Enantioselective Addition of Alcohols to Ketenes Catalyzed by a Planar-Chiral Azaferrocene: Catalytic Asymmetric Synthesis of Arylpropionic Acids

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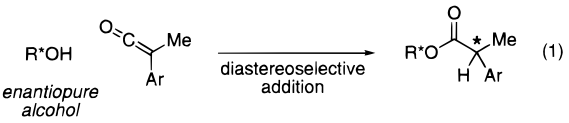
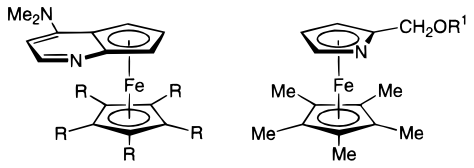
Due to their biological activity, arylpropionic acids constitute an important family of targets for asymmetric synthesis.[1] Although catalytic enantioselective reactions have the potential to provide particularly efficient access to these compounds, a relatively narrow range of such processes has been explored. Most of the studies reported to date have focused on transition metal-catalyzed additions to olefins (e.g., asymmetric hydrogenation and hydroformylation of substituted styrenes). Optically active arylpropionic acid derivatives can also be synthesized through the stereoselective addition of an alcohol to an arylmethylketene. Nearly all investigations of this process have relied upon the use of a stoichiometric quantity of a chiral alcohol to induce asymmetry (eq 1).[2]



Indeed, to the best of our knowledge the only publications that describe effective enantioselective catalysis of this reaction are those of Pracejus, who studied the alkaloid-catalyzed addition of methanol to two ketenes, phenylmethylketene (maximum ee: 76%) and phenyl-α-*o*-trimethyleneketene (maximum ee: 40%).[3]

A few years ago, we initiated a program directed at the development of planar-chiral heterocycles as enantioselective nucleophilic catalysts, focusing our attention on chiral DMAP derivatives (**1**) and chiral azaferrocenes (**2**). For the processes



R = Me: (-)-**1a**
Ph: (-)-**1b**

R[1] = Me: (+)-**2a**
TES: (+)-**2b**
TBS: (+)-**2c**
TBDPS: (+)-**2d**

that we have studied to date, namely, the kinetic resolution of secondary alcohols,[4] the deracemization/ring-opening of azlactones,[5] and the rearrangement of *O*-acylated enolates,[6] the chiral DMAP derivatives have consistently provided higher stereoselectivity than the chiral azaferrocenes. Recently, we turned our attention to the catalytic enantioselective addition of alcohols to ketenes, in the hope that our planar-chiral heterocycles might improve upon the benchmark established by Pracejus. In this report, we describe the achievement of this objective: With a chiral azaferrocene as the catalyst, MeOH adds to an array of arylalkylketenes with good levels of enantioselectivity and in excellent yields (eq 2).

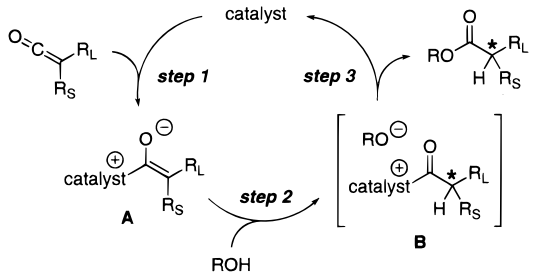
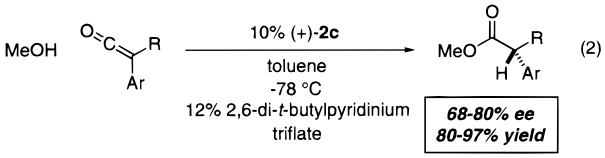
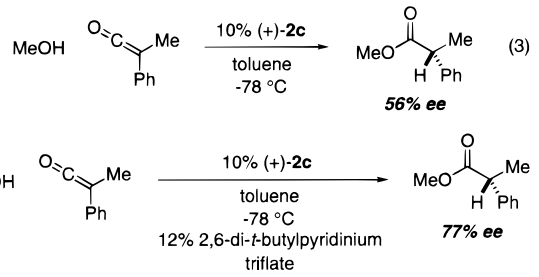


Figure 1. A possible mechanism for the azaferrocene-catalyzed addition of an alcohol to a ketene.



In early experiments, we established that planar-chiral azaferrocene **2c** catalyzes the addition of MeOH to phenylmethylketene with significant enantioselection (eq 3). One possible mechanism for this transformation is the nucleophile-catalyzed pathway illustrated in Figure 1.[7,8] Taking this mechanism as our working hypothesis, we speculated that for step 2, use of an alternate (to ROH) proton source might affect the enantioselectivity of the reaction. We therefore screened several acids, and we were pleased to discover that addition of 2,6-di-*tert*-butylpyridinium triflate (12 mol %) appreciably enhances asymmetric induction (eq 4; cf. eq 3).[9]



(1) For reviews of routes to optically active arylpropionic acids, see: (a) Sonawane, H. R.; Bellur, N. S.; Ahuja, J. R.; Kulkarni, D. G. *Tetrahedron: Asymmetry* **1992**, *3*, 163−192. (b) Rieu, J.-P.; Boucherle, A.; Cousse, H.; Mouzin, G. *Tetrahedron* **1986**, *42*, 4095−4131.

