Asymmetric Catalysis

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

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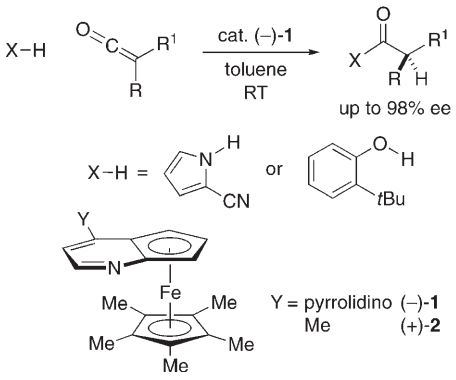
We recently described the ability of a planar-chiral derivative of 4-dimethylaminopyridine (DMAP) **1** to achieve catalytic asymmetric additions of nitrogen and oxygen nucleophiles to ketenes to generate amides and esters [Eq. (1)].[1] We believe

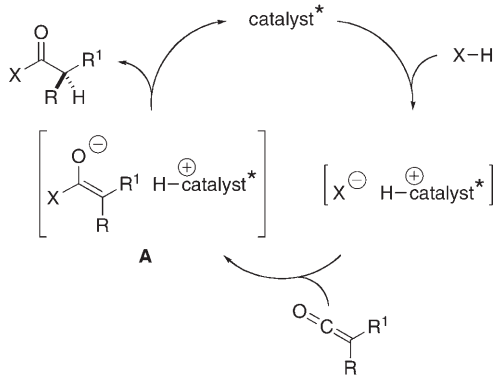


(1)

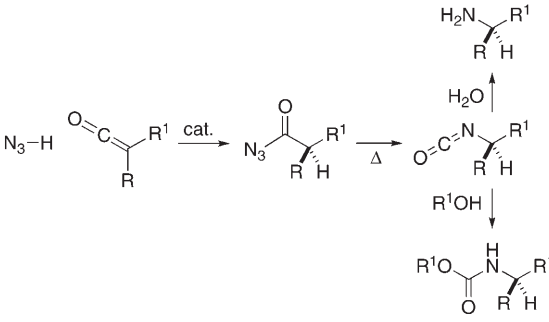
that these reactions likely proceed through the pathway illustrated in Scheme 1, wherein the protonated catalyst serves as a chiral Brønsted acid (see **A**),[2,3] thereby generating a new stereocenter.

To the best of our knowledge, there are no previous examples of catalytic asymmetric additions of HN_3 to ketenes to produce acyl azides.[4–6] In view of the acidity of HN_3 ($pK_a = 5$),[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 HN_3 proceeded with low enantio-

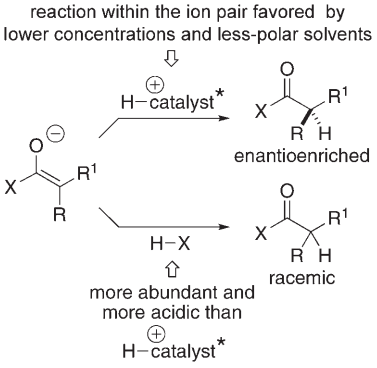


Scheme 1. Catalytic enantioselective addition of X–H to ketenes: A possible mechanism (Brønsted acid catalysis).



(2)

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 ($[H\text{-catalyst}^*]^+$) and achiral HX compete in the protonation of the enolate of ion pair **A** [Scheme 1, Eq. (3)].



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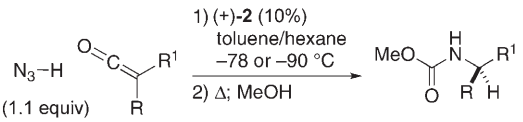
On the basis of this analysis, we hypothesized that higher *ee* values might be achieved by an increase in the acidity of the [H-catalyst*]$^+$ (that is, attenuation of the Brønsted basicity of the catalyst). We therefore decided to examine the use of planar-chiral pyridines that lack a strong electron-donating 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 HN_3 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 HN_3 to ketenes.[a]

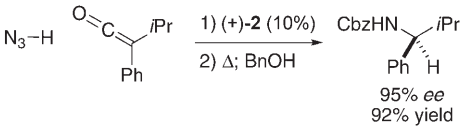


Entry	R	R^1	Yield [%]	*ee* [%]
1	Ph	*i*Pr	93	96
2	*p*-ClC_6H_4	*i*Pr	90	92
3	*p*-$(MeO)C_6H_4$	*i*Pr	94	97
4	3-thienyl	*i*Pr	92	94
5	Ph	cyclohexyl	92	96
6	Ph	cyclopentyl	93	96
7	Ph	*t*Bu	94	76
8	Ph	Et	89	4
9	*o*-tol	Et	93	94
10	*o*-tol	Me	90	80
11	*p*-$(MeO)C_6H_4$	Et	92	55
12	*o*-$(MeO)C_6H_4$	Me	90	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 HN_3 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 HN_3 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].



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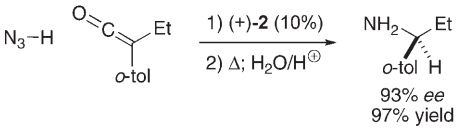
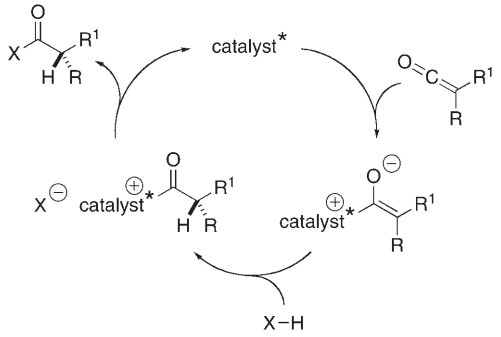


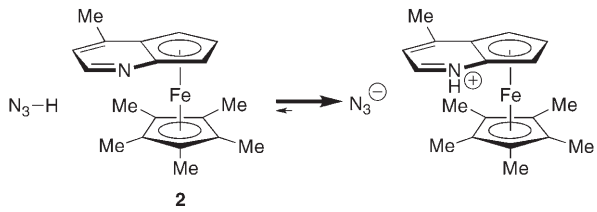
(5)

We believe that these enantioselective additions of HN_3 to ketenes proceed by a chiral Brønsted acid catalyzed pathway, as illustrated in Scheme 1 (X = N_3), 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 = N_3)[12] include: 1) treatment of **2** with HN_3 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



(6)

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 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].

