Asymmetric [3 + 2] annulations catalyzed by a planar-chiral derivative of DMAP†

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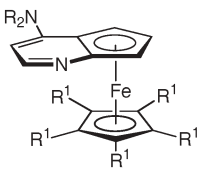
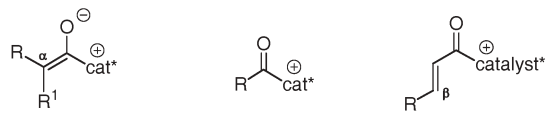
A planar-chiral DMAP derivative catalyzes an intriguing [3 + 2] annulation reaction of silylated indenes to produce diquinanes that bear three contiguous stereocenters (one quaternary and two tertiary).

During the past several years, we have developed applications of planar-chiral derivatives of DMAP (DMAP = 4-(dimethylamino)pyridine; *e.g.*, **1–4**) as asymmetric nucleophilic catalysts for a variety of processes. In some of these transformations, the key intermediate is a chiral enolate (**A**), which reacts at the α position with an electrophile to furnish the enantioenriched target (*e.g.*, arypropionic acid derivatives,[1] β-lactams,[2] and β-lactones[3]). In other processes, the critical species is a chiral acylpyridinium ion (**B**), which acylates a nucleophile (*e.g.*, kinetic resolutions of alcohols/amines[4] and C-acylations of enolates[5]). In this communication, we describe a third mode of reactivity for these DMAP derivatives, specifically, transformations wherein the central role is played by a chiral α,β-unsaturated acylpyridinium ion (**C**), which reacts in the β position with a nucleophile.

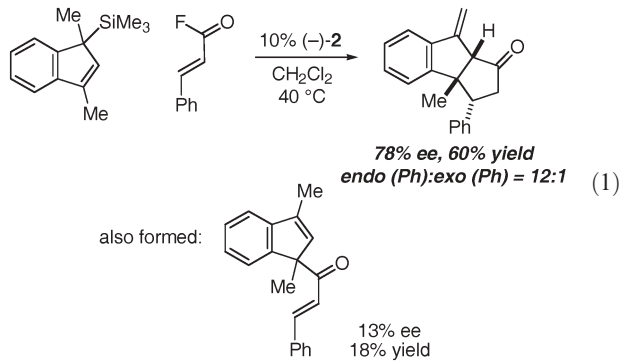


NR_2 =		R^1 =	
dimethylamino		Me	(–)-**1**
pyrrolidino		Me	(–)-**2**
dimethylamino		Ph	(–)-**3**
pyrrolidino		Ph	(–)-**4**



A	**B**	**C**
α carbon serves as a nucleophile	carbonyl carbon serves as an electrophile	β carbon serves as an electrophile

In an early study, we determined that complex (−)-**2** catalyzes the diastereo- and enantioselective synthesis of a diquinane derivative[6] from a silylated indene and cinnamoyl fluoride (eqn (1)).[7] Three contiguous stereocenters (one quaternary and two tertiary) are created in this intriguing annulation process.



(1)

A possible mechanism for this transformation is illustrated in Fig. 1. According to this hypothesis, the nucleophilic catalyst reacts with the acid fluoride to furnish ion pair **1**. The fluoride ion then binds to the silyl group of the indene[8] to provide a new ion pair (**2**). Conjugate addition of the indenyl nucleophile to its α,β-unsaturated acylpyridinium counterion produces a zwitterion (**3**) that bears two new stereocenters. Next, fragmentation releases the catalyst and affords ketene **4**, which cyclizes *via* an ene-type process to generate the observed product.[9]

If cinnamic anhydride, rather than cinnamoyl fluoride, is employed as the substrate, a comparable ee, but a lower yield, is observed (eqn (2)), perhaps due to less efficient activation of the indene by acetate,[10] as compared to fluoride, anion. The use of acid fluoride that is generated *in situ* leads to results that are similar to acid fluoride that is separately prepared and purified by chromatography (eqn (2)). Cinnamoyl chloride is not a suitable

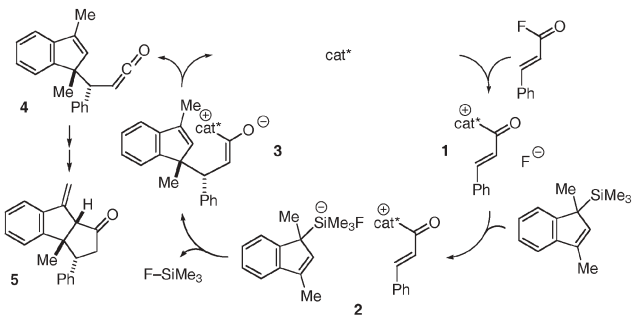


Fig. 1 Possible mechanism for nucleophile-catalyzed asymmetric annulations of indenes with α,β-unsaturated carbonyl compounds.