(2) For example, see: (a) Jähme, J.; Rüchardt, C. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 885−887. (b) Larsen, R. D.; Corley, E. G.; Davis, P.; Reider, P. J.; Grabowski, E. J. J. *J. Am. Chem. Soc.* **1989**, *111*, 7650−7651. (c) For related work involving thiols, see: Fehr, C.; Stempf, I.; Galindo, J. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1044−1046. For an overview, see: Fehr, C. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2566−2587.

(3) (a) Pracejus, H. *Justus Liebigs Ann. Chem.* **1960**, *634*, 9−22. (b) Pracejus, H.; Kohi, G. *Justus Liebigs Ann. Chem.* **1969**, *722*, 1−11. (c) Pracejus, H.; Tille, A. *Chem. Ber.* **1963**, *96*, 854−865. (d) Pracejus, H.; Mätje, H. *J. Prakt. Chem.* **1964**, *24*, 195−205. (e) For polymer-bound variants of the Pracejus catalyst, see: Yamashita, T.; Yasueda, H.; Nakamura, N. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 2165−2166.

(4) (a) Ruble, J. C.; Fu, G. C. *J. Org. Chem.* **1996**, *61*, 7230−7231. (b) Ruble, J. C.; Latham, H. A.; Fu, G. C. *J. Am. Chem. Soc.* **1997**, *119*, 1492−1493. (c) Ruble, J. C.; Tweddell, J.; Fu, G. C. *J. Org. Chem.* **1998**, *63*, 2794−2795.

(5) Liang, J.; Ruble, J. C.; Fu, G. C. *J. Org. Chem.* **1998**, *63*, 3154−3155.

(6) Ruble, J. C.; Fu, G. C. *J. Am. Chem. Soc.* **1998**, *120*, 11532−11533.

(7) For a report of the *N*-acetylation of 2,3,4,5-tetramethyl-1-azaferrocene by acetyl chloride, see: Kuhn, N.; Schulten, M.; Zauder, E.; Augart, N.; Boese, R. *Chem. Ber.* **1989**, *122*, 1891−1896.

(8) A pathway involving Brønsted-base catalysis is also possible. For a discussion of the mechanism of addition reactions to ketenes, see: (a) Tidwell, T. T. *Ketenes*; Wiley: New York, 1995; Chapter 5.5.1. (b) Andraos, J.; Kresge, A. J. *J. Am. Chem. Soc.* **1992**, *114*, 5643−5646. (c) Seikaly, H. R.; Tidwell, T. T. *Tetrahedron* **1986**, *42*, 2587−2613.

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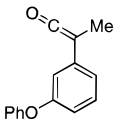
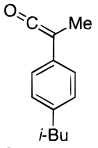
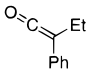
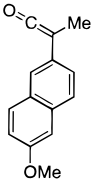
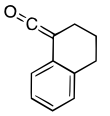
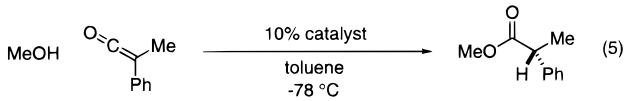
Table 1. Catalytic Asymmetric Addition of Alcohols to Ketenes[a]

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

[a] All data are the average of two runs.

We have explored the use of a range of planar-chiral azaferrocenes and DMAP derivatives as catalysts for the enantioselective addition of MeOH to phenylmethylketene (eq 5). In the case of



(5)

catalyst	% ee
(+)-**2a**	27
(+)-**2b**	28
(+)-**2c**	77
(+)-**2d**	68
(+)-**1a**	<5
(+)-**1b**	<5

azaferrocenes, the stereoselection is a strong function of the steric demand of the 2-substituent: we observe the highest ee in the case of the CH_2OTBS group (catalyst **2c**) and lower ee's for both smaller (**2a** and **2b**) and larger (**2d**) substituents. In contrast to the azaferrocenes, the planar-chiral DMAP derivatives (**1a** and **1b**) are not effective at inducing asymmetry in this addition reaction (eq 5; <5% ee).

