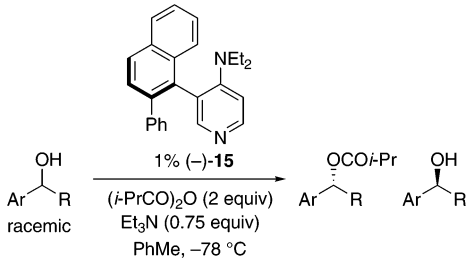
Spivey developed a three-step route (24% overall yield) to the atropisomeric-DMAP derivatives, furnishing (±)-**15** (Ar = Ph) from commercially available 3,5-dibromo-4-chloropyridine via a 3,4-pyridyne intermediate (Scheme 7).[40d] This protocol involves a Suzuki coupling between 3,5-dibromo-4-chloropyridine and boronic ester **17** as the first step in 80% yield. The 4-chloro-substituent in dihalopyridine **18** proved resistant to amination via either S_NAr or Buchwald−Hartwig coupling with diethyl amine, presumably due to steric constraints. They reasoned that the steric situation would be more favorable for an elimination−addition pathway via 3,4-pyridyne formation. To this end, preparation of biaryl **15** by treatment of dihalopyridine **18** with *i*-PrMgCl and quenching with water resulted in 3-debromination. Refluxing the debrominated product with lithium diethylamide and diethylamine gave clean formation of a readily separable 1:2 mixture of the desired 4-diethylamino product **15** and its 3-diethylamino isomer **19**.

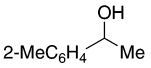
A gram-scale method for the classical resolution of **15** (Ar = Ph) using *N*-Boc-*O*-benzyl-(*S*)-tyrosine as a resolving agent affords enantiomerically pure biaryl **15** in ∼34% isolated yield. More recently, analogues with different biaryl groups, including a terphenyl group, have been prepared from a common triflate precursor.[40b,42] The enantiomerically pure catalysts were obtained by separation using semipreparative chiral HPLC (eq 10).[42]



(10)

Table 1. Kinetic Resolutions of Secondary Alcohols with Spivey's Catalyst (15)



substrate	s
	13
	8.4
	20
	25

In 2000, the first applications of these catalysts in the kinetic resolution of secondary alcohols were reported (Table 1).[40b] Using atropisomeric catalyst **15**, modest levels of selectivity ranging from $s = 8$ to 25 for a series of secondary alcohols were observed. The selectivity factor initially decreases as the steric demand of the alkyl group increases (Me to *i*-Pr), but the order changes for the most bulky alkyl group (*t*-Bu). If ortho substitution is present on the aryl ring, a marked increase in selectivity is observed. Catalyst derivatives based on *N*-methylindolines (e.g., catalyst **14**) generally showed inferior levels of selectivity under these conditions. This was even the case for analogues containing more sterically demanding terphenyl groups (e.g., catalyst **16**) for better projection of chirality.[40b]

The scope for the kinetic resolution was extended to include a range of structurally diverse secondary alcohols with selectivities ranging from 6 to 20 (for conditions, see Table 1 and Figure 16).[40d] These results mirror behavior

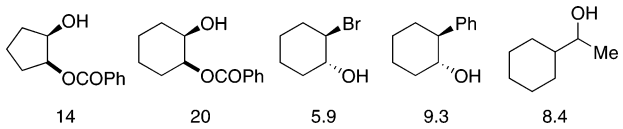


Figure 16. Kinetic resolutions of diverse alcohols by Spivey's catalyst (−)-**15** (Ar = Ph).

found with Fuji's catalyst (**5**), for which $\pi-\pi$ interactions were postulated.

Spivey proposed a transition-state representation for kinetic resolution using catalyst **15** and a secondary alcohol that is based on minimization of steric interactions (Figure 17).[40d] This model envisages attack by the alcohol, oriented so as to minimize steric repulsion with both the naphthalene and the isopropyl groups, from the opposite face of the acylpyridinium ring to the phenyl substituent. The irregular selectivity exhibited by most of the *cis*-1,2-diol monobenzoates was originally proposed to arise from the intervention of attractive $\pi-\pi$ interactions. Recent, computational studies by Zipse suggest the probable absence of $\pi-\pi$ interactions due to the rigidity of the σ framework.[43]

Another interesting observation noted by Spivey was that minor changes in the nature of the 4-dialkylamino group of

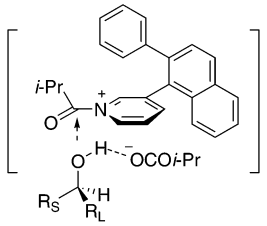
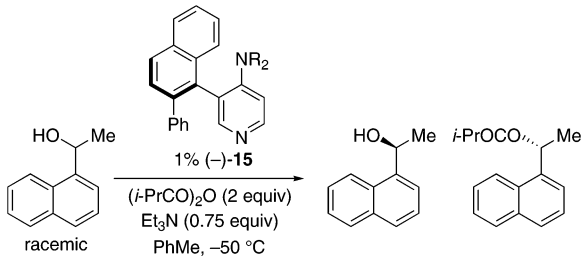


Figure 17. Transition-state representation of a kinetic resolution involving Spivey's catalyst, $(i\text{-PrCO})_2O$, and a secondary alcohol.

Table 2. Kinetic Resolution of (±)-1-(1-Naphthyl)ethanol



NR_2	s
pyrrolidino	3.5
NMe_2	10
NEt_2	24
N*n*-Pr_2	25
N*i*-Pr_2	15
N*n*-Bu_2	31
N*n*-$pent_2$	30
N*n*-hex_2	9

the biaryl catalysts had a noticeable influence on the selectivities in the resolution of (±)-1-(1-naphthyl)ethanol (Table 2).[42] The selectivities range from 4 for the 4-(pyrrolidino)pyridine biaryl analogue to 31 for 4-di-*n*-butylamino-derived catalyst. There appears to be no clear correlation between steric bulk and chain length, although the sense of induction is the same in all cases.

Recent efforts by Spivey have been directed toward biaryl catalysts containing terphenyl 'blocking groups' (e.g., catalyst **20**).[44] These derivatives are the most selective atropisomeric catalysts thus far for kinetic resolution of secondary alcohols. Selectivities up to 39 for (±)-1-(1-naphthyl)ethanol have been observed (Ac_2O, toluene, −78 °C), although the rate of acylation was slower.

2.1.1.3. Planar-Chiral Catalysts. A conceptually different approach to developing an effective chiral nucleophilic catalyst was pursued by Fu beginning in 1996.[45] The two mirror planes of symmetry of DMAP were eliminated through π complexation of a metal (ML_n) to the pyridine ring and incorporation of a substituent (R) in the 2 position of the pyridine ring (Figure 18). The resulting catalyst is now well differentiated and contains a tunable chiral environment in the vicinity of the nucleophilic nitrogen.

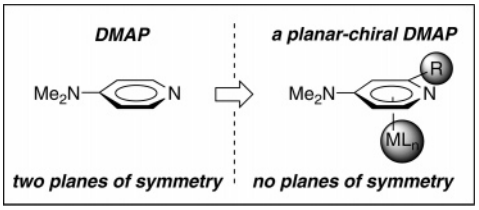


Figure 18. Design of a planar-chiral DMAP derivative.

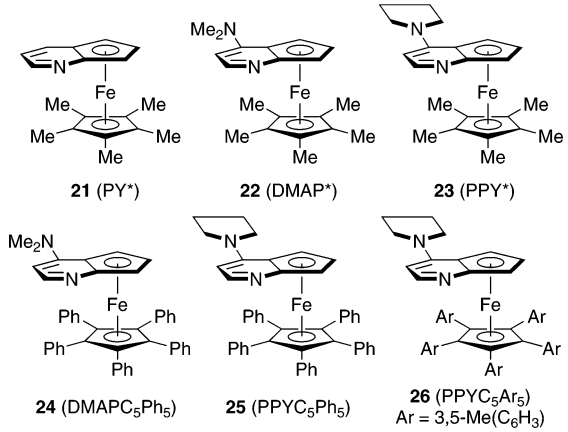
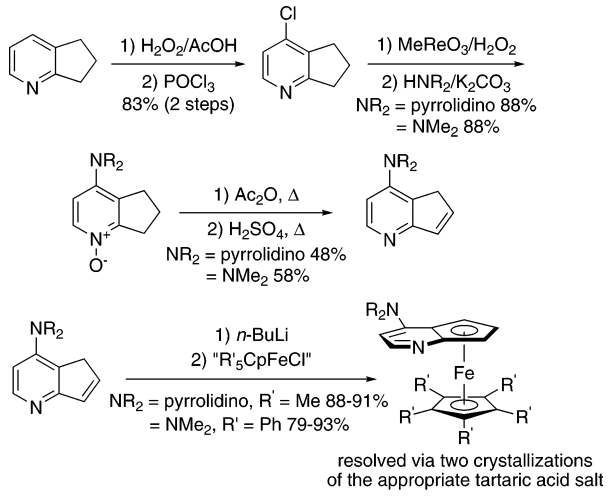


Figure 19. Fu's planar-chiral DMAP derivatives.

Scheme 8

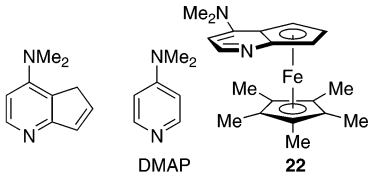


The most effective catalysts contain either a dimethylamino or pyrrolidino substituent in the 4 position of the pyridine to enhance the nucleophilicity (Figure 19). π-Complexed pentamethyl- or pentaphenylcyclopentadienyl groups are the most convenient ligands complexed to iron.

The nature of the metal fragment, ML_n, is quite important to the ability of the catalyst to function. An electron-rich metal enhances the nucleophilicity of the catalyst, and the choice of ligand provides a means to tune the chiral environment of the catalyst. To date, nearly all studies have focused on iron complexes, although other metals such as ruthenium have also been examined.[46]

An improved synthesis of these planar-chiral catalysts has recently been realized (Scheme 8). The racemic catalysts can be prepared in yields ranging from 31% to 34% over seven steps.[47] A classical resolution with di-*p*-toluoyl-tartaric acid provides enantiopure PPY* (**23**). On the other hand, dibenzoyl-tartaric acid is the most effective resolving agent for $DMAPC_5Ph_5$ (**24**). In recent years, two of these planar-chiral catalysts have become commercially available,[48] thereby facilitating use of these catalysts.

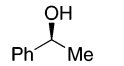
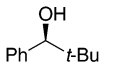
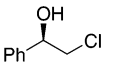
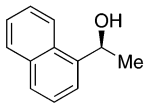
Vedejs demonstrated that placement of a bulky chiral group in the 2 position of DMAP prevented catalytic turnover.[6] However, if an annulated cyclopentadiene ring is present in the 2,3 position, it is small enough to avoid a loss of catalyst activity. Computationally, Zipse has shown that this analogue stabilizes cation formation by -78.4 kJ·mol^{-1}, only slightly less than DMAP (Figure 20).[49] Interestingly, the highest stabilization calculated in his study is predicted



ΔH_{rxn} (kJmol^{-1}) (acetyl-transfer reaction)	-78.4	-82.1	-128.0

Figure 20. Calculated reaction enthalpies for the acetyl-transfer reaction.

Table 3. Kinetic Resolution of Arylalkylcarbinols by (−)-DMAPC$_5$Ph$_5$ (24)[a]

unreacted alcohol, major enantiomer	s (selectivity factor) Et_2O 2% catalyst r.t.	s (selectivity factor) *t*-amyl alcohol 1% catalyst 0 °C
	14	43
	52	95
	12	32
	22	65

[a] Conditions: 0.59 or 0.75 equiv of Et_3N; 0.60 or 0.75 equiv of Ac_2O.

for planar-chiral DMAP* (**22**), for which the acetylated cation is stabilized by -128.0 kJ·mol^{-1}. The acetylation energy is dramatically larger (more negative) than a DMAP derivative that only contains an annulated ring in the 2,3 position due to the electron-donating ability of the ferrocenyl moiety.

In 1996, Fu and Ruble introduced the first examples of planar-chiral DMAP catalysts for the kinetic resolutions of secondary alcohols.[45] In this preliminary communication, Ruble and Fu demonstrated that DMAP* (**22**) provided higher reaction rates in the resolution of (±)-1-phenylethanol with diketene when compared to PY* (**21**) and azaferrocene-derived catalysts.

