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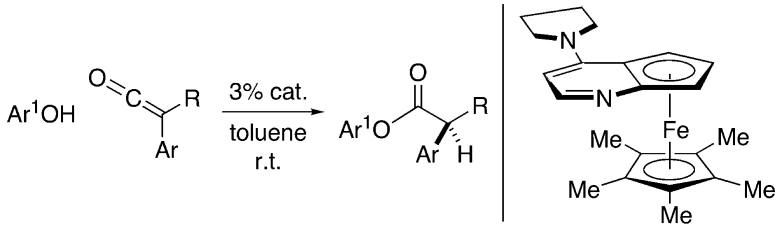

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Catalytic Asymmetric Synthesis of Esters from Ketenes

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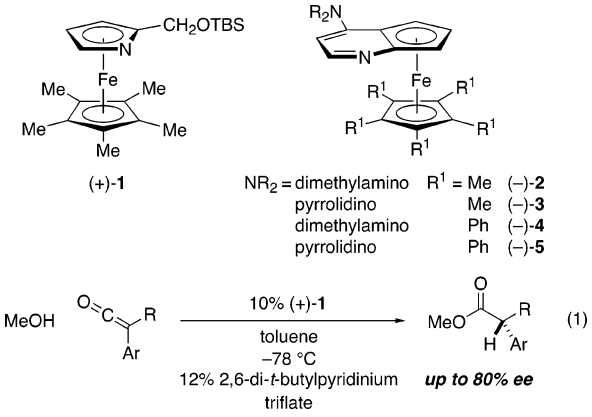
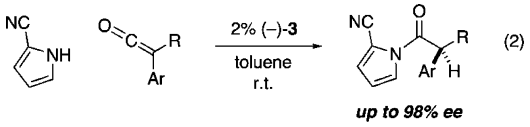
During the past several years, we have established that planar-chiral heterocycles, such as **1**−**5**, serve as enantioselective catalysts for an array of processes, including kinetic resolutions of alcohols and amines, C-acylations that generate all-carbon quaternary stereocenters, and coupling reactions of ketenes.[1] As part of these studies, in 1999, we reported that azaferrocene **1** catalyzes the addition of MeOH to aryl alkyl ketenes (eq 1).[2] Although the enantioselectivity is only moderate (up to 80% ee), this is the most effective catalytic asymmetric method for the synthesis of esters from ketenes that has been described to date.[3−5]



In our 1999 investigation, we suggested that the addition of MeOH to ketenes catalyzed by **1** might proceed through the nucleophile-catalyzed pathway illustrated in Figure 1 (top). In contrast, in 2002, on the basis of stereochemical, spectroscopic, and kinetic data, we concluded that the enantioselective addition of 2-cyanopyrrole to ketenes catalyzed by **3** (eq 2) likely involves a Brønsted acid-catalyzed mechanism (Figure 1, bottom; X−H = 2-cyanopyrrole).[6]



To the best of our knowledge, the process illustrated in eq 2 represents the first example of a planar-chiral heterocycle serving as a chiral Brønsted acid catalyst. Naturally, we were interested in determining if this mode of reactivity can be exploited in other contexts. In view of the modest progress that has been described toward the development of an effective catalyst for the enantioselective synthesis of esters from ketenes (eq 1; ≤80% ee), we decided to explore the possibility that Brønsted acid catalysis by planar-chiral heterocycles could furnish a solution to this challenge.

An elementary analysis suggests that, to favor a mechanism in which the catalyst serves as a Brønsted acid, rather than a nucleophile, it might be desirable to drive the equilibrium depicted in eq 3 toward the right. When MeOH and azaferrocene **1** are mixed, there is no evidence by ^{1}H NMR for formation of an ion pair (eq 4; cf. eq 1). Clearly, increasing the acidity of ROH and/or the basicity of the catalyst should encourage the desired deprotonation. Indeed, we have determined that phenol reacts with PPY derivative **3** to quantitatively produce an ion pair (eq 5).