We have established that in the presence of azaferrocene catalyst **2c**, MeOH adds with good enantioselectivity to an array of arylalkylketenes (Table 1).[10,11] For arylmethylketenes, the ee is relatively insensitive to remote electronic effects, and the methyl esters of ibuprofen, naproxen, and fenoprofen can be generated in 74−77% enantiomeric excess (entries 2−4). On the other hand, the ee is relatively sensitive to steric effects: the presence of a larger alkyl substituent on the ketene leads to lower enantioselection (entry 5; cf. entry 1). In the case of phenyl-α-*o*-trimethyleneketene, one of the two substrates studied by Pracejus (maximum ee: 40%), azaferrocene **2c**, catalyzes formation of the methyl ester in 80% ee (entry 6).

For the addition of MeOH to phenylmethylketene, we observe somewhat lower enantioselectivity when we decrease the catalyst loading (77% ee with 10% catalyst; 64% ee with 0.5% catalyst). Interestingly, we have found that the esters are produced with the greatest enantiomeric excess when the reactions are run at ca. −70 °C, and that the ee drops both at lower and at higher temperatures (Figure 2).[12]

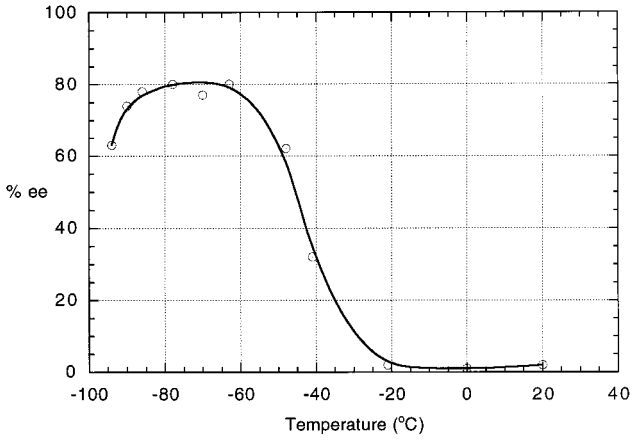
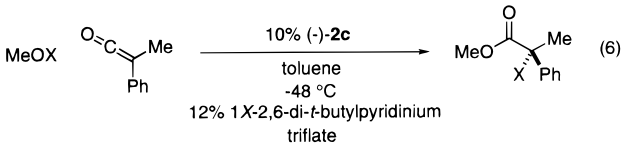


Figure 2. Enantiomeric excess as a function of temperature for the addition of MeOH to phenyl-α-*o*-trimethyleneketene.

We have initiated studies directed at elucidating the origin of enantioselection as well as the mechanism of this azaferrocene-catalyzed addition process. In a preliminary investigation, we have established that the ee of the product varies linearly with the ee of the catalyst, an observation that provides no evidence for the involvement of two or more catalyst molecules in the stereochemistry-determining step. Furthermore, we have determined that the reaction exhibits a deuterium kinetic isotope effect of 3.2 (eq 6).



(6)

$$\frac{k\,(X = H)}{k\,(X = D)} = 3.2$$

In summary, we have demonstrated that planar-chiral heterocycles can serve as effective catalysts for the enantioselective addition of alcohols to ketenes. In contrast to our previous studies, wherein DMAP derivatives had provided uniformly higher stereoselection than azaferrocenes, for this process an azaferrocene is the catalyst of choice. Compared to the alkaloid catalyst developed by Pracejus, azaferrocene **2c** appears to be both more generally applicable and more enantioselective. We believe that the new benchmark that we have established for the catalytic asymmetric addition of alcohols to arylmethylketenes represents a useful advance in the development of efficient approaches to the synthesis of enantiopure arylpropionic acid derivatives. Studies aimed at developing an improved mechanistic understanding and at further optimizing the stereoselectivity of this reaction are underway.

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Supporting Information Available: Experimental procedures and compound characterization data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) Interestingly, the enantioselectivity is a strong function of the counterion (triflate is the best of the several that we have screened).

(10) Lower enantioselectivity is observed in solvents other than toluene (e.g., THF and CH_2Cl_2).

(11) Representative procedure (Table 1, entry 1): Under N_2, a solution of phenylmethylketene (45.0 mg, 0.341 mmol) in toluene (2.8 mL) was added by cannula to a −78 °C mixture of catalyst (+)-**2c** (13.7 mg, 0.034 mmol), 2,6-di-*tert*-butylpyridinium triflate (14.0 mg, 0.041 mmol), and MeOH (20.7 μL, 0.511 mmol) in toluene (4.0 mL). The resulting homogeneous solution was stirred at −78 °C for 24 h, and then the reaction was quenched by the addition of *n*-propylamine (0.2 mL). The solvent was removed by rotary evaporation, and the residue was immediately purified by flash chromatography (5% → 10% EtOAc/hexanes), which afforded 49.1 mg (88%) of a colorless liquid. For ee determination, the ester was reduced, trifluoroacetylated, and analyzed by GC (Chiraldex G-TA), which revealed a 77% ee.

(12) We have observed analogous behavior with other arylalkylketenes.