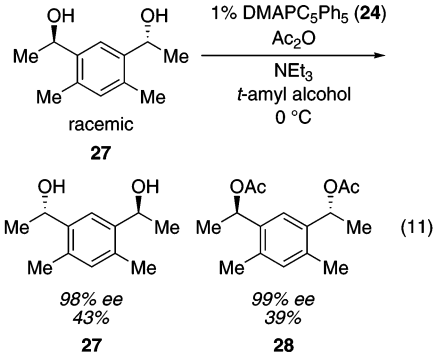
Fu reported a second-generation kinetic resolution the following year involving the treatment of secondary alcohols with Ac_2O.[50] He found that increasing the steric demand of the 7 position of the pyrindinyl ring by addition of a methyl or a trimethylsilyl substituent resulted in ineffective catalysts. On the other hand, replacement of the η^5-C_5Me_5 group of DMAP* (**22**) with a more sterically demanding η^5-C_5Ph_5 provided an effective catalyst for secondary alcohol resolutions. Thus, in the presence of 2% of $DMAPC_5Ph_5$ (**24**) and one equivalent of Et_3N, selectivity factors from 12 to 52 were obtained (Table 3).

It was subsequently determined that solvent plays a critical role in determining enantioselectivity. *tert*-Amyl alcohol was found to be the optimal solvent in terms of reactivity as well as selectivity (e.g., $s = 14$ for (±)-1-phenylethanol at rt), and reactions could be performed at 0 °C to further increase enantioselectivity. Thus, *s* values ranging from 32 to 95 were obtained for various arylalkylcarbinol substrates (Table 3).[51]

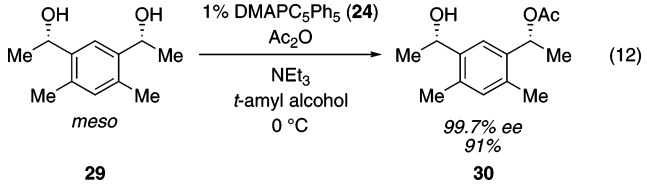
The nature of the metal and its effect on the selectivity factors have also been examined. For the kinetic resolution of (±)-1-phenylethanol, Ru-$DMAPC_5Ph_5$ gave inferior levels

of selectivity compared to $DMAPC_5Ph_5$ (**24**) ($s = 10$ versus $s = 43$).[46] This may be attributed to a longer Ru metal−ligand bond.

The kinetic resolution of racemic and *meso*-diols has been investigated. Racemic diol **27** undergoes acetylation to provide diol **27** and diacetate **28** in excellent enantiomeric excess (≥98% ee); approximately 16% of the monoacetate is produced (eq 11).[51] *meso*-Diol **29** undergoes an efficient desymmetrization process to afford the monoacetate **30** in >99% ee and 91% yield (eq 12).



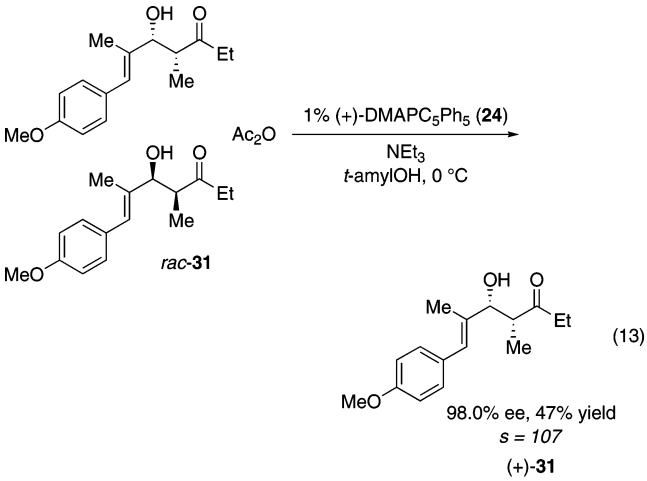
(11)



(12)

Several families of allylic alcohols also undergo kinetic resolutions with good selectivity using 1−2.5 mol % $DMAPC_5Ph_5$ (**24**) in *tert*-amyl alcohol at 0 °C (Table 4).[52] Allylic alcohols that do not possess a substituent either geminal or cis to the hydroxy-bearing group are usually resolved with modest selectivity, although the presence of a phenyl substituent in the trans position leads to substantially improved enantioselection (entry 4).

An application of this methodology is demonstrated by the successful resolution of racemic **31**, a key intermediate in the Sinha−Lerner total synthesis of epothilone A (eq 13).[53]

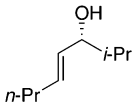
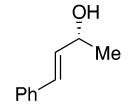
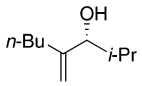
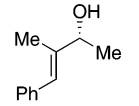
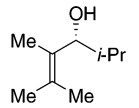


(13)

Propargylic alcohols can be resolved with moderate selectivity factors (*s* values up to 20) by $DMAPC_5Ph_5$ (**24**) in *tert*-amyl alcohol (Table 5).[54] In contrast to trends observed with arylalkylcarbinols, the highest selectivity factors are obtained with smaller alkyl substituents and no added base. The kinetic resolution of propargylic alcohols by $DMAPC_5Ph_5$ (**24**) is more efficient when the remote position of the alkyne is substituted with an unsaturated group (e.g., aryl, carbonyl, alkynyl, alkenyl) rather than with an alkyl group (selectivity factor for (±)-3-octyn-2-ol = 3.9).

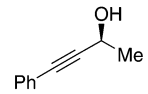
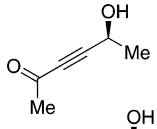
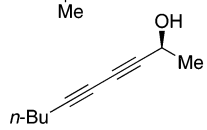
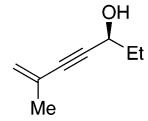
In 2005, Johannsen reported chiral DMAP derivatives with a planar-chiral ferrocene substituent at C2 or C3 (catalysts **32** and **33**; Figure 21).[55] The synthesis of these catalysts commence from enantiopure ferrocene sulfoxide **34** (Scheme 9). A naphthyl blocking group is introduced in 66% yield over four steps. Cleavage of the chiral sulfoxide auxiliary, transmetalation with tin, followed by Stille coupling with 2-bromo-4-nitropyridine or 3-bromo-4-nitropyridine *N*-oxide affords intermediates **35** and **36**, respectively, in 55% yield (three steps). Intermediate **35** can then be used to access

Table 4. Kinetic Resolution of Allylic Alcohols by (+)-$DMAPC_5Ph_5$ (24)[a]

entry	unreacted alcohol, major enantiomer	selectivity factor (ee of unreacted alcohol)
1		5.4
2		64
3		25
4		80
5		29

[a] Conditions: 1−2.5% catalyst; 0.59 equiv of NEt_3; 0.59 equiv of Ac_2O; *tert*-amylOH, 0 °C.

Table 5. Kinetic Resolution of Propargylic Alcohols by (−)-$DMAPC_5Ph_5$ (24)[a]

entry	unreacted alcohol, major enantiomer	selectivity factor (ee of unreacted alcohol)
1		20
2		12
3		10
4		7.9

[a] Conditions: 1% catalyst; 0.75 equiv of Ac_2O; *tert*-amylOH, 0 °C.

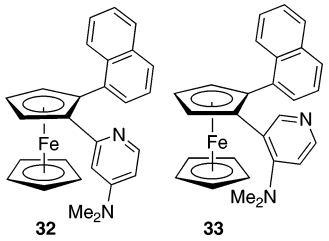


Figure 21. Johannsen's planar-chiral catalysts.

planar-chiral DMAP derivative **32** in 83% yield (2 steps). Similarly, intermediate **36** was treated with PCl_3 and then $HNMe_2$, affording planar-chiral DMAP derivative **33** in 18% yield (two steps).[55]

The authors found that the C3-substituted catalyst **33** is preferentially acylated over the C2-substituted derivative **32** by approximately 16 $kJ \cdot mol^{-1}$, corresponding to a difference in reactivity of almost 3 orders of magnitude. As would be expected, this large difference is due to steric interactions in the 2-substituted DMAP derivative. The catalysts were tested in the kinetic resolution of (±)-1-phenylethanol, for which only catalyst **33** displayed high reactivity, although no selectivity was observed.

In 2007, Richards reported a straightforward synthesis of a C_2-symmetric DMAP derivative **37** with ferrocene substituents at C3 and C5 (Scheme 10).[56] The chirality of this catalyst is derived from (*S*,*S*)-hexane-2,5-diol. A Stille coupling is used to introduce the ferrocene subunits, furnishing catalyst **37** in 54% yield over three steps.

Modest levels of selectivity ($s = 2.5-5.0$) were observed for the kinetic resolution of arylalkylcarbinols using catalyst **37** (Table 6).

The currently accepted mechanism for the chiral DMAP-catalyzed acylation of secondary alcohols is illustrated in Figure 22. Acylpyridinium formation with the acyl donor forms chiral adduct **38** in a reversible fashion.[57] In the rate- as well as the stereochemistry-determining step, an acyl group is transferred preferentially to one enantiomer of the secondary alcohol to form an enantioenriched ester, enantioenriched alcohol, along with protonated catalyst. Regeneration of the catalyst is then facilitated by an auxiliary base such as triethylamine.

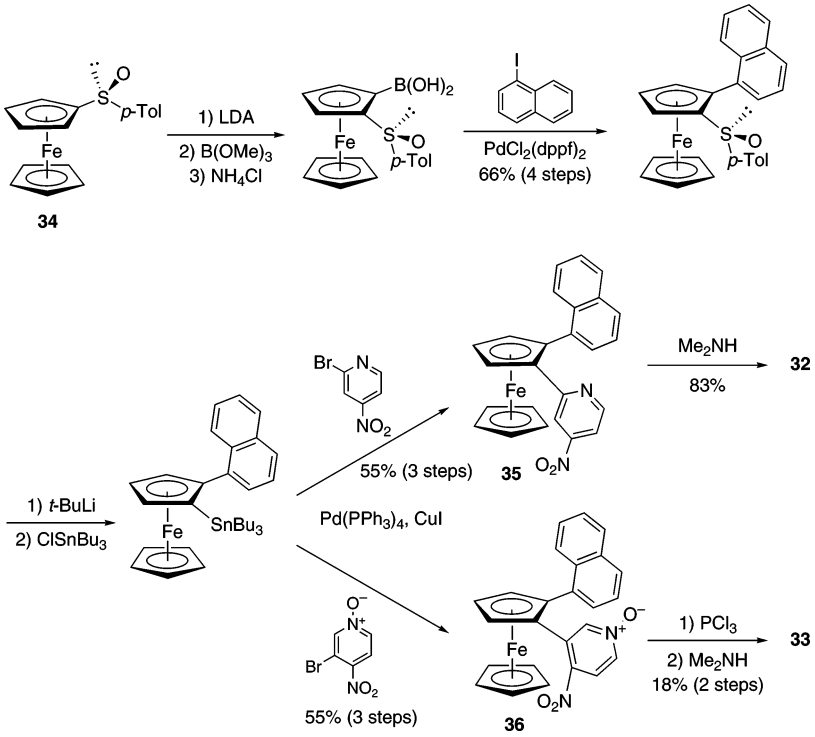
In addition to chiral derivatives of DMAP, a variety of other effective organocatalysts exist for the resolution of alcohols, including a chiral diamine reported by Oriyama,[58] chiral phosphines developed by Vedejs,[59] and catalysts based on β-turn peptide fragments that contain nucleophilic *N*-alkyl-imidazole residues developed by Miller.[7a] Furthermore, Birman and Li recently reported a benzotetramisole catalyst that furnishes selectivity factors up to 355 for the kinetic resolution of secondary alcohols.[60]

A real test for the use of low molecular weight chiral catalysts for kinetic resolution is whether they will offer the selectivities possible with enzymes and be economically viable in an industrial setting. Few of the chiral DMAP derivatives are commercially available with the exception of the Fu planar-chiral catalysts. In addition, the full synthetic scope of most of the catalysts discussed has yet to be explored. Hopefully, in the near future the strengths and limitations of these catalysts will be more clearly defined.

2.1.2. Resolutions of Amines

Amines represent a much more challenging class of substrates for kinetic resolutions using acylating agents. This arises from the fact that very basic amines are easily acylated without the involvement of the chiral catalyst, leading to significant background reactions. In 2000, Ie and Fu reported a development in this field.[61] It involved the use of a *stoichiometric* quantity of a preformed acylated planar-chiral adduct prepared upon treatment of $PPYC_5Ph_5$ (**25**) with AcCl. This adduct was then treated with 8 equiv of a racemic primary amine, and the resulting amide could be generated with enantioselectivities up to 91% ee (Table 7).