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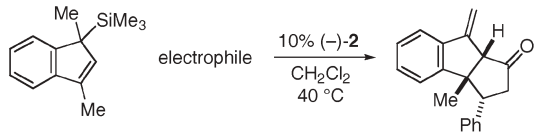
‡ Correspondence concerning the crystal structure illustrated in Fig. 2 should be directed to P. Müller: pmueller@MIT.EDU.

annulation partner (eqn (2)), presumably due to the ineffectiveness of chloride anion as an activator of the silylindene.

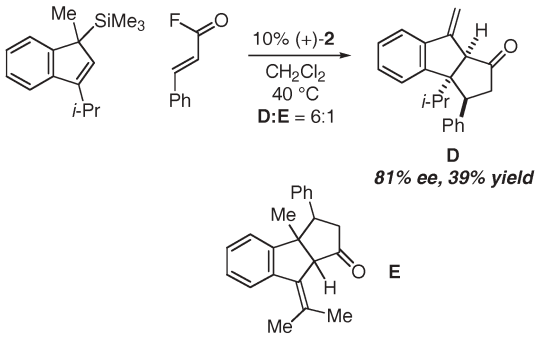


(2)

electrophile	ee (%)	yield (%)
cinnamoyl fluoride	78	60
cinnamic anhydride	78	31
cinnamoyl chloride/$[Ph_3SiF_2]NBu_4$	74	54
cinnamoyl chloride	–	<2

We have determined that an array of cinnamoyl fluorides and related compounds may be used in this catalytic asymmetric annulation process. Thus, electronically diverse (Table 1, entries 2–4), as well as *ortho*-substituted (entries 5 and 6; somewhat lower yields are obtained), aryl substituents can be employed. In addition, heteroaryl groups are tolerated in the β position (entries 7 and 8).[11]

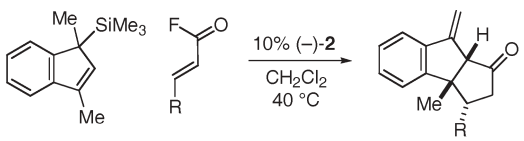
Interestingly, this enantioselective [3 + 2] reaction can be applied to annulations of unsymmetrical indenes. Thus, an isopropyl/methyl-substituted substrate reacts to provide a 6 : 1 ratio of **D** : **E** (eqn (3)).



(3)

We have obtained an X-ray crystal structure of the *N*-cinnamoylated pyridinium salt derived from (+)-**2**§ (Fig. 2).[12] The cinnamoyl group is essentially coplanar with the heterocycle, allowing overlap between the π systems of these subunits. With regard to the orientation around the N–C (carbonyl carbon) bond, the carbonyl oxygen, rather than the larger alkenyl group, is

Table 1 Catalytic asymmetric [3 + 2] annulations



Entry	R	Yield[a,b] (%)	ee[a] (%)	dr[a]
1	Ph	60	78	12 : 1
2	3-F–C_6H_4	51	58	7 : 1
3	3,5-$(MeO)_2C_6H_3$	61	70	8 : 1
4	4-Br–C_6H_4	52	70	9 : 1
5	2-Me–C_6H_4	41	66	7 : 1
6	1-Naphthyl	42	70	9 : 1
7	2-Furyl	47	75	6 : 1
8	3-Furyl	48	77	9 : 1

[a] Average of two experiments. [b] Isolated yield of the major diastereomer.

