Asymmetric Cycloadditions

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Catalytic Asymmetric Cycloaddition of Ketenes and Nitroso Compounds: Enantioselective Synthesis of α-Hydroxycarboxylic Acid Derivatives**

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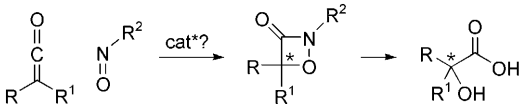
Enantioenriched α-hydroxycarboxylic acid derivatives are not only present as subunits in a range of bioactive compounds, but they also serve as useful intermediates in organic chemistry.[1] Consequently, the development of efficient and versatile methods for their synthesis is an important objective. In the case of α-hydroxycarboxylic acid derivatives wherein the alcohol group is tertiary, several catalytic asymmetric routes have been described, such as the cyanosilylation of ketones,[2,3] the addition of organometallic reagents to α-ketoesters,[2,4] and the phase-transfer alkylation of oxazolidin-2,4-diones.[5] Nevertheless, the development of methods with broader scope is desirable.[6]

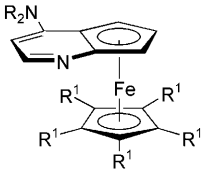
One potential route to enantioenriched α-hydroxycarboxylic acid derivatives is through the ring opening of a 1,2-oxazetidin-3-one, which might be accessed by a catalytic asymmetric [2+2] cycloaddition of a ketene with a nitroso compound [Eq. (1)]. However, there are only a handful of



(1)

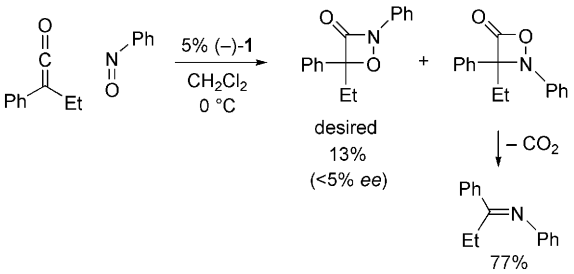
investigations of the cycloaddition itself,[7] and there have been no studies of catalysis of the transformation or of enantioselective variants.[8] Herein, we establish that such [2+2] cycloadditions are indeed subject to catalysis and that a planar-chiral 4-dimethylaminopyridine (DMAP) derivative can provide the target 1,2-oxazetidin-3-ones with high *ee* values.

In previous studies, we established that planar-chiral DMAP derivatives such as **1** (see below) can serve as catalysts for [2+2] cycloadditions of ketenes with imines, aldehydes, and azo compounds.[9,10] In a preliminary investigation, we determined that **1** also catalyzes the cycloaddition of phenyl ethyl ketene with nitrosobenzene [Eq. (2)].[11] However, a



NR_2 = pyrrolidino R^1 = Me (–)-**1**
NR_2 = dimethylamino R^1 = Ph (–)-**2**

mixture of regioisomers was produced (as often occurs in the uncatalyzed process[12]) favoring the undesired heterocycle, which decarboxylates to afford an imine. In addition to being the minor product, the desired 1,2-oxazetidin-3-one is essentially racemic.



(2)

Although we were pleased to determine that such [2+2] cycloadditions are amenable to catalysis, the regioselectivity and enantioselectivity were disappointing. In our earlier studies of [2+2] cycloadditions of ketenes with imines, aldehydes, and azo compounds, controlling the regioselectivity of the reaction had not been an issue.[9] Nevertheless, relative to enantioselectivity, regioselectivity appeared to be the more tractable challenge to initially address.

For nucleophile-catalyzed reactions of ketenes with nitrosoarenes, the aromatic group provides a means to rationally modify the steric and electronic properties of the nitroso compound,[13] so as to control the propensity of the presumed enolate intermediate to produce zwitterion **A** or **B** (Figure 1). In particular, we determined that, by incorporating an electron-withdrawing substituent (CF_3) in the *ortho* position of the aromatic ring, the regioselectivity for the nucleophile-catalyzed cycloaddition of phenyl ethyl ketene can be reversed (1:6→30:1; Eq. (2) vs. Table 1, entry 1). Furthermore, the desired 1,2-oxazetidin-3-one was formed with promising enantioselectivity.

The effects of certain reaction parameters are outlined in Table 1. In the absence of a catalyst, the undesired isomer was the major product (Table 1, entry 2). An array of other catalysts, including a range of amines and phosphines, were

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