Scheme 9



Scheme 10

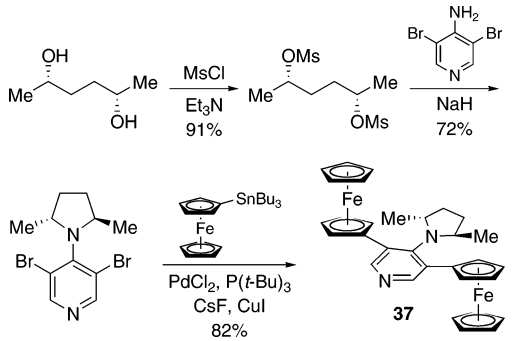
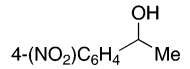
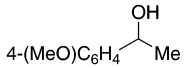
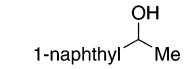
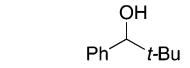


Table 6. Kinetic Resolutions of Arylalkylcarbinols with Richards' Catalyst (−)-37

Conditions: 0.5% catalyst **37**
0.7 equiv Ac_2O
0.7 equiv *i*-Pr_2NEt
PhMe, −40 °C

substrate	s
	5.0
	2.4
	2.7
	2.5

These results suggested that good enantiodifferentiation might be possible using planar-chiral derivatives of DMAP as catalysts under the appropriate reaction conditions. In order to address the significant background reactions observed with Ac_2O, other acylating agents were examined. A number of acylating agents, namely, O-acylated azlactones, were found to react much more readily with the catalyst than with a primary amine. Using O-acylated azlactones, (±)-1-phenylethylamine can be resolved with a selectivity factor of 12

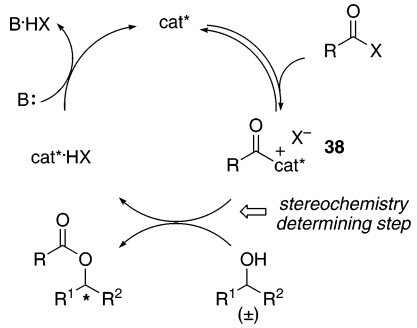
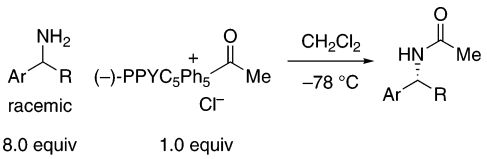


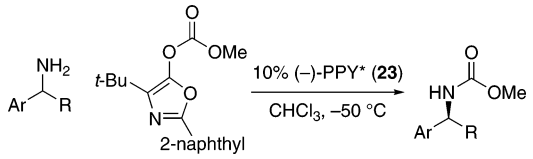
Figure 22. Mechanism for the kinetic resolution of secondary alcohols.

Table 7. Enantioselective Acylation of Amines by (−)-PPYC_5Ph_5 (25)



entry	Ar	R	% ee of amide
1	Ph	Me	87
2	1-naphthyl	Me	90
3	2-MeC_6H_4	Me	91

Table 8. Kinetic Resolution of Amines Catalyzed by (−)-PPY* (23)



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

using 10% of PPY* (**23**).[62] The resolution appeared to be quite general for benzylic primary amines (Table 8).

Mechanistically, it is believed that the first step of the reaction is catalyst acylation by the O-acylated azlactone to furnish an ion pair **39**, which is the resting state of the catalytic cycle (Figure 23). The transfer of the acyl group to

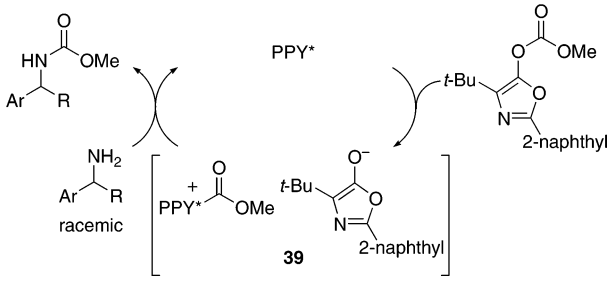


Figure 23. Proposed mechanism for amine acylations catalyzed by PPY* (**23**).

the amine and regeneration of the catalyst is the rate- as well as stereochemistry-determining step.

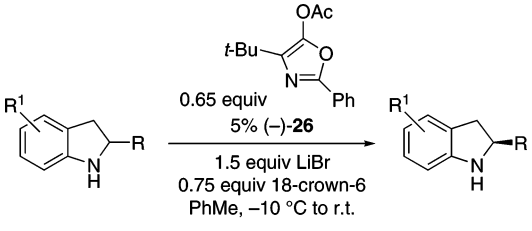
Recently, Arp and Fu reported an expansion in the scope of kinetic resolutions of amines to include indolines.[63] Under the conditions developed for benzylic primary amines there was no acylation of the indolines due to their comparatively low nucleophilicity. Exploratory studies using stoichiometric chiral reagents found that addition of halide salts resulted in increased levels of selectivity with catalyst **26**. In particular, addition of LiBr/18-crown-6 leads to the highest *s* value that has been observed to date in these resolutions. Interestingly, the use of other crown ethers results in lower selectivity as does omission of 18-crown-6 and/or LiBr. A large number of acylating agents were surveyed, and O-acylated azlactones[64] were again found to be the most effective.

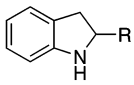
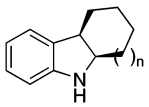
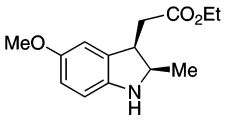
The catalysts employed in this resolution were structurally modified in order to further increase the selectivity. Although PPY* (**23**) is virtually inactive, use of a bulky pentacyclopentadienyl leads to a more effective acylation catalyst that can achieve the desired kinetic resolution with a useful selectivity factor (Table 9). The optimal selectivity factor was achieved using PPY derivative **26** (Ar = 3,5-$Me_2C_6H_3$), whereas its slightly more demanding analogue of **26** (Ar = 3,5-$Et_2C_6H_3$) provided a slightly lower selectivity.

The scope of this resolution is fairly broad for an array of 2-substituted indolines, including functionalized compounds (entries 1−4). 2,3-Disubstituted indolines are also suitable substrates (entries 5−7).

The roles of LiBr and 18-crown-6 are not fully understood in this resolution, especially since this crown ether is considered to be a mismatch for the lithium cation, and other

Table 9. Kinetic Resolution of Indolines by (−)-26



entry	indoline		s
1		R = Me	25
2		*n*-Pr	26
3		CH_2CH_2Ph	18
4		CH_2OTBS	14
5		n = 1	9.8
6		2	31
7			19

suitable crown ethers gave lower selectivities. ^{1}H NMR studies indicate that the resting state of the catalyst during these indoline resolutions is the free catalyst, which contrasts with observations made in resolutions of benzylic amines.

In 2006, Anstiss and Nelson reported the desymmetrization of a centrosymmetric piperazine using Fu's $DMAPC_5Ph_5$ (**24**), Spivey's catalyst (**15**), and Vedejs' TADMAP catalyst (**40**).[65] Enantioselectivities up to 70% were possible with low to moderate yields (Table 10). Superior levels of enantioselectivity (up to 84% ee) were obtained using chiral acylating reagents.

2.1.3. Dynamic Kinetic Resolutions of Azlactones

One straightforward route to the synthesis of protected α-amino acids involves the ring opening of azlactones by alcohols or water. Azlactones have a propensity to racemize ($pK_a \approx 9$); therefore, a dynamic kinetic resolution (or deracemization) should be possible.

In 1966, Steglich reported one of the first clear examples of a nonenzymatic dynamic kinetic resolution of an azlactone with a chiral amino ester.[66] Since this time numerous examples involving chiral reagents or catalysts have appeared in the literature.[9a,67,68]

In 1998, Fu reported the methanolysis of azlactones catalyzed by DMAP* (**22**) using benzoic acid as an additive.[69] Modest levels of enantioselectivity, 44−61% ee, for a range of protected amino acids were obtained (Table 11). The selectivity of the dynamic kinetic resolution increases as the steric demand of the alcohol increases, reaching 78% ee when *i*-PrOH is employed as the nucleophile. Unfortunately, ring opening under these conditions is extremely slow ($t_{1/2} = 1$ week). Under otherwise identical conditions, Ru-DMAP* (**22**) was also tested and found to display slightly enhanced stereoselectivity (57% ee versus 54% ee (R = H)).[46]

In 2005, Johannsen also briefly examined this dynamic kinetic resolution process using planar-chiral catalyst **33**, and he obtained selectivities up to 42% ee for the benzyl-substituted azlactone.[55] Using *i*-PrOH as the alcohol led to a decrease in selectivity and reaction rates.

Chiral DMAP-catalyzed dynamic kinetic resolutions of azlactones do not yet approach the current state-of-the-art results provided by other low molecular weight catalysts[70] or enzymatic[71] dynamic kinetic resolutions, but these results serve to illustrate the breadth of the utility of chiral DMAP derivatives, and further progress can be expected.

2.2. Cycloadditions

2.2.1. Synthesis of β-Lactams

The medicinal importance of β-lactams, such as penicillins and cephalosporins, as antibiotics is enormous. This makes the synthesis of non-natural analogues a pressing objective. In addition to their biological importance, β-lactams also serve as useful building blocks for the synthesis of β-amino acids and β-amino alcohols.[72]

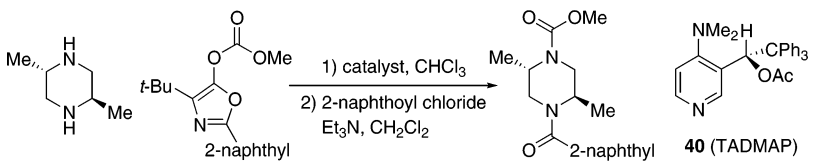
One efficient and convergent method for the facile synthesis of β-lactams involves the Staudinger reaction,[73] which is an overall [2+2] cycloaddition of a ketene with an imine. The pioneering work of Lectka has established that a quinine derivative can effect a highly stereoselective coupling of a range of monosubstituted ketenes and one symmetrical disubstituted ketene with an electron-deficient imine.[74]

In 2002, Hodous and Fu demonstrated the utility of planar-chiral DMAP catalysts in the Staudinger reaction with the successful coupling of disubstituted ketenes with a range of imines.[75] PPY* (**23**) gave the highest levels of selectivity in this [2+2] cycloaddition reaction (Table 12). Broad scope is observed for a variety of aryl-, heteroaryl-, and alkyl-derived tosylimines with symmetric disubstituted ketenes allowing for the rapid synthesis of a range of trisubstituted β-lactams (entries 1−3). Staudinger reactions of unsymmetrical ketenes furnish two contiguous (one quaternary and one tertiary) stereocenters with very good ee, yield, and dr (entries 4−5).

The presumed mechanism for this reaction is illustrated in Figure 24. Reaction of the catalyst with the ketene affords a zwitterionic adduct **41**, which couples with the tosyl imine. Cyclization affords the β-lactam and liberates the catalyst.

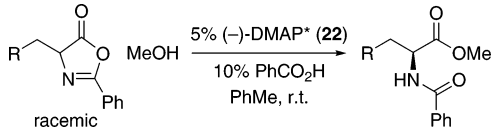
Obviously, in the case of these α,α-disubstituted β-lactams, the trans diastereomer cannot be generated from the cis

Table 10. Desymmetrization of a Piperizine



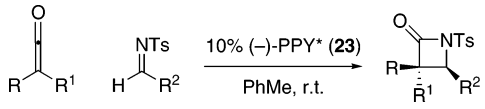
entry	catalyst	mol %	temp. (°C)	% ee	% yield
1	(+)-**24**	20	−18	44	25
2	(−)-**15**	5	−42	−70	20
3	(−)-**40**	5	−42	64	22

Table 11. Dynamic Kinetic Resolution of Azlactones



R	% ee	% yield
H	54	98
Me	44	94
CH=CH$_2$	61	94
i-Pr	55	95
Ph	56	94
CH$_2$SMe	50	94

Table 12. Staudinger Reactions Catalyzed by (−)-PPY* (23)



entry	R	R^1	R^2	% ee	% yield
1	−(CH$_2$)$_6$−		Ph	81	84
2	Et	Et	2-furyl	92	93
3	−(CH$_2$)$_6$−		cyclopropyl	94	89
4	Ph	*i*-Bu	Ph	98 (8:1 dr)	88
5	Ph	Et	cyclopropyl	98 (10:1 dr)	98

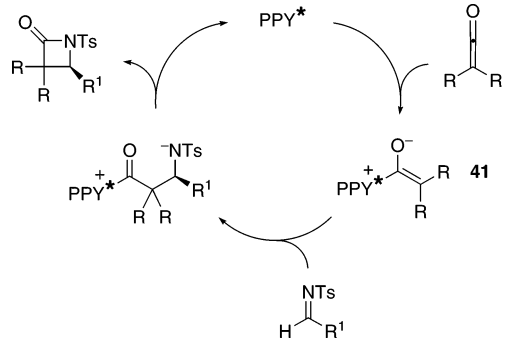
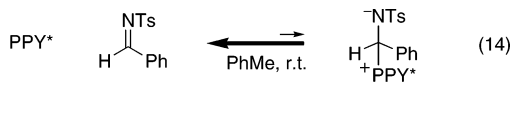


Figure 24. Mechanism for Staudinger reactions catalyzed by PPY* (**23**).

isomer through base-induced epimerization. Therefore, in order to access the trans diastereomer, the Staudinger reaction itself has to be trans selective. Development of a trans-selective variant was possible through the use of *N*-triflyl imines. Table 13 illustrates the scope and trans-selectivity that is possible when the *N*-triflyl protecting group is used.[76]

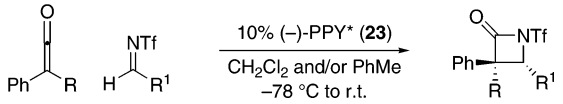
This observed dependence of the cis/trans diastereoselectivity on the choice of the *N*-sulfonyl group prompted a mechanistic investigation. Although there is no evidence by ^{1}H NMR of an interaction between PPY* (**23**) and an *N*-tosyl imine (eq 14), the catalyst reacts quantitatively with a more electrophilic *N*-triflyl imine to furnish adduct **42** (eq 15).