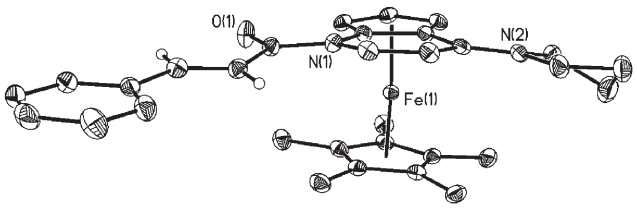


Fig. 2 ORTEP illustration, with thermal ellipsoids drawn at the 35% probability level, of *N*-cinnamoylated (+)-**2** (for the sake of clarity, the PF_6 counterion and most of the hydrogens have been omitted).

positioned on the side of the upper cyclopentadienyl ring, presumably for steric reasons. The α,β-unsaturated carbonyl system lies in an s-*cis* conformation. The crystal structure suggests that nucleophiles might prefer to add to the si face of the β carbon, which is consistent with the stereochemistry that we observe in the annulation process (*cf.* eqn (3)).

Thus, we have established that planar-chiral DMAP derivatives catalyze intriguing [3 + 2] annulation reactions of silylated indenes to produce diquinanes that bear three contiguous stereocenters (one quaternary and two tertiary). We believe that this process represents the first example of a mode of reactivity for these DMAP derivatives wherein a transiently generated α,β-unsaturated acylpyridinium ion (*e.g.*, **C**) serves as an acceptor in a stereoselective conjugate addition reaction. In future work, we will exploit the utility of such intermediates in other catalytic asymmetric processes.

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Notes and references

§ Crystallographic data for *N*-cinnamoylated (+)-**2** (Fig. 2): $C_{31}H_{35}F_6FeN_2OP$, formula weight: 652.43, tetragonal, *P*4(3)2(1)2, a = b = 11.9811(3) Å, c = 40.4968(19) Å, V = 5813.2(3) Å^3, Z = 8, μ = 0.641 mm^{-1}, reflections collected: 124357, independent reflections: 7504 [R(int) = 0.0955], final R indices [$I > 2\sigma(I)$]: $R1$ = 0.0405, $wR2$ = 0.0862, R indices (all data): $R1$ = 0.0501, $wR2$ = 0.0904.

Crystallographic data for the product of entry 4 of Table 1 (generated by (+)-**2**): $C_{20}H_{17}BrO$, formula weight: 353.25, orthorhombic, *P*2(1)2(1)2(1), a = 7.2277(14) Å, b = 14.583(3) Å, c = 15.656(3) Å, V = 1650.2(5) Å^3, Z = 4, μ = 2.490 mm^{-1}, reflections collected: 9518, independent reflections: 3593 [R(int) = 0.0238], final R indices [$I > 2\sigma(I)$]: $R1$ = 0.0328, $wR2$ = 0.0694, R indices (all data): $R1$ = 0.0437, $wR2$ = 0.0728. CCDC 294368 and 294369. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b603172b.

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6 For a review that includes methods for the synthesis of diquinanes, see: G. Mehta and A. Srikrishna, *Chem. Rev.*, 1997, **97**, 671.
7 The use of other potential chiral nucleophilic catalysts, including quinidine and a variety of tertiary phosphines, does not lead to ring formation.
8 For leading references to the role of hypervalent silicon in synthetic organic chemistry, see: S. Rendler and M. Oestrich, *Synthesis*, 2005, 1727.
9 (a) A ^{1}H NMR study indicates that, during the catalytic process, the resting state of the catalyst is as the free catalyst. (b) In the absence of catalyst **2**, no reaction is observed.
10 For examples of and leading references to acetate-induced activation of silylated nucleophiles, see: Y. Kawano, N. Kaneko and T. Mukaiyama, *Chem. Lett.*, 2005, **34**, 1508; A. H. Mermerian and G. C. Fu, *J. Am. Chem. Soc.*, 2005, **127**, 5604.
11 (a) Highly sterically demanding indenes or acid fluorides are not suitable annulation partners. (b) Attempted reaction of acid fluorides that bear an alkyl, rather than an aryl, group in the β position leads to little or none of the desired product. (c) The absolute configurations of the annulation products were assigned on the basis of an X-ray crystallographic analysis of the product of the annulation illustrated in entry 4 of Table 1 (catalyzed by (+)-**2**).
12 This was synthesized by reaction of (+)-**2** with cinnamoyl chloride, followed by exchange of the counterion through treatment with $AgPF_6$ (for details, see the electronic supplementary information, ESI†).

