Enantioselective Synthesis of Protected Amines by the Catalytic Asymmetric Addition of Hydrazoic Acid to Ketenes**

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We recently described the ability of a planar-chiral derivative of 4-dimethylaminopyridine (DMAP) **1** to achieve catalytic asymmetric additions of nitrogen and oxygen nucleophiles to ketenes to generate amides and esters [Eq. (1)].^[1] We believe



that these reactions likely proceed through the pathway illustrated in Scheme 1, wherein the protonated catalyst serves as a chiral Brønsted acid (see A),^[2,3] thereby generating a new stereocenter.

To the best of our knowledge, there are no previous examples of catalytic asymmetric additions of HN₃ to ketenes to produce acyl azides.^[4-6] In view of the acidity of HN₃ (p K_a = 5),^[7] we postulated that this process might be accomplished by the cycle depicted in Scheme 1. Since acyl azides can be converted into amine derivatives by a Curtius rearrangement [Eq. (2)], this sequence would yield a family of compounds that are distinct from the acyl derivatives generated in our earlier studies [Eq. (1)]. Of course, as a result of the ubiquity of chiral amines, the development of enantioselective methods for their synthesis is an important objective.^[8,9]

Unfortunately, under the conditions that had proved useful for the addition of pyrroles and phenols to ketenes [Eq. (1)], the reaction of HN₃ proceeded with low enantio-

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Scheme 1. Catalytic enantioselective addition of X-H to ketenes: A possible mechanism (Brønsted acid catalysis).



selectivity (27% *ee* and 34% yield for phenyl isopropyl ketene). During our earlier studies of pyrroles and phenols, we had obtained the highest *ee* values when the additions were conducted at low concentrations and in nonpolar solvents. One rationale for these observations is that the chiral counterion ([H-catalyst*]⁺) and achiral HX compete in the protonation of the enolate of ion pair **A** [Scheme 1, Eq. (3)].



(3)

(2)



Communications

On the basis of this analysis, we hypothesized that higher *ee* values might be achieved by an increase in the acidity of the [H-catalyst*]⁺ (that is, attenuation of the Brønsted basicity of the catalyst). We therefore decided to examine the use of planar-chiral pyridines that lack a strong electron-donating group in the 4-position. We were pleased to determine that catalyst **2**, a relative of **1** with lower Brønsted basicity, effected the addition of HN₃ to phenyl isopropyl ketene with excellent enantioselectivity (Table 1, entry 1; under identical conditions, catalyst **1** gave < 5% ee).^[10]

Table 1: Catalytic enantioselective addition of HN₃ to ketenes.^[a]

	N_3-H C R^1 (1.1 equiv) R	1) (+)-2 (10%) toluene/hexane -78 or -90 °C 2) Δ; MeOH		
Entry	R	R ¹	Yield [%]	ee [%]
1	Ph	iPr	93	96
2	p-ClC ₆ H ₄	<i>i</i> Pr	90	92
3	p-(MeO)C ₆ H ₄	<i>i</i> Pr	94	97
4	3-thienyl	<i>i</i> Pr	92	94
5	Ph	cyclohexyl	92	96
6	Ph	cyclopentyl	93	96
7	Ph	<i>t</i> Bu	94	76
8	Ph	Et	89	4
9	o-tol	Et	93	94
10	o-tol	Me	90	80
11	p-(MeO)C ₆ H ₄	Et	92	55
12	o-(MeO)C ₆ H₄	Me	90	70

[a] All data are the average of two experiments. The reactions in entries 1–7 and entries 8–12 were carried out at -78 °C and -90 °C, respectively.

We have established that the use of more electron-rich aromatic substituents led to higher ee values (Table 1, entries 1-3). Heteroaryl-substituted ketenes proved to be suitable substrates (entry 4), as were aryl cycloalkyl ketenes (entries 5 and 6). The planar-chiral pyridine derivative 2 also could catalyze enantioselective additions of HN₃ to highly hindered ketenes, although a more modest ee value was observed (entry 7). Unfortunately, in the case of phenyl ethyl ketene, nearly racemic product was obtained (entry 8); control experiments revealed that, for unhindered ketenes, the uncatalyzed addition of HN3 was rapid even at low temperature.^[11] However, if the aryl group was ortho-substituted, the background reaction was found to be much slower, thus allowing the enantioselective process catalyzed by 2 to prevail (Table 1, entry 9). Entry 10 illustrates that this strategy is even useful for an aryl methyl ketene. Similarly, the presence of an electron-rich aromatic group diminished the rate of the uncatalyzed addition and permitted the formation of the carbamate from an unhindered ketene to proceed with significant ee values (Table 1, entries 11 and 12).

As expected, the isocyanate that was produced through a Curtius rearrangement of the acyl azide could be converted not only into a methyl carbamate, but also into other protected amines, as well as the free amine [for example, Eq. (4) and Eq. (5); Bn = benzyl, tol = tolyl].

$$N_{3}-H \xrightarrow{O}_{O-\text{tol}} Fr \xrightarrow{1) (+)-2 (10\%)}_{2) \Delta; BnOH} \xrightarrow{CbzHN}_{Ph H} Fr \qquad (4)$$

$$N_{3}-H \xrightarrow{O}_{O-\text{tol}} Et \xrightarrow{1) (+)-2 (10\%)}_{2) \Delta; H_{2}O/H^{\oplus}} \xrightarrow{NH_{2}}_{O-\text{tol}} Et \xrightarrow{O-\text{tol}}_{H} \qquad (5)$$

We believe that these enantioselective additions of HN₃ to ketenes proceed by a chiral Brønsted acid catalyzed pathway, as illustrated in Scheme 1 (X = N₃), wherein protonated **2** is a key intermediate. Some of the observations that we have made that are consistent with this mechanism and generally less well accommodated by a nucleophilic catalysis pathway (Scheme 2; X = N₃)^[12] include: 1) treatment of **2** with HN₃ led



Scheme 2. Catalytic enantioselective addition of X-H to ketenes: A potential alternative mechanism (nucleophilic catalysis).

to protonation of the catalyst [Eq. (6)]; 2) catalyst **2**, which lacks an electron-donating 4-dialkylamino group, proved to be effective even at very low temperature; 3) higher *ee* values



were obtained in less-polar solvents, at lower concentrations, with slower addition of HN_3 , and with a catalyst of lower Brønsted basicity; 4) the sense of stereoselectivity was the same as for the addition of pyrroles and phenols to ketenes [Table 1 versus Eq. (1)].

In conclusion, on the basis of a mechanistic hypothesis, we have tuned the structure and reactivity of a chiral catalyst and thereby developed the first effective method for the catalytic asymmetric addition of hydrazoic acid to ketenes. Through a Curtius rearrangement of the resulting acyl azide, this approach provides a novel route to enantioenriched amine derivatives. We anticipate that, for a range of chiral Brønsted acid catalyzed (as opposed to nucleophile-catalyzed) processes, these new planar-chiral pyridines may prove to be more useful than their DMAP-derived relatives.

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- [10] Consistent with expectations, it is advantageous to add the $\rm HN_3$ by syringe pump over 1–2 h, rather than all at once.
- [11] In contrast, under our standard reaction conditions, HN_3 does not add to phenyl isopropyl ketene at an appreciable rate in the absence of a catalyst.
- [12] For an additional discussion, see reference [1].