42

On the basis of these observations, it was suggested that the triflyl amide may be reacting preferentially via an "imine-first" pathway (Figure 25) and that this may be the origin of the observed reversal in diastereoselectivity.

Table 13. Catalytic Asymmetric Synthesis of *trans*-β-Lactams



entry	R	R^1	trans:cis	% ee[a]	% yield[b]
1	Me	Ph	98:2	81	83
2	Et	Ph	86:14	63	60
3	*i*-Bu	Ph	97:3	63	72
4	Me	4-FC$_6$H$_4$	96:4	85	84
5	Me	4-(MeO)C$_6$H$_4$	81:19	82	76
6	Me	*o*-tolyl	81:19	99	89

[a] Enantiomeric excess of the trans diastereomer. [b] Yield of the mixture of diastereomers.

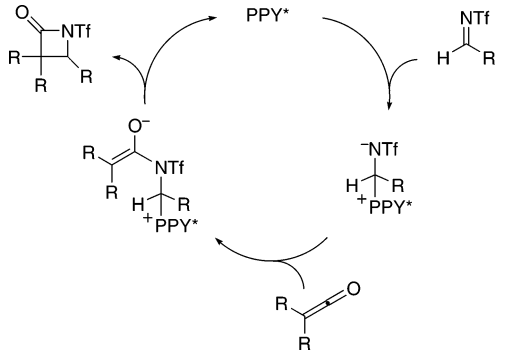


Figure 25. Possible mechanism for Staudinger reactions of *N*-triflyl imines.

In conclusion, relatively few methods have been described for the catalytic asymmetric synthesis of β-lactams,[74,77] and those that have are typically cis selective. Planar-chiral DMAP derivatives serve as versatile catalysts for the synthesis of highly functionalized β-lactams, and the cis/trans selectivity can be controlled through appropriate use of the protecting group on the imine.

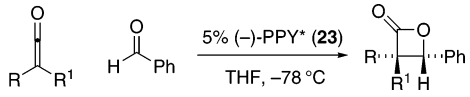
2.2.2. Synthesis of β-Lactones

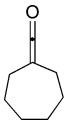
β-Lactones serve as useful intermediates in organic synthesis since the strain of the four-membered lactone provides an opportunity for a range of functionalizations. For example, treatment of β-lactones with nucleophiles can react via two modes: either at the carbonyl group through an addition−elimination sequence or at the C−O single bond through an S$_N$2 process. A number of recent total syntheses, such as those of (−)-laulimalide[78] and (−)-malyngolide,[79] have exploited enantiopure β-lactones as intermediates. In addition, numerous biologically active β-lactone-containing natural products[80] and unnatural products have been described, including salinosporamide A.[81]

Cinchona alkaloid-based catalysts provide access to β-lactones from monosubstituted ketenes.[82] In an analogous manner to the [2+2] cycloaddition of ketenes with imines, expansion of the scope of this reaction to access α,α-disubstituted β-lactones has been realized by Wilson and Fu.[83]

Wilson and Fu tested the conditions developed for the enantioselective Staudinger-type cycloaddition of ketenes with imines, replacing the imine with an aldehyde. In this experiment, essentially none of the desired β-lactone was formed. Interestingly, simply by lowering the reaction tem-

Table 14. Catalytic Asymmetric Synthesis of β-Lactones



entry	R	R^1	% ee	% yield
1	Et	Et	91	92
2			82	71
3[a]	*i*-Pr	Me	91	48
4[a]	cyclopentyl	Me	88	53

[a] Cis:trans selectivity = 4.2-4.6:1. The ee value is for the cis diastereomer, and the yield is for the mixture of diastereomers.

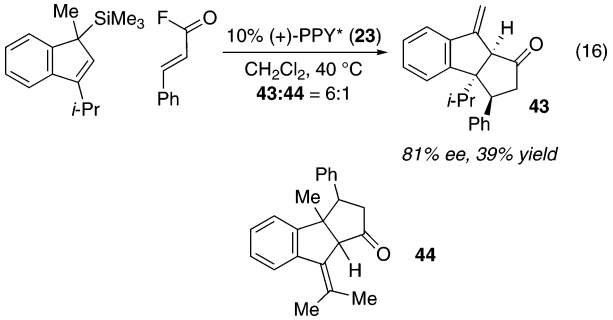
perature from room temperature to −78 °C the targeted [2+2] cycloaddition product was generated in high yield using PPY* (**23**) as a catalyst (Table 14). In the case of unsymmetrical ketenes, β-lactones that bear two contiguous stereocenters (one quaternary and one tertiary) can be prepared with the cis diastereomer being formed predominantly (entries 3 and 4). Under these reaction conditions, arylalkylketenes, monosubstituted ketenes, very electron-rich aldehydes, and nonaromatic aldehydes are not suitable substrates.

2.2.3. [3+2] Annulations

In processes such as kinetic resolution of alcohols and amines, the critical species is a chiral acylpyridinium ion that acylates a nucleophile (section 2.1). In cycloaddition reactions, the key intermediate is a chiral enolate, which reacts at the α position with an electrophile to furnish enantioenriched β-lactams and β-lactones (sections 2.2.1 and 2.2.2). Generation of a chiral α,β-unsaturated acylpyridinium ion as a reactive intermediate allows a third mode of reactivity in which a nucleophile reacts in the β position. Fu recently realized such a reactivity mode in the context of an overall [3+2] annulation process.[84]

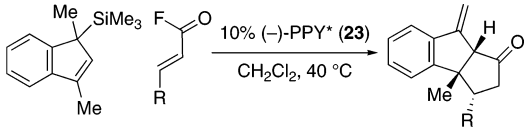
PPY* (**23**) was found to catalyze the diastereo- and enantioselective synthesis of a diquinane derivative from a silylated indene and an α,β-unsaturated electrophile in moderate ee and yield (Table 15). Three contiguous stereocenters (one quaternary and two tertiary) are formed in this process. The scope of the [3+2] annulation is broad, as electronically diverse aryl substituents (entries 1−4) as well as a heteroaryl group are tolerated in the β position (entry 5).

This enantioselective [3+2] reaction can be applied to annulations of unsymmetrical indenes. Thus, an isopropyl/methyl-substituted indene reacts to provide a 6:1 ratio of **43:44** in 81% ee (39% yield) for the major diastereomer (eq 16).



(16)

Table 15. Catalytic Asymmetric [3+2] Annulations



entry	R	dr[a]	% ee	% yield[b]
1	Ph	12:1	78	60
2	3-F-C_6H_4	7:1	58	51
3	3,5-(MeO)C_6H_3	8:1	70	61
4	1-naphthyl	9:1	70	42
5	3-furyl	9:1	77	48

A possible mechanism for this transformation is illustrated in Figure 26. PPY* (**23**) reacts with the acid fluoride to furnish ion pair **45**. The liberated fluoride then binds to the silyl group of the indene,[85] providing a new ion pair **46**. Conjugate addition of the indenyl nucleophile to its α,β-unsaturated acylpyridinium counterion produces a zwitterion **47** that bears two new stereocenters. Finally, fragmentation releases the catalyst and affords ketene **48**, which cyclizes via an ene-type process to generate the diquinane product.

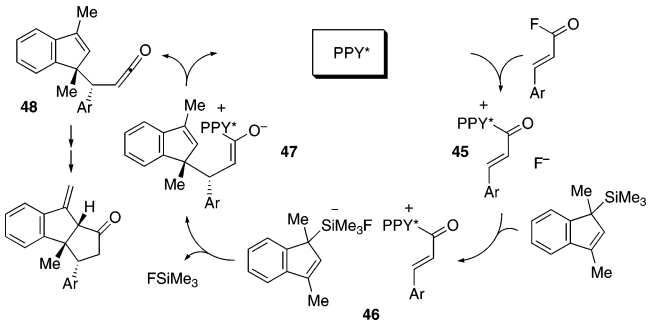
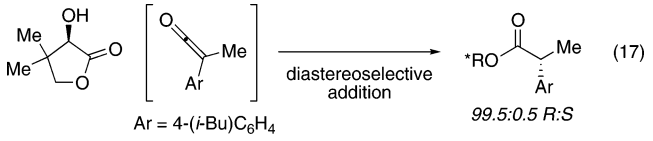


Figure 26. Possible mechanism for nucleophile-catalyzed [3+2] annulation.

Other coupling partners were examined in order to test the proposed mechanism. When cinnamoyl fluoride was replaced with cinnamic anhydride, a comparable ee but lower yield was observed. Less efficient activation of the silylated indene by the acetate, as compared to the fluoride anion, could account for this observation. Consistent with the proposed mechanism, cinnamoyl chloride is not a suitable annulation partner due to the inability of the chloride anion to activate the silylindene.

2.3. Asymmetric Protonations of Ketenes

Due to their biological activity, arylpropionic acids constitute an important family of targets for asymmetric synthesis.[86] One route to optically active arylpropionic acid derivatives involves the stereoselective addition of an alcohol to an arylalkylketene. Nearly all investigations of this process have relied upon the use of a stoichiometric amount of a chiral alcohol, such as (*R*)-pantolactone, to induce asymmetry (up to 99.5:0.5; eq 17).[87]



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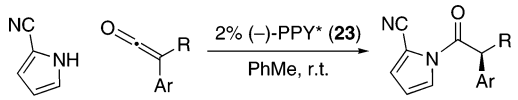
One of the earliest attempts to conduct the reaction in a catalytic asymmetric manner was reported by Pracejus as

Table 16. Enantioselective Addition of 2-Cyanopyrrole to Ketenes



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

[a] 5% catalyst was used.

early as 1960. Pracejus examined the quinidine-catalyzed addition of methanol to two ketenes, and he was able to obtain modest levels of enantioselection to a maximum of 76% ee.[88]

Fu examined catalytic enantioselective addition of alcohols to ketenes. The first report involved the treatment of ketenes with MeOH in the presence of planar-chiral azaferrocenes, which furnished modest levels of enantioselection (68−80% ee).[89]

The limitations of the Pracejus and Fu methods in terms of reaction scope and enantioselection prompted further exploration in this area. Of particular interest was the nature of the nucleophile used in the reaction. In 2002, Hodous and Fu reported a study of the addition of an achiral nitrogen nucleophile to a ketene.[90] The nucleophilicity of the amine was crucial for success as simple amines can rapidly add to ketenes in the absence of a catalyst. Initial studies focused on less reactive nitrogen nucleophiles, and it was determined that pyrroles do not react at room temperature with ketenes such as phenylethylketene. In contrast, additions proceed rapidly when a planar-chiral DMAP derivative is present. After surveying a variety of pyrroles, commercially available 2-cyanopyrrole was found to give the highest levels of enantioselection in a reaction with phenylethylketene catalyzed by PPY* (**23**) (Table 16, entry 1).

Examination of a variety of ketenes established that this new method displayed an increase in reaction scope and enantioselectivity (81−98% ee) compared to earlier studies. Particularly noteworthy are the results for sterically demanding phenyl-isopropylketene and phenyl-*tert*-butylketene (entries 2−3), which furnish α-stereocenters that are relatively difficult to generate by other methods (e.g., alkylation). An increase in the size of the aryl group generally leads to an increase in enantiomeric excess (entry 4), and heteroaryl substituents are tolerated in this process (entry 5).

The *N*-acylpyrrole products could be derivatized under mild conditions with ≤2% racemization. For example, chiral acids, esters, and amides can be generated through reactions with hydroxide, alcohols, and amines, respectively. In addition, by appropriate choice of reducing agent, an aldehyde or alcohol can be produced selectively.

