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Enantioselective Addition of Amines to Ketenes Catalyzed by a Planar-Chiral Derivative of PPY: Possible Intervention of Chiral Brønsted-Acid Catalysis

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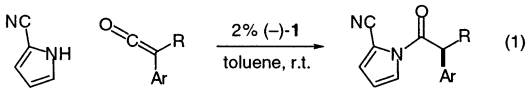
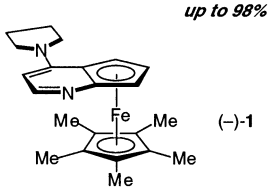
The catalytic asymmetric addition of nucleophiles to ketenes represents an attractive strategy for the synthesis of enantioenriched carbonyl derivatives, including biologically and industrially significant classes of compounds such as arylpropionic acids.[1] For the catalyzed addition of alcohols to ketenes, enantiomeric excesses as high as 75−80% have been obtained.[2] In contrast, to the best of our knowledge there are no examples of catalytic asymmetric additions of achiral nitrogen nucleophiles to ketenes.[3] In this communication, we describe a method for achieving this objective (eq 1).



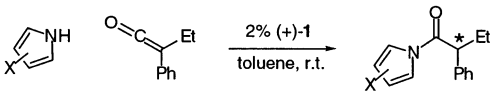


Because simple amines can rapidly add to ketenes in the absence of a catalyst, we focused our investigation on less-reactive nitrogen nucleophiles. In early studies, we determined that pyrroles do not react at room temperature with ketenes such as phenyl ethyl ketene. In contrast, additions can proceed swiftly when commercially available planar-chiral 4-(pyrrolidino)pyridine (PPY) derivative **1**[4,5] is employed as a catalyst; significantly, in the presence of enantiopure **1** and an appropriate pyrrole, the *N*-acylpyrrole can be generated in high enantiomeric excess (Table 1).

With pyrrole itself as the nucleophile, the new stereocenter is produced in moderate ee (Table 1, entry 1). Although incorporation of an alkyl substituent into the 2-position leads to racemic product (entry 2), the presence of an electron-withdrawing group provides enantioenriched *N*-acylpyrroles (entries 3−5), with commercially available 2-cyanopyrrole furnishing excellent stereoselection (91% ee; entry 5). A pyrrole that bears electron-withdrawing groups in the 3- and 4-positions affords fair ee (entry 6), as does indole (entry 7). 2,5-Disubstituted pyrroles do not appear to be suitable reaction partners (entry 8).

We next turned our attention to determining the range of ketenes that are suitable substrates for this new catalytic enantioselective process (Table 2).[6] We have established that very good ee's and yields are obtained for reactions of a wide array of phenyl alkyl ketenes (R = Me → *t*-Bu; entries 1−4); particularly noteworthy are the results for sterically demanding phenyl isopropyl ketene and phenyl *tert*-butyl ketene (entries 3 and 4), 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 leads to an increase in enantiomeric excess (entries 5 vs 2 and entries 6 vs 1), and heteroaryl substituents are tolerated in this process (entry 7).

Table 1. Dependence of Enantioselectivity on the Structure of the Pyrrole



Entry	Pyrrole	ee (%)[a]
1	R = H	42
2	R = Et	0
3	R = NO_2	21
4	R = Ac	78
5	R = **CN**	**91**
6	diethyl 3,4-pyrroledicarboxylate	63
7	indole	49
8	ethyl 3,5-dimethyl-2-pyrrolecarboxylate	–[b]

[a] Average of two runs. [b] No *N*-acylpyrrole was produced.

Table 2. Catalytic Enantioselective Addition of 2-Cyanopyrrole to a Range of Ketenes (eq 1)

entry	Ar	R	ee (%)[a]	yield (%)[a]
1	Ph	Me	**81**	91
2	Ph	Et	**90**	93
3	Ph	*i*-Pr	**95**	96
4[b]	Ph	*t*-Bu	**81**	90
5	*o*-tol	Et	**98**	95
6	*o*-anisyl	Me	**94**	94
7	3-(*N*-methylindolyl)	Bn	**86**	80

[a] Average of two runs. [b] 5% catalyst.