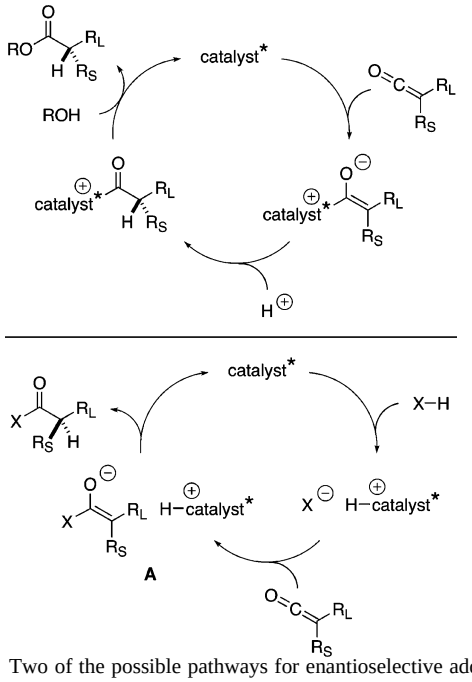
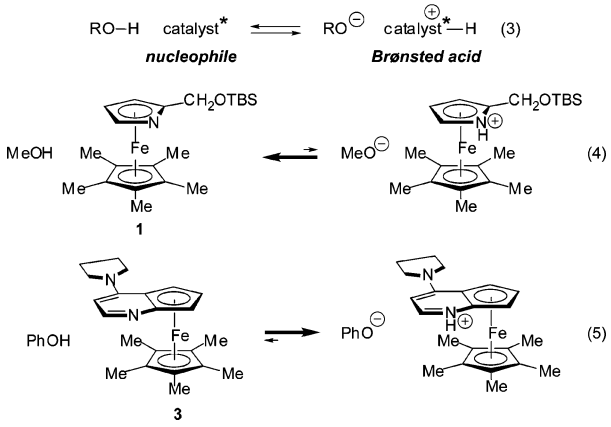


Figure 1. Two of the possible pathways for enantioselective additions to ketenes: nucleophilic catalysis (top); Brønsted acid catalysis (bottom).



Furthermore, if a ketene is added to a mixture of a phenol and (−)-**3**, an addition reaction occurs to furnish nonracemic aryl esters. The structure of the nucleophile has a substantial influence on the enantiomeric excess of the product. Thus, phenol reacts with phenyl ethyl ketene to afford the desired ester with modest enantioselectivity (47% ee; Table 1, entry 1). The presence of an electron-withdrawing para substituent leads to a decrease in enantiomeric excess (entry 2), whereas an electron-donating group provides higher enantioselectivity (entry 3). The incorporation of an ortho

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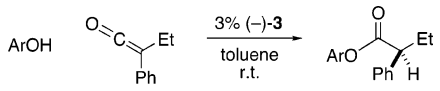
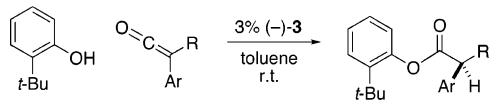
Table 1. Catalytic Enantioselective Synthesis of Esters from Ketenes: Dependence of Enantiomeric Excess on the Structure of the Phenol[a]



entry	ArOH	ee (%)
1	PhOH	47
2	4-(trifluoromethyl)phenol	35
3	4-methoxyphenol	72
4	2-methoxyphenol	80
5	2-methylphenol	81
6	2-isopropylphenol	80
7	2-phenylphenol	88
8	2-*tert*-butylphenol	91

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

Table 2. Catalytic Enantioselective Synthesis of Esters from Ketenes[a]



entry	Ar	R	ee (%)	isolated yield (%)
1	Ph	Me	79	87
2	Ph	Et	91	89
3	Ph	*i*-Bu	84	79
4	Ph	cyclopentyl	87	88
5	Ph	*i*-Pr	91	66
6	*o*-tol	Et	92	84
7	*o*-anisyl	Me	94	78
8	*p*-Cl	*i*-Pr	89	97
9	3-thienyl	*i*-Pr	79	94

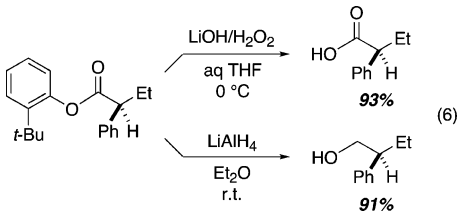
[a] All data are the average of two experiments.

substituent on the phenol results in enhanced enantiomeric excess (entries 4−8), with a large *tert*-butyl group producing the best selectivity among the phenols that we have examined to date.