An investigation of the origin of stereoselection was pursued by Hodous and Fu, focusing on the coupling of 2-cyanopyrrole with phenyl-*tert*-butylketene. When 2-cyanopyrrole was treated with PPY* (**23**), deprotonation of the pyrrole and formation of an ion pair **49** resulted. This ion pair, not PPY* (**23**) itself, is the resting state of the catalyst during the reaction. The reaction was found to be first order in phenyl-*tert*-butylketene, first order in PPY* (**23**), and zero order in 2-cyanopyrrole. A primary kinetic isotope effect of

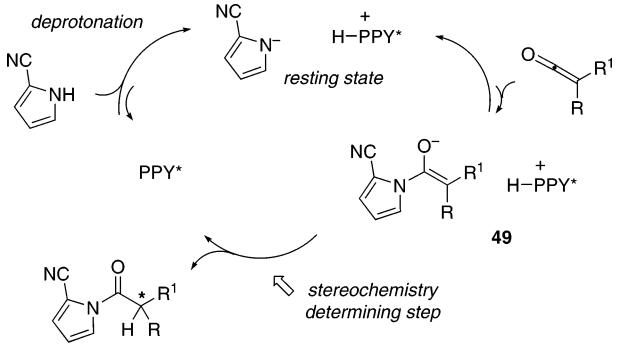
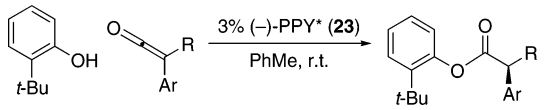


Figure 27. Mechanism for the enantioselective addition of 2-cyanopyrroles to ketenes.

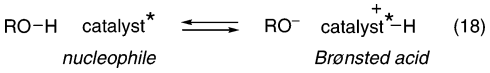
Table 17. Catalytic Enantioselective Synthesis of Esters from Ketenes



entry	Ar	R	% ee	% yield
1	Ph	Et	91	89
2	Ph	Me	79	87
3	Ph	*i*-Pr	91	66
4	*o*-tolyl	Et	92	84
5	3-thienyl	*i*-Pr	79	94

~5 is observed (1-*H*-2-cyanopyrrole versus 1-*D*-2-cyanopyrrole). On the basis of these data, Hodous and Fu proposed that enantioselective additions of pyrroles to ketenes catalyzed by PPY* (**23**) proceed through the pathway illustrated in Figure 27. In the stereochemistry-determining step of the catalytic cycle, proton transfer occurs to produce a chiral *N*-acylpyrrole and liberate catalyst **23**. The role of catalyst **23** is to serve, in protonated form, as a chiral Brønsted acid. This contrasts with the typical mode of reactivity for these catalysts where they function as chiral nucleophiles (Lewis bases).

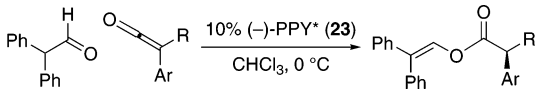
This first example of a planar-chiral DMAP derivative serving as a chiral Brønsted acid was further exploited by Wiskur and Fu for the enantioselective synthesis of esters from ketenes.[91] In order to favor a mechanism in which the catalyst serves as a Brønsted acid, rather than a nucleophile, more acidic alcohols were examined in order to generate an ion pair (eq 18).



It was determined that phenol reacts with PPY* (**23**) to quantitatively produce an ion pair (eq 18). Wiskur and Fu then examined a number of different phenols and discovered that addition of sterically demanding 2-*tert*-butylphenol to phenylethylketene proceeds with the highest level of selectivity (91% ee, 89% yield; Table 17, entry 1). The scope of the reaction was then examined. Although only moderate ee was obtained for the reaction of phenylmethylketene (entry 2), good ee's were observed for a range of other phenylalkylketenes (entries 3−5). The reaction predominantly affords the enantiomer that had been anticipated on the basis of the mechanistic hypothesis of chiral Brønsted acid catalysis.

In 2005, Schaefer and Fu described an interesting variant of this asymmetric protonation of ketenes in which a carbonyl

Table 18. Catalytic Asymmetric Couplings of Aldehydes with Ketenes



entry	Ar	R	% ee	% yield
1	Ph	Et	91	84
2	Ph	Me	78	74
3	Ph	*i*-Pr	98	95
4	Ph	*t*-Bu	88	96
5	*o*-tolyl	Et	98	99

compound serves as the proton source.[92] In a typical experiment, a ketene was added dropwise to a mixture of a carbonyl compound and PPY* (**23**). Diphenylacetaldehyde is the reaction partner of choice with phenylethylketene (91% ee, 84% yield; Table 18, entry 1), whereas a related ketone and an aliphatic aldehyde are not suitable.

This methodology proved to be the most general in terms of reaction scope as a broad array of enol esters of α-arylalkanoic acids can be prepared via couplings of ketenes with diphenylacetaldehyde. Thus, reactions of phenylalkylketenes in which the alkyl group ranges in size from methyl to *tert*-butyl proceed with moderate to excellent enantiomeric excess (entries 2−4). The reaction is also tolerant of ortho-substituted aryl groups (entry 5).

The resulting enol esters are more reactive than the aryl esters produced by addition of 2-*tert*-butylphenol to ketenes and can be readily converted into other useful families of compounds. For example, they can be hydrolyzed and reduced under mild conditions without racemization.

Two possible mechanisms were proposed for the coupling of ketenes with diphenylacetaldehyde to generate enol esters. One possible pathway (top of Figure 28) involves nucleophilic addition of PPY* (**23**) to the ketene furnishing chiral enolate **50**. This enolate then undergoes diastereoselective protonation by diphenylacetaldehyde to furnish ion pair **51**. Acylation of the enolate by the resulting acylpyridinium ion then produces the enantioenriched enol ester and regenerates the catalyst. Alternatively, PPY* (**23**) may be acting as a Brønsted base/acid (bottom of Figure 28). According to this pathway, PPY* (**23**) deprotonates the aldehyde, furnishing an achiral enolate (**52**). This nucleophilic enolate then adds to the electrophilic ketene to produce a new achiral enolate (**53**), which undergoes enantioselective protonation by its counterion (protonated PPY*, a chiral Brønsted acid), thereby generating the enol ester.

Schaefer and Fu made a number of experimental observations relevant to the reaction pathway. When PPY* (**23**) was mixed with one equivalent of diphenylacetaldehyde, there was no evidence for deprotonation of the aldehyde to form an ion pair, which contrasts with the previous method involving 2-*tert*-butylphenol. On the other hand, in the presence of PPY* (**23**), the α proton of diphenylacetaldehyde exchanges rapidly with D_2O at 0 °C (in the absence of PPY* (**23**), there is essentially no exchange after 3 days at room temperature). In addition, the sense of stereochemical induction is the same as that observed using 2-*tert*-butylphenol.

The catalytic asymmetric methodologies for the synthesis of α-arylalkanoic acids involving chiral DMAP catalysts allow access to this useful class of compounds in often excellent enantiomeric excess. The three reported methodologies involving Fu's planar-chiral catalysts afford esters or amides that can be readily derivatized and represents a

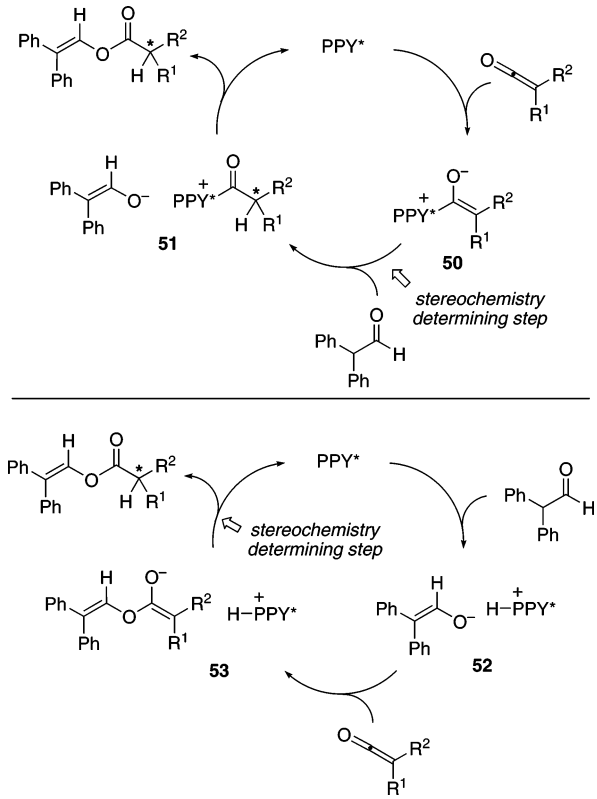
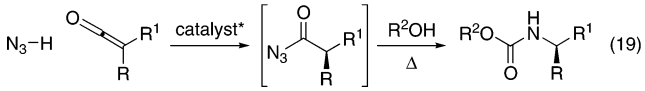


Figure 28. Proposed mechanisms for the enantioselective coupling of diphenylacetaldehyde to ketenes.

practical alternative to using stoichiometric quantities of chiral alcohols.[93] Furthermore, these methodologies allow access to α-chiral arylalkanoic acid derivatives that cannot be readily accessed by alkylation chemistry using chiral auxiliaries.

In 2007, Fu extended the chiral Brønsted acid mode of reactivity of planar-chiral DMAP derivatives to the synthesis of chiral amines.[94] In this case, the Brønsted acid source is HN_3. Use of HN_3 generates an acyl azide intermediate, which can undergo a Curtius rearrangement to furnish enantioenriched amines (eq 19).



(19)

Previous studies have shown that Brønsted acids derived from pyrroles and phenols furnish the highest levels of enantioselectivity when addition of the nucleophile is conducted at low concentrations and in nonpolar solvents. One rationale for these observations is that the achiral HX competes for protonation of the enolate of the ion pair. A survey of a variety of planar-chiral catalysts revealed that in order to obtain acceptable ee values with HN_3 acting as the Brønsted acid a planar-chiral pyridine (**54**) lacking a strong electron-donating group in the 4 position would be necessary. This increases the acidity of the ion pair formed between catalyst and HN_3 relative to HN_3. Planar-chiral catalyst (**54**), containing a methyl group in the 4 position of the pyridine, was prepared with this goal in mind (Scheme 11).

Catalyst **54** was prepared in an analogous manner to PPY* (**23**) through complexation of **56** (available in two steps from the pyridine *N*-oxide **55**) to a ferrocenyl subunit. Suzuki coupling with methylboronic acid and separation of the

Scheme 11

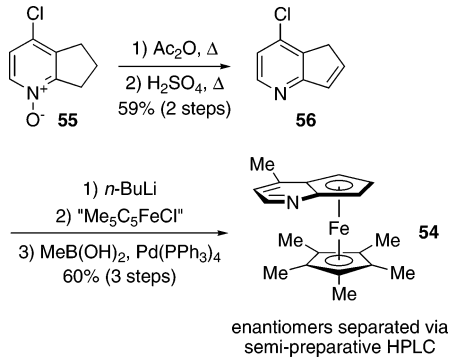
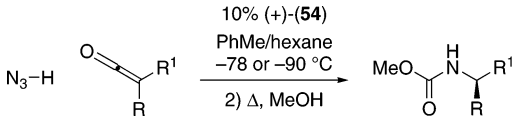


Table 19. Catalytic Asymmetric Addition of HN_3 to Ketenes



entry	Ar	R	% ee	% yield
1	Ph	*i*-Pr	96	93
2	Ph	cyclohexyl	96	92
3	Ph	*t*-Bu	76	94
4	*o*-tolyl	Et	94	93
5	Ph	Et	4	89

enantiomers on chiral semipreparative HPLC furnished the enantiomerically pure catalyst **54**.

Planar-chiral pyridine derivative **54** furnished the highest ee values for ketenes with a bulky alkyl (Table 19, entries 1−3) or aryl (entry 4) substituent. Control experiments reveal that for unhindered ketenes such as phenylethylketene the uncatalyzed addition of HN_3 is rapid even at low temperature (entry 5).

Mechanistically, HN_3 addition to the ketene is believed to proceed in a similar fashion to that observed with 2-cyanopyrrole (Figure 29). When the catalyst (**54**) is treated

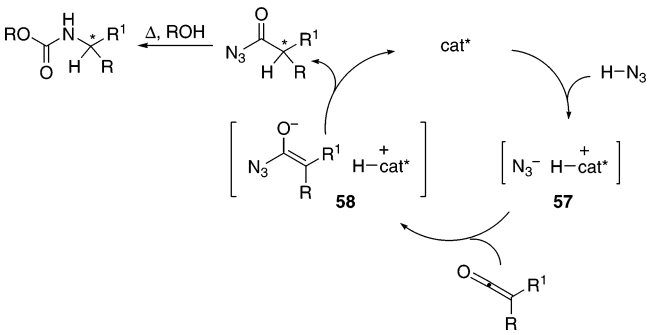


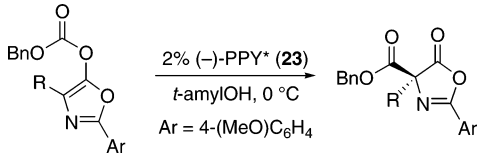
Figure 29. Mechanism for the enantioselective addition of HN_3 to ketenes.

with HN_3, deprotonation occurs, resulting in formation of an ion pair (**57**; chiral Brønsted acid). The azide anion adds to the ketene forming an achiral-enolate (**58**). In the stereochemistry-determining step of the catalytic cycle, proton transfer from the Brønsted acid produces a chiral acyl azide and liberates the catalyst **54**. In a subsequent step, thermally induced rearrangement of the acyl azide then furnishes the carbamate.

