

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

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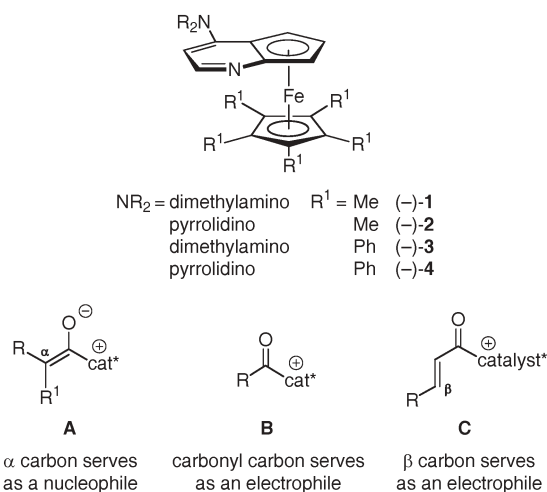
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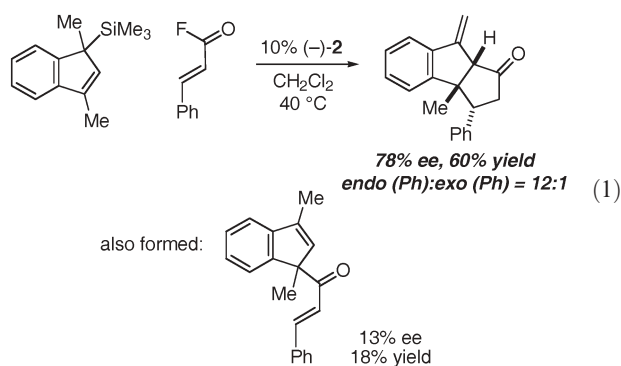
A planar-chiral DMAP derivative catalyzes an intriguing [3 + 2] annulation reaction of silylated indenes to produce diquinanes that bear three contiguous stereocenters (one quaternary and two tertiary).

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., arylpropionic acid derivatives,¹ β -lactams,² and β -lactones³). In other processes, the critical species is a chiral acylpyridinium ion (B), which acylates a nucleophile (e.g., kinetic resolutions of alcohols/amines⁴ and C-acylations of enolates⁵). 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.



In an early study, we determined that complex (–)-2 catalyzes the diastereo- and enantioselective synthesis of a diquinane derivative⁶ 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.



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 indene⁸ 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

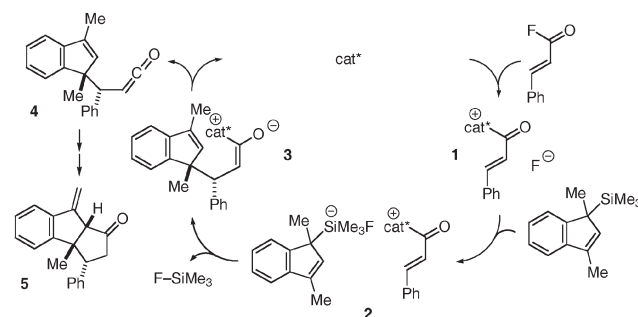


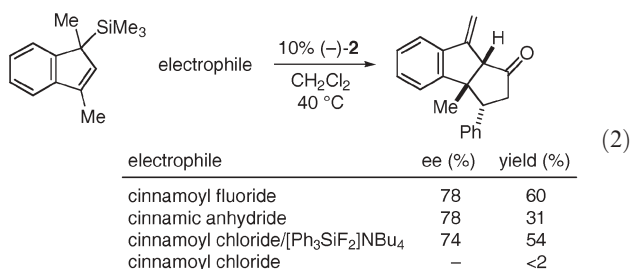
Fig. 1 Possible mechanism for nucleophile-catalyzed asymmetric annulations of indenes with α,β -unsaturated carbonyl compounds.

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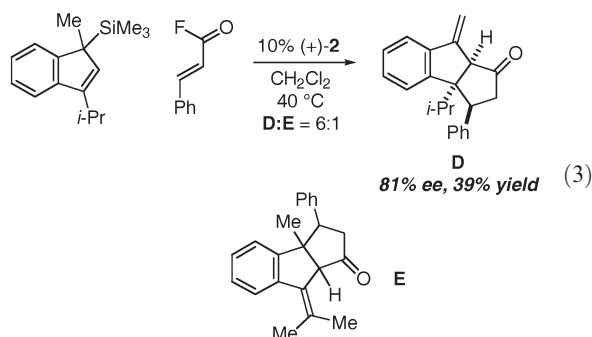
‡ Correspondence concerning the crystal structure illustrated in Fig. 2 should be directed to P. Müller: pmueller@MIT.EDU.

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



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 indenenes. Thus, an isopropyl/methyl-substituted substrate reacts to provide a 6 : 1 ratio of **D** : **E** (eqn (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

$\xrightarrow[\text{CH}_2\text{Cl}_2, 40^\circ\text{C}]{\text{10\% (-)-2}}$

Entry	R	Yield ^{a,b} (%)	ee ^a (%)	dr ^a
1	Ph	60	78	12 : 1
2	3-F–C ₆ H ₄	51	58	7 : 1
3	3,5-(MeO) ₂ C ₆ H ₃	61	70	8 : 1
4	4-Br–C ₆ H ₄	52	70	9 : 1
5	2-Me–C ₆ H 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.

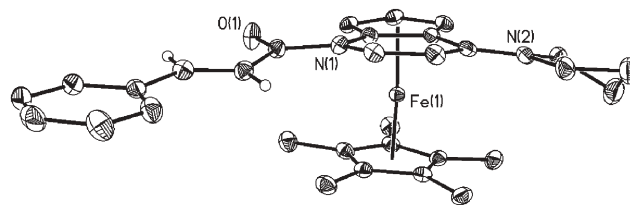


Fig. 2 ORTEP illustration, with thermal ellipsoids drawn at the 35% probability level, of *N*-cinnamoylated (+)-**2** (for the sake of clarity, the PF₆ counterion and most of the hydrogens have been omitted).

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 indenenes 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): C₃₁H₃₅F₆FeN₂OP, 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) Å³, *Z* = 8, μ = 0.641 mm⁻¹, reflections collected: 124357, independent reflections: 7504 [*R*(int) = 0.0955], final *R* indices [*I* > 2 σ (*I*)]: *R*1 = 0.0405, *wR*2 = 0.0862, *R* indices (all data): *R*1 = 0.0501, *wR*2 = 0.0904.

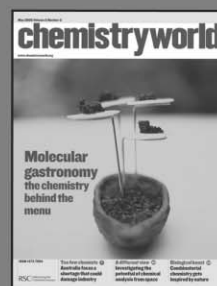
Crystallographic data for the product of entry 4 of Table 1 (generated by (+)-**2**): C₂₀H₁₇BrO, formula weight: 353.25, orthorhombic, *P*2(1)2(1)2(1), *a* = 7.2277(14) Å, *b* = 14.583(3) Å, *c* = 15.656(3) Å, *V* = 1650.2(5) Å³, *Z* = 4, μ = 2.490 mm⁻¹, reflections collected: 9518, independent reflections: 3593 [*R*(int) = 0.0238], final *R* indices [*I* > 2 σ (*I*)]: *R*1 = 0.0328, *wR*2 = 0.0694, *R* indices (all data): *R*1 = 0.0437, *wR*2 = 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 ^1H 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 indenones 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†).

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