This combination of 2-*tert*-butylphenol and **3** provides the most effective and versatile method reported to date for the catalytic asymmetric synthesis of esters from ketenes (Table 2);[7,8] the reaction predominantly affords the enantiomer that we had anticipated on the basis of our mechanistic hypothesis (chiral Brønsted acid catalysis ⟹ the same sense of stereoselection as in eq 2). Although we obtain only moderate enantiomeric excess for the reaction of phenyl methyl ketene (entry 1), we observe good enantiomeric excesses for a range of other phenyl alkyl ketenes (entries 2−5). If the aromatic substituent of the ketene is ortho-substituted, the ester is generated with high enantioselectivity (entries 6 and 7). The process tolerates both electron-rich and electron-poor aryl groups (entries 7 and 8), but it furnishes somewhat lower enantiomeric excess for a 3-thienyl-substituted ketene (entry 9). It is worth noting that none of the methods that had been described earlier for the catalytic enantioselective synthesis of esters from ketenes[2,3] had been shown to be effective for ketenes with an ortho-substituted aromatic substituent or with an alkyl group larger than ethyl (maximum enantiomeric excess for an ethyl-substituted ketene: 68%[2]).[9,10]

Although phenyl esters are reactive toward a variety of nucleophiles, transformations of more hindered aryl esters (e.g., BHT esters; BHT = 2,6-di-*tert*-butyl-4-methylphenol) can be difficult.[11] As illustrated in eq 6, we have established that 2-*tert*-butylphenyl esters may be converted into useful derivatives in excellent yield (without racemization).

Thus, we have designed and developed an effective catalytic asymmetric method for synthesizing esters from ketenes. Ongoing studies are directed at furnishing additional support for our hypothesis that planar-chiral heterocycles can serve as chiral Brønsted acid catalysts for an array of interesting processes.



(6)

Acknowledgment. Support has been provided by the NIH (National Institute of General Medical Sciences: R01-GM57034), Merck Research Laboratories, and Novartis.

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

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(6) Hodous, B. L.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 10006−10007.

(7) **General Procedure:** In the air, catalyst (−)-**3** (0.011 mmol; 0.030 equiv) was weighed into a flask, which was then purged with argon. Toluene (30 mL) and 2-*tert*-butylphenol (0.390 mmol; 1.04 equiv) were added. A solution of ketene (0.375 mmol; 1.00 equiv) in toluene (1.0 mL) was added by syringe over 30 min to the solution of catalyst and 2-*tert*-butylphenol. The reaction mixture was stirred at room temperature for 2 h, and then *n*-propylamine (0.05 mL) was added. The resulting solution was passed through a plug of silica gel (a 1:1 mixture of Et_2O:hexanes was used to elute the ester, and then a 1:9 mixture of NEt_3:EtOAc was used to elute catalyst **3**). The ester was then purified by flash chromatography.

(8) Notes: (a) Upon increasing the scale of the General Procedure, we have obtained essentially identical enantiomeric excess and yield. (b) The catalyst can typically be recovered in ≥80% yield. (c) In a preliminary study, we have obtained 50% ee for the addition of a phenol to a dialkylketene (cyclopentyl methyl ketene). (d) Price of 2-*tert*-butylphenol: $55 for 2 L (Aldrich).

(9) A wide variety of α-alkyl-α-arylacetic acid derivatives are bioactive. For leading references, see: (a) Fenvalerate: *The Merck Index*, 13th ed.; Merck: Whitehouse Station, NJ, 2001; pp 710−711. (b) Bodor, N.; Woods, R.; Raper, C.; Kearney, P.; Kaminski, J. J. *J. Med. Chem.* **1980**, *23*, 474−480. (c) Brooks, C. D. W. et al. *Pure Appl. Chem.* **1988**, *70*, 271−274. (d) Robichaud, J. et al. *J. Med. Chem.* **2003**, *46*, 3709−3727. (e) Sonawane, H. R.; Bellur, N. S.; Ahuja, J. R.; Kulkarni, D. G. *Tetrahedron: Asymmetry* **1992**, *3*, 163−192. (f) Rieu, J.-P.; Boucherle, A.; Cousse, H.; Mouzin, G. *Tetrahedron* **1986**, *42*, 4095−4131.

(10) The fact that the ester is generated in high enantiomeric excess despite the presence of an achiral proton donor (the phenol) that is more abundant and more acidic than protonated **3** is readily accommodated within the mechanism outlined in the bottom of Figure 1; the enolate of ion pair **A** prefers to react with its chiral counterion, rather than participating in a bimolecular reaction with the phenol. This would suggest that, at higher concentration or in a more polar solvent, intermolecular protonation by the phenol might become competitive, leading to an erosion in enantiomeric excess; this is indeed observed.

(11) For example, see: Doyle, M. P.; Bagheri, V.; Wandless, T. J.; Harn, N. K.; Brinker, D. A.; Eagle, C. T.; Loh, K.-L. *J. Am. Chem. Soc.* **1990**, *112*, 1906−1912.

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