2.4. C-Acylations

The synthesis of chiral quaternary carbon stereocenters is an important challenge in asymmetric catalysis.[95] The enantioselective delivery of an acyl group to a prochiral enolate in an intramolecular or intermolecular fashion represents an efficacious method for the synthesis of quaternary carbons.

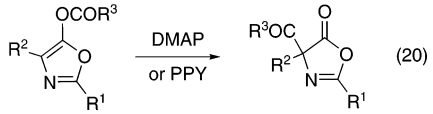
Table 20. Rearrangements of O-Acylated Azlactones



R	% ee	% yield
Me	91	94
Et	90	93
CH_2Ph	90	93
allyl	91	93
CH_2CHMe_2	92	95
CH_2CH_2SMe	88	94

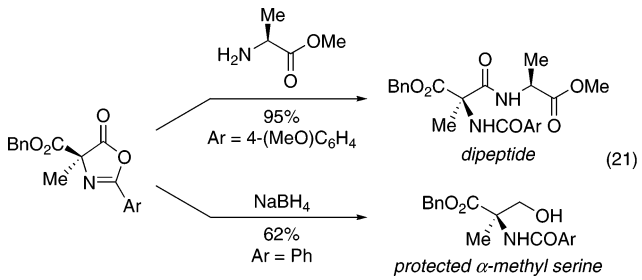
2.4.1. O-to-C Rearrangements of Acyl Groups

In 1970, Steglich and Höfle reported that DMAP and PPY catalyze the rearrangement of O-acylated azlactones to their C-acylated isomers, thereby generating both a new carbon−carbon bond and a new quaternary stereocenter (eq 20).[96] The products of these rearrangement processes represent useful building blocks for synthetic organic chemistry since nucleophiles react preferentially at the azlactone carbonyl group to provide protected α-alkylated α-amino acids.[97]



In view of Steglich's discovery that the rearrangement of O-acylated azlactones is subject to catalysis by DMAP, Ruble and Fu explored rearrangements with planar-chiral catalyst PPY* (**23**).[98] Optimization studies of the rearrangement revealed that an aryl group present in the 2 position of the azlactone furnished the highest enantioselectivities with the 4-methoxyphenyl group leading to the most rapid rates of rearrangement. Under the optimized conditions, PPY* (**23**) catalyzes the rearrangement of an array of O-acylated azlactones with high enantioselectivity and in excellent yield (Table 20).

The utility of these rearranged products was demonstrated by their conversion to dipeptide and α-methylserine derivatives (eq 21).



The rate of rearrangement was found to be zero order in substrate. This observation is consistent with the pathway outlined in Figure 30, wherein the resting state of the system is ion pair **59**. The crossover experiment illustrated in Scheme 12 indicates that reaction of the O-acylated azlactone with

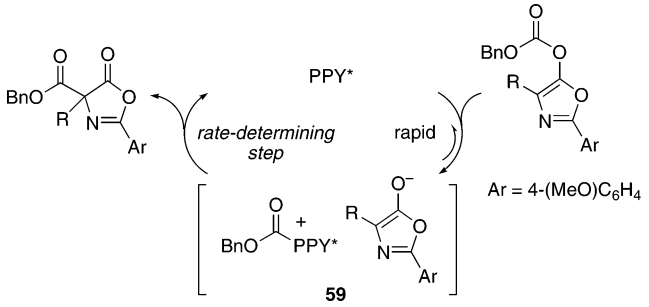
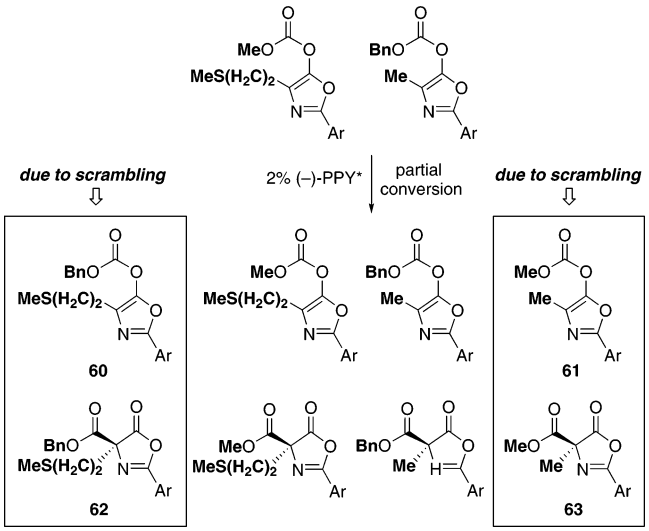


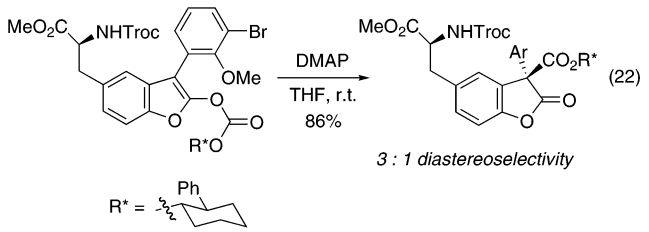
Figure 30. Mechanism for the rearrangement of O-acylated azlactones.

Scheme 12



PPY* (**23**) (Figure 30, first step) is reversible (thereby forming scrambled "starting materials" **60** and **61**) and that the counterions of the ion pair can exchange (thereby forming compounds **60**−**63**). In addition, Ruble and Fu demonstrated that the rearranged products are configurationally stable under the reaction conditions, which provides evidence that the final step (Figure 30) is irreversible.

In 1986, Black demonstrated that DMAP also catalyzes the rearrangement of O-acylated benzofuranones to their C-acylated isomers.[99] This rearrangement was then employed by Moody[100] to generate the quaternary stereocenter in studies directed toward the synthesis of the originally assigned structure of the potent anti-cancer agent diazonamide A.[101] A few years later, Vedejs described a modestly diastereoselective variant of the Black rearrangement (eq 22).[102]



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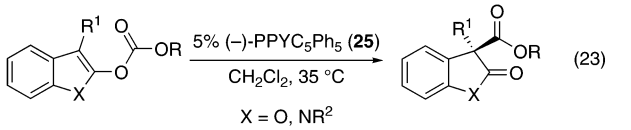

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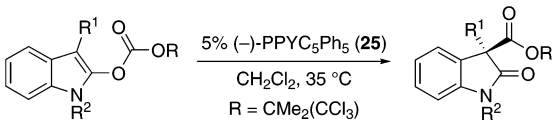
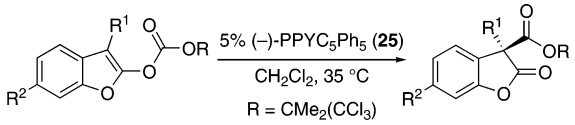
Table 21. Rearrangement of Oxindole Derivatives



entry	R^1	R^2	% ee	% yield
1	Ph	Me	99	91
2	2-thienyl	Me	95	81
3	Ph	Bn	98	88
4[a]	benzyl	Me	94	82
5[a]	Me	Me	93	72

[a] 10% catalyst was used.

Table 22. Rearrangement of Benzofuranone Derivatives



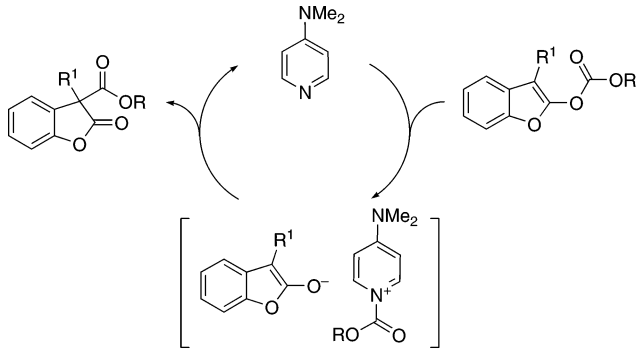
entry	R^1	R^2	% ee	% yield
1	Ph	H	97	81
2	Bn	H	88	95
3[a]	Me	Me	90	93

[a] This reaction was run at −12 °C with 10% catalyst.

On the basis of the reassigned structure of diazonamide A,[101] a C-acylation strategy involving an oxindole instead of a benzofuranone would be required. In light of the potential significance of the reaction products, Hills and Fu reported their findings on the use of planar-chiral DMAP catalysts in asymmetric rearrangements of O-acylated oxindoles and benzofuranones (eq 23).[103] In preliminary studies, they discovered that $PPYC_5Ph_5$ (**25**) successfully catalyzes the rearrangement of an oxindole-derived carbonate to provide a new quaternary stereocenter with promising ee (R = Me; 58% ee). It was subsequently determined that an increase in the bulk of the carbonate group and electronic activation, specifically, the use of a trichloro-*tert*-butyl group (derived from commercially available 2,2,2-trichloro-1,1-dimethylethyl chloroformate), led to excellent enantiomeric excess (98% ee).

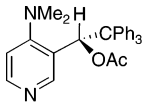
With trichloro-*tert*-butoxycarbonyl as the migrating group, rearrangements catalyzed by $PPYC_5Ph_5$ (**25**) afford a variety of oxindole derivatives with high enantioselectivity (Table 21). The O-to-C rearrangements proceed cleanly with either aromatic or heteroaromatic groups in the 3 position (R^1; entries 1−3). 3-Alkyl-substituted O-acylated oxindoles can also be employed as substrates, although these rearrangements are slower and require 10% catalyst loading in order to obtain a satisfactory yield (entries 4−5). The reaction is not limited to *N*-methyl-substituted oxindoles: catalyst **25** also rearranges the *N*-benzyl-protected heterocycle in high ee (entry 3).

The conditions developed by Hills and Fu for O-to-C rearrangements of oxindole derivatives were directly applicable to O-acylated benzofuranones (Table 22). Thus, for both 3-aryl- and 3-alkyl-substituted compounds, $PPYC_5Ph_5$ (**25**) generates the new carbon−carbon bond of the quaternary stereocenter with very good enantioselection. Under these standard reaction conditions, the benzofuranone-derived substrates react more rapidly than the oxindole-derived compounds.



64

Figure 31. Mechanism of DMAP-catalyzed rearrangements of O-acylated benzofuranones.



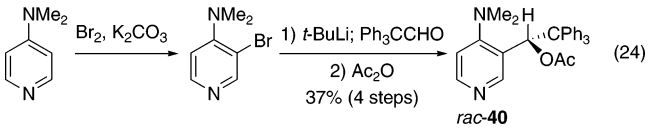
40 (TADMAP)

Figure 32. Vedejs second-generation catalyst.

Concerning the mechanism for the rearrangement, Black suggested that DMAP-catalyzed rearrangements of O-acylated benzofuranones proceed through the pathway illustrated in Figure 31. In support of this proposed mechanism, Hills and Fu have been able to obtain a low-resolution X-ray crystal structure of the ion pair (**64**) with $PPYC_5Ph_5$ (**25**).[103]

More recently, Vedejs demonstrated that introduction of a chiral center at C3 of DMAP (TADMAP **40**; short for 2,2,2-triphenyl-1-acetoxyethyl DMAP, Figure 32) furnishes a competent catalyst that delivers high levels of enantioselectivity in intramolecular O-to-C-acyl rearrangements.[104] It was hypothesized that the *N*-acylpyridinium intermediate would be restricted to a geometry where the dialkylamino group is nearly coplanar with the pyridine ring, thereby maximizing nitrogen lone pair delocalization. The preferred orientation of the C3 substituent would place the benzylic hydrogen toward the *ortho*-dialkylamino group. Gotor also examined additional analogues of this catalyst involving less sterically demanding substituents than the trityl group.[105]

Synthesis of the 3-substituted DMAP derivative **40** developed by Vedejs is very efficient. Triphenylacetaldehyde was treated with the aryllithium derived from 3-bromo-4-(dimethylamino)pyridine, and the resulting alkoxide was quenched with Ac_2O. Thus, racemic **40** was prepared on gram scale in four steps from DMAP in 37% overall yield (eq 24).[104]

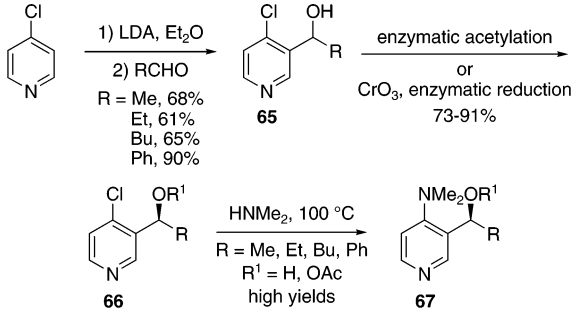


rac-**40** (24)

Enantiomerically pure **40** was obtained via a classical resolution using (−)-camphorsulfonic acid as the resolving agent. Using this protocol, 7.4 g of racemate was resolved to give 0.7 g (9% yield) of (−)-**40** (>99% ee) and 1.0 g (14% yield) of (+)-**40** (98.3% ee) with 4.7 g (64%) of scalemic material available for further resolution.[104]