We anticipated that, in contrast to simple amides, we would be able to derivatize our *N*-acylpyrroles under relatively mild conditions, thereby enhancing the utility of this new catalytic asymmetric addition reaction. Although a few transformations of *N*-acylpyrroles have been described,[7] none involve a 2-cyanopyrrole. We were pleased to discover that these *N*-acylpyrroles can be converted into a wide array of useful compounds with essentially no erosion in enantiomeric excess (Figure 1; ≤2% racemization in all cases). Thus, chiral acids (**2**),[8] esters (**3**),[9] and amides (**4**)[10] can be generated through reactions with water, alcohols, and amines, respectively. In addition, by appropriate choice of reducing agent, an aldehyde (**5**; $LiAlH(Ot\text{-}Bu)_3$)[11] or an alcohol (**6**; $NaBH_4$)[12] can be produced selectively.

We have pursued an investigation of the mechanism and origin of stereoselection for the enantioselective addition of pyrroles to ketenes catalyzed by **1**. We chose to focus our attention on the coupling of 2-cyanopyrrole with phenyl *tert*-butyl ketene, since this reaction proceeds at a convenient rate at room temperature ($t_{1/2} \approx$

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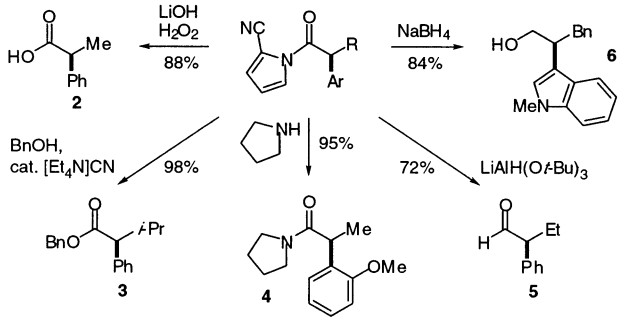

Figure 1. Transformations of the *N*-acylpyrroles.

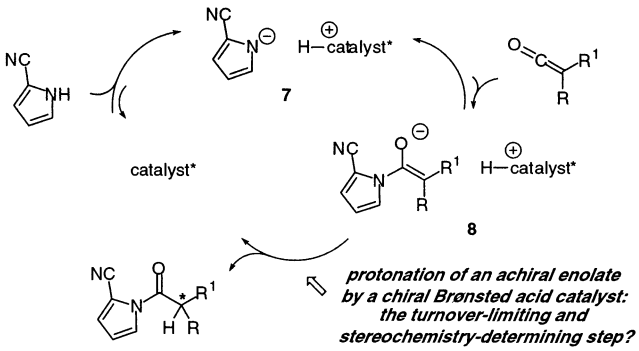

Figure 2. Possible mechanism for the enantioselective addition of pyrroles to ketenes catalyzed by **1**.

50 min), and we have made the following observations: (1) Treatment of 2-cyanopyrrole with **1** leads to deprotonation of the pyrrole and formation of an ion pair; this ion pair, not **1** itself, is the resting state of the catalyst during the reaction. (2) The reaction is first-order in phenyl *tert*-butyl ketene, first-order in **1**, and zero-order in 2-cyanopyrrole. (3) A primary kinetic isotope effect of ~5 is observed (1-*H*-2-cyanopyrrole vs 1-*D*-2-cyanopyrrole). (4) The ee of the *N*-acylpyrrole varies linearly with the ee of **1**.[13,14]

On the basis of these data, we believe that enantioselective additions of pyrroles to ketenes catalyzed by PPY derivative **1** proceed through the pathway illustrated in Figure 2. Deprotonation of 2-cyanopyrrole by the catalyst furnishes ion pair **7**. The nucleophilic pyrrole anion then adds to the ketene, generating a new ion pair (**8**), which consists of an achiral enolate and a chiral Brønsted acid (protonated **1**). In the turnover-limiting and stereochemistry-determining step of the catalytic cycle, proton transfer occurs to produce a chiral *N*-acylpyrrole and to liberate catalyst **1**. Deprotonation of 2-cyanopyrrole by **1** then regenerates ion pair **7**, completing the catalytic cycle.