Gotor reported an alternative method for the synthesis of various analogues of TADMAP (Scheme 13).[105] Thus, treatment of 4-chloropyridine with 2 equiv of LDA followed by quenching with an appropriate aldehyde furnished the

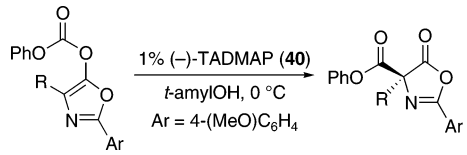
Scheme 13



65

66 **67**

Table 23. Steglich Rearrangement by (−)-TADMAP (40)

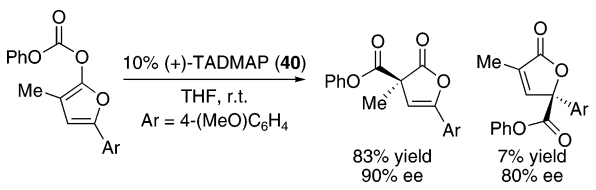


R	% ee	% yield
Me	91	95
CH_2Ph	95	99
allyl	91	90
CH_2CHMe_2	91	90
Ph	58	95

corresponding secondary alcohols **65** in good yields. Kinetic resolution of **65** by lipase-catalyzed transesterification with vinyl acetate or via oxidation with CrO_3 followed by enzymatic reduction (e.g., Baker's yeast) afforded enantiomerically pure alcohols **66** (R^1 = H) in excellent yields (73−91%). Displacement of the chloride with $HNMe_2$ furnished the chiral DMAP derivatives **67** in near quantitative yields.[105]

TADMAP catalyst (**40**) was applied to a catalytic asymmetric Steglich rearrangement (Table 23).[104] *tert*-Amyl alcohol gave the best overall results, although the solvent effect was small. The presence of a 4-methoxyphenyl group in the azlactone was again beneficial in terms of selectivity and reaction rate. The yields and levels of enantioselectivity were similar to those reported by Fu and Ruble. The presence of an aryl group (R = Ph) leads to greatly diminished levels of selectivity.[106]

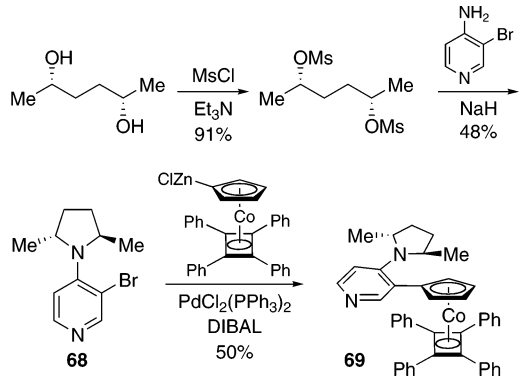
Vedejs also demonstrated that furan enol carbonates rearrange to give a 10:1 mixture of α- and γ-C-carboxylated isomers (eq 25). TADMAP-catalyzed carboxyl migrations of benzofuran and indole-derived enol carbonates also proceed with fair to excellent enantioselectivity (49−92% ee).



83% yield 90% ee 7% yield 80% ee (25)

In 2006, Gotor reported that analogues of TADMAP (**67**) possessing less bulky substituents than the trityl group (R = Me, Bu, Ph) furnish inferior levels of selectivity in Steglich rearrangements of enol carbonates (ee's up to 70%). Furthermore, hindered protecting groups on the secondary alcohol of the catalyst, such as O-benzyloxycarbonyl (Cbz),

Scheme 14

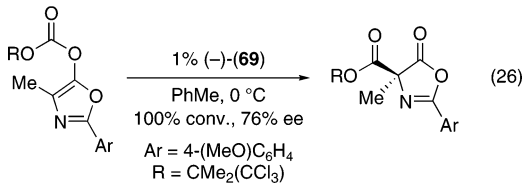


appeared to be detrimental to the enantioselectivity of the rearrangement (R^1 = Ac or Cbz; 55% ee versus 41% ee).[105]

In addition to the research of Fu, other planar-chiral catalysts have also been applied to the Steglich rearrangement. Johannsen reported the application of planar-chiral catalyst **33** to the rearrangement of an O-acylated azlactone.[55] The rearrangement proceeded in 69% yield and with low enantioselectivity (25% ee).

Richards reported application of their first-generation chiral PPY derivative to the Steglich rearrangement.[107] This catalyst was constructed by appending a cobalt−tetraphenylcyclobutadiene moiety to the C3 position of PPY derivative **68**, furnishing catalyst **69** in 22% yield over three steps from (*S*,*S*)-hexane-2,5-diol (Scheme 14).

Catalyst **69** was applied to the asymmetric Steglich rearrangement of azlactones. The highest level of enantioselectivity (up to 76%) was possible when toluene was used as a solvent (eq 26), which is in contrast to the other successful catalysts. Interestingly, when *tert*-amyl alcohol was used as a solvent, racemic material resulted.



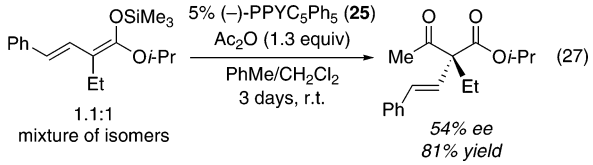
2.4.2. Acylations of Silyl Ketene Acetals

In 2003, Mermerian and Fu reported an *inter*molecular asymmetric delivery of an acyl group to a prochiral enolate.[108] In the proposed mechanism for this transformation, the catalyst reacts with an anhydride to generate an acylpyridinium ion (**70**) along with an acetate counterion (Figure 33). The resulting ion pair is a more active acylating agent than the anhydride itself, and the Lewis-basic acetate is capable of complexing to the Lewis-acidic silicon of a silyl ketene acetal, affording an enolate (**71**). Coupling of the activated components of this new ion pair then furnishes a new quaternary stereocenter.

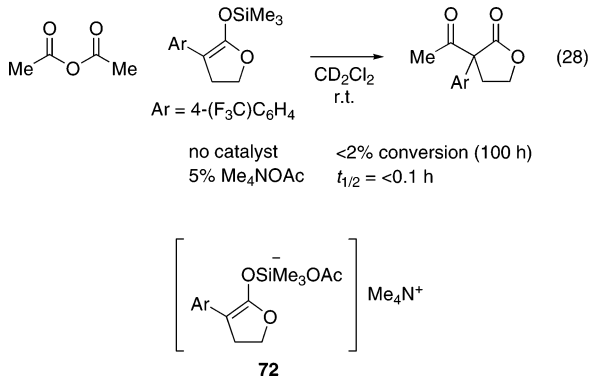
In order to avoid the issue of the *E*/*Z* geometry of the proposed enolate intermediate, the first substrate class that was examined was silyl ketene acetals derived from lactones. With this substrate class, the silyl ketene acetal and Ac_2O do not react in the absence of catalyst. However, $PPYC_5Ph_5$ (**25**) catalyzed the formation of the desired C-acylated products in good yields (Table 24).[108] In a mixture of Et_2O and CH_2Cl_2, satisfactory ee values could be obtained for a variety of aryl- (entries 1−3) and heteroaryl-substituted cyclic silyl ketene acetals (entries 4−5).

The scope of this reaction was extended to include acyclic silyl ketene acetals.[109] Thus, $PPYC_5Ph_5$ (**25**) catalyzes the C-acylation of silyl ketene acetals (1−2:1 mixture of olefin isomers) in very good enantiomeric excess (Table 25). The high ee and high yield obtained establishes that both the *E*- and the *Z*-isomers of the silyl ketene acetals are being converted efficiently into the same enantiomer of product. Optimization of the OR^1 group of the ester revealed that as the ester group increased in size the ee increased. In the case of the very bulky *tert*-butyl ester, high enantioselectivity is achieved at the cost of reduced yield; therefore, the optimum ester from the standpoint of ee and yield was the isopropyl ester. For electron-rich and electron-poor aromatic groups (Ar), the desired quaternary stereocenter is produced in good ee (entries 1−4).

This nucleophile-catalyzed C-acylation process was not limited to aryl-substituted compounds. An alkenyl-substituted silyl ketene acetal is also a suitable substrate (eq 27), although only modest enantiomeric excess is obtained.



In support of the proposed mechanism for the transformation (Figure 33), Mermerian and Fu observed that the C-acylation of silyl ketene acetals by anhydrides is catalyzed by Me_4NOAc (eq 28). Since it is unclear how Me_4NOAc might activate Ac_2O, it is believed that the rate acceleration is likely due to activation of the silyl ketene acetal through generation of either an enolate or a hypervalent silicate (**72**).[110,111] In addition, the enantioselectivity for C-acylations catalyzed by $PPYC_5Ph_5$ (**25**) is essentially independent of the choice of the SiR_3 group of the silyl ketene acetal. This observation would suggest that a free enolate rather than a hypervalent silicate (**72**) is an intermediate.



2.4.3. Acylations of Silyl Ketene Imines

As an extension of the C-acylations of silyl ketene acetals, silyl ketene imines were also examined. Asymmetric acylation of these ambident nucleophiles on carbon would allow access to enantiomerically enriched nitriles in which the cyano group is bound to an all-carbon quaternary stereocenter. Silyl ketene imines are readily prepared upon treatment of a nitrile with a Brønsted base and a silylating agent.[112]

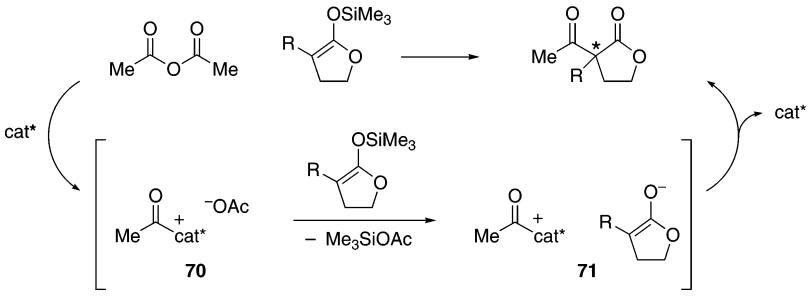
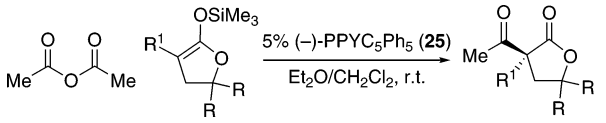


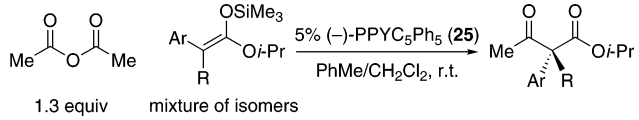
Figure 33. Possible pathway for nucleophile-catalyzed asymmetric C-acylation of silyl ketene acetals.

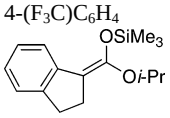
Table 24. Intermolecular C-Acylation of Silyl Ketene Acetals



entry	R^1	R	% ee	% yield
1	Ph	Me	90	80
2	4-(MeO)C_6H_4	Me	95	78
3	4-(F_3C)C_6H_4	H	90	84
4	2-thienyl	Me	76	84
5	3-(*N*-methylindolyl)	Me	94	92

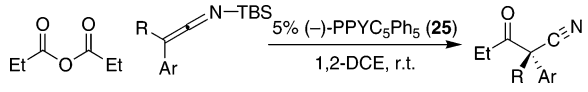
Table 25. C-Acylations of Acylic Silyl Ketene Acetals



entry	Ar	R	isomer ratio	% ee	% yield
1	Ph	Et	1.8:1	85	92
2	4-(MeO)C_6H_4	Et	1.4:1	90	83
3	4-(F_3C)C_6H_4	Et	2.1:1	92	96
4[a]			1.4:1	81	82

[a] CH_2Cl_2 was used as solvent.

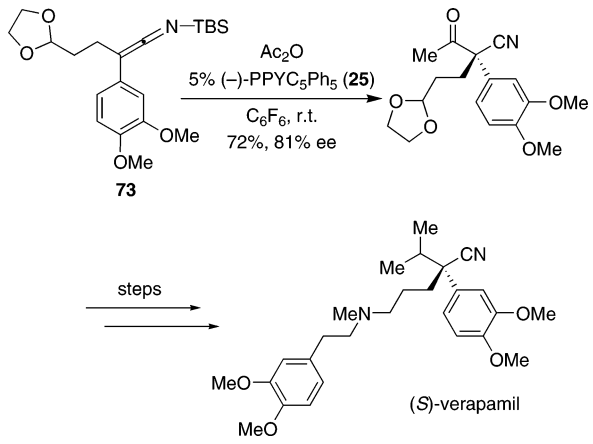
Table 26. Catalytic Asymmetric Synthesis of Quaternary Nitriles



entry	R	Ar	% ee	% yield
1	Me	Ph	81	89
2	CH_2CHMe_2	Ph	83	93
3	cyclopentyl	Ph	69	53
4	Et	4-(MeO)C_6H_4	81	65
5	Et	4-(F_3C)C_6H_4	53	50
6	Et	3-thienyl	77	72

Mermerian and Fu observed that in the presence of $PPYC_5Ph_5$ (**25**), silyl ketene imines undergo C-acylation to furnish α-cyano carbonyl compounds. Upon choosing the appropriate acylating agent, namely, anhydrides, good ee values can be obtained for the process (Table 26).[113] The reaction is sensitive to steric effects with the sterically demanding cyclopentyl-substituted compound reacting with somewhat diminished stereoselectivity (entry 3). With respect to variation of the aromatic ring, introduction of an electron-withdrawing group leads to an erosion in ee (entry 5).

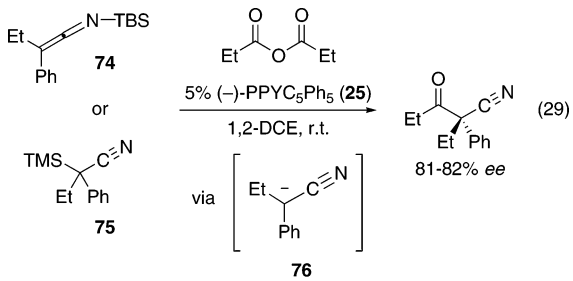
Scheme 15



Heteroaryl ketene imines furnish ee values that are comparable to the phenyl-substituted substrate (entry 6).

The synthetic utility of the reaction was demonstrated in an enantioselective synthesis of the drug verapamil in 31% overall yield from silyl ketene imine **73** (Scheme 15). The target quaternary stereocenter was generated in 81% ee.

In analogy to the chemistry of silyl ketene acetals, Mermerian and Fu believe that the acylations of silyl ketene imines proceed through a pathway that involves dual activation (Figure 34). To provide support for this mechanism, compounds **74** and **75** were subjected to the reaction conditions. The two compounds furnished the α-cyano carbonyl with the same sense and level of enantioselectivity (eq 29). This result is consistent with a common intermediate involving a silicon-free nitrile anion **76** for the two acylation processes (Figure 34).



2.5. Halogenations

The enantioselective synthesis of alkyl halides has received a great deal of interest in recent years.[114] Most of the processes furnish secondary alkyl halides, whereas limited progress has been made in the development of stereoselective methodologies to access tertiary halides.[115,116]

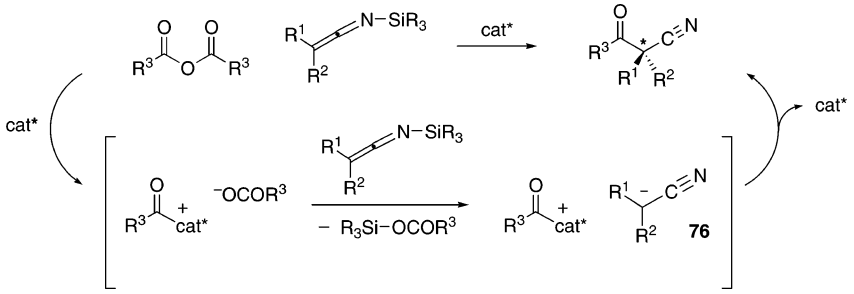
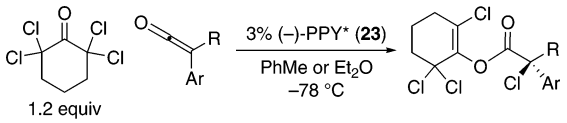


Figure 34. Proposed pathway for nucleophile-catalyzed asymmetric C-acylation of silyl ketene imines.

Table 27. α-Chlorination of Ketenes Catalyzed by (−)-PPY* (23)



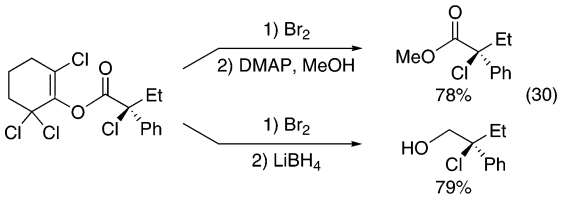
1.2 equiv

entry	Ar	R	% ee	% yield
1	Ph	Me	91	74
2	Ph	Et	94	86
3	Ph	*i*-Bu	85	76
4	*o*-tolyl	Et	67	84
5[a]	Ph	cyclopentyl	65	79

[a] Reaction conducted at −78 °C at room temperature.

In 2007, Fu reported the utility of planar-chiral DMAP derivative, PPY* (**23**), in the successful chlorination of ketenes to furnish enantioenriched tertiary halides (Table 27).[117] A variety of chlorinating agents were surveyed, and 2,2,6,6-tetrachlorocyclohexanone proved to be the best in terms of selectivity and yield. Modest scope is observed for the chlorination with the best enantioselectivities obtained with ketene substrates lacking sterically demanding substituents (entries 1−3). Reduced levels of enantioselectivity are observed when the substrate contains either an ortho-substituted aryl group (entry 4) or an α-branched alkyl substituent (entry 5).

Functionalization of the enol esters can be accomplished through treatment with Br_2 followed by addition of a nucleophile. Nucleophiles such as MeOH or lithium borohydride furnish a methyl ester or an alcohol, respectively, without erosion in enantiomeric excess (eq 30).



(30)

Two possibilities for the mechanism have been postulated for the enantioselective chlorination (Figure 35). In one scenario, an ion pair **77** can be formed by reaction of PPY* (**23**) with 2,2,6,6-tetrachlorocyclohexanone followed by Cl transfer to the achiral enolate **78** to generate the new stereocenter. In an alternative mechanism, PPY* (**23**) adds to the ketene to afford a chiral enolate (**79**), and the achiral chlorinating agent subsequently reacts furnishing a new stereocenter (intermediate **80**) and regenerating the catalyst. Several relevant experimental observations were made; however, they do not preclude either mechanism. The first observation was

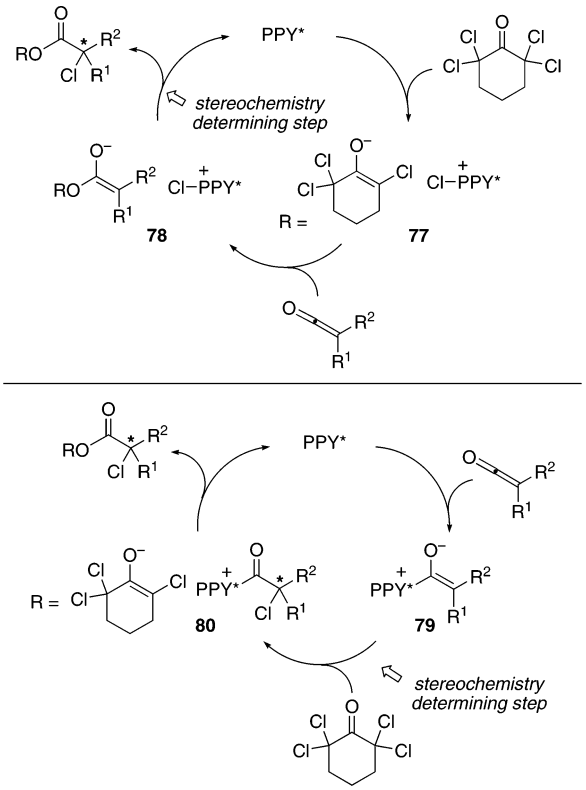


Figure 35. Proposed mechanisms for the enantioselective chlorination of ketenes.

that, according to ^{1}H NMR, the resting state of the catalyst during the reaction is the free catalyst (not chlorinated or acylated). Second, no reaction occurs between 2,2,6,6-tetrachlorohexanone and catalyst at −78 °C or room temperature. Last, the ee value of the product correlates linearly with that of the catalyst, consistent with the presence of monomeric species in the stereochemistry-determining step.

2.6. Michael Addition Reactions

The enantioselective Michael addition reaction provides a powerful tool for carbon−carbon bond formation.[118] Recently, considerable attention has been directed toward application of chiral organocatalysts in this reaction stimulated by the desire to develop environmentally friendly processes.[119]

In 2004, Kotsuki reported the utility of chiral DMAP catalysts in the successful Michael addition reaction involving ketones and nitroolefins.[120] These chiral DMAP derivatives were prepared from cyclic sulfamate **81** (derived from L-prolinol) upon treatment with pyridyllithium reagents (eq 31). Hydrolysis of the resulting sulfamic acid salts under

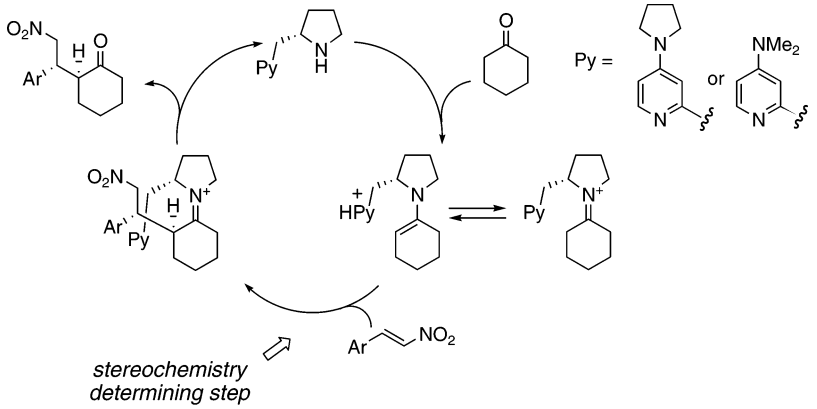
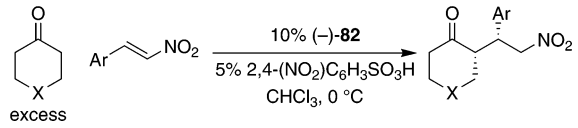


Figure 36. Mechanism for the Michael addition reaction.

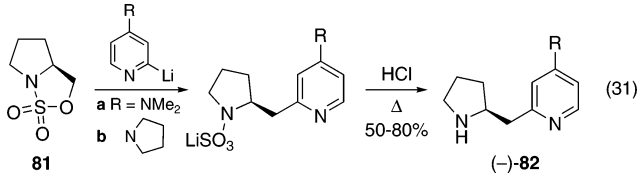
Table 28. Michael Addition Reactions Catalyzed by (−)-82a,b



entry	catalyst	X	Ar	syn:anti	% ee[a]	% yield
1	**82a**	CH_2	Ph	98:2	95	98
2	**82b**	CH_2	Ph	98:2	99	95
3	**82a**	CH_2	1-naphthyl	97:3	98	92
4	**82b**	CH_2	1-naphthyl	97:3	93	100
5	**82a**	CH_2	2-thienyl	94:6	88	92
6	**82b**	CH_2	2-thienyl	93:7	90	98
7	**82a**	S	Ph	99:1	96	95
8	**82b**	S	Ph	98:2	92	98

[a] Enantiomeric excess of the syn diastereomer.

acidic conditions furnished catalysts **82a,b** in moderate to high yields (50−80%; two steps).



(31)

Catalysts **82a,b** were found to successfully promote Michael addition reactions of ketones and nitroolefins (Table 28). These catalysts furnished high yields (92−100%) and high levels of diastereoselectivity (>93:7 syn:anti) and enantioselectivity (88−99% ee) of the desired Michael adduct when 2,4-dinitrobenzenesulfonic acid was used as an additive. Modest scope was observed for cyclohexanone (entries 1−6) and tetrahydrothiopyran-4-one (entries 7−8) substrates and a variety of aryl (entries 1−4, 7, 8) or heteroaryl (entries 5, 6) nitroolefins.[120]

Mechanistically it is believed that treatment of the ketone with catalyst **82** results in enamine formation, which undergoes a face-selective Michael addition to the electrophilic nitroolefin. The DMAP component of the catalyst was anticipated to serve two roles, both as a base component to facilitate enamine formation via α-hydrogen abstraction and to effectively shield one face of the enamine (Figure 36). The corresponding benzene analogue of catalyst **82** was prepared and showed no catalytic activity.

3. Conclusion

During the past decade, chiral DMAP derivatives have established themselves as effective enantioselective catalysts for a broad range of transformations in organic synthesis. Their nucleophilicity and chiral environment can be tuned using a variety of scaffold designs. As a result, chiral analogues of DMAP now provide state-of-the-art methods for the asymmetric synthesis of a number of chiral building blocks.

The challenge in developing a useful enantioselective variant of DMAP is to introduce an effective chiral environment without significantly eroding the nucleophilicity of the catalyst. The high reactivity of DMAP is a consequence of the capacity of the lone pair of the dimethylamino group to donate to the pyridine nitrogen.

Undoubtedly, further improvements in catalyst design and synthesis will lead to additional progress in the development of powerful new asymmetric processes catalyzed by chiral derivatives of DMAP.

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