In the pathway depicted in Figure 2, the role of catalyst **1** is to serve, in protonated form, as a chiral ***Brønsted acid***.[15] This contrasts with other applications of planar-chiral catalyst **1** and related compounds, wherein they function as chiral ***nucleophiles*** (***Lewis bases***).[16]

In summary, we have developed the first method for the catalytic enantioselective addition of amines (specifically, pyrroles) to ketenes, and we have demonstrated that the resulting acylpyrroles can be transformed into a broad spectrum of useful derivatives. On the basis of mechanistic studies, we suggest that the planar-chiral catalyst plays an unanticipated role in this process as a chiral Brønsted acid.

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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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(6) Notes: (a) Approximately 80% of the catalyst can be recovered at the end of the reaction. (b) In a gram-scale reaction, comparable ee and yield were obtained.

(7) (a) For leading references, see: Evans, D. A.; Scheidt, K. A.; Johnston, J. N.; Willis, M. C. *J. Am. Chem. Soc.* **2001**, *123*, 4480−4491. (b) See also: Arai, Y.; Masauda, T.; Masaki, Y. *Chem. Lett.* **1997**, 145−146.

(8) A number of important nonsteroidal antiinflammatory drugs are arylpropionic acids (e.g., ibuprofen and naproxen). For leading references, see ref 1.

(9) This process resembles that employed for the synthesis of fenvalerate, a commercial insecticide, which also involves the acylation of an alcohol with an isopropyl-substituted arylacetic acid derivative. For an overview of fenvalerate, see: Yoshioka, H. *CHEMTECH* **1985**, *15*, 482−486.

(10) This acylated pyrrolidine represents the core of RPR 111905 and RPR 107880, non-peptide substance P antagonists: (a) Mutti, S.; Daubié, C.; Decalogne, F.; Fournier, R.; Rossi, P. *Tetrahedron Lett.* **1996**, *37*, 3125−3128. (b) Mutti, S.; Daubié, C.; Malpart, J.; Radisson, X. *Tetrahedron Lett.* **1996**, *37*, 8743−8746.

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(13) Additional observations: (a) By ^{1}H NMR spectroscopy, we have determined that the potassium salt of 2-cyanopyrrole reacts with phenyl *tert*-butyl ketene to generate an enolate (see compound **8** in Figure 2), which furnishes an *N*-acylpyrrole upon treatment with a suitable proton source. (b) By ^{1}H NMR spectroscopy, we detect no interaction upon mixing phenyl *tert*-butyl ketene (or phenyl ethyl ketene) with 1 equiv of **1**. (c) Although both processes involve transformations of ketenes, the stereoselectivity and reactivity profile of catalyst **1** is very different for Staudinger reactions (reference 5c) versus additions of 2-cyanopyrrole (this work). For example, the same enantiomer of the catalyst provides the *opposite* absolute stereochemistry at the carbon α to the carbonyl group of the product. In addition, the reactivity pattern for Staudinger reactions and pyrrole additions is significantly different: e.g., PPY derivative **1** effectively catalyzes pyrrole additions, but not Staudinger reactions, of hindered ketenes. Collectively, these observations are consistent with the idea that catalyst **1** may be performing distinct mechanistic roles in these two processes.

(14) (a) For a discussion of a mechanism for the addition of an amine to a ketene, see: Allen, A. D.; Tidwell, T. T. *J. Org. Chem.* **1999**, *64*, 266−271, and references therein. (b) For a discussion of a mechanism for a base-catalyzed addition of an alcohol to a ketene, see: Cannizzaro, C. E.; Strassner, T.; Houk, K. N. *J. Am. Chem. Soc.* **2001**, *123*, 2668−2669 and references therein. See also: Buschmann, H.; Scharf, H.-D.; Hoffmann, N.; Esser, P. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 477−515.

(15) For a review, see: Yanagisawa, A.; Yamamoto, H. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: New York, 1999; Chapter 34.2.

(16) For example, see refs 5a and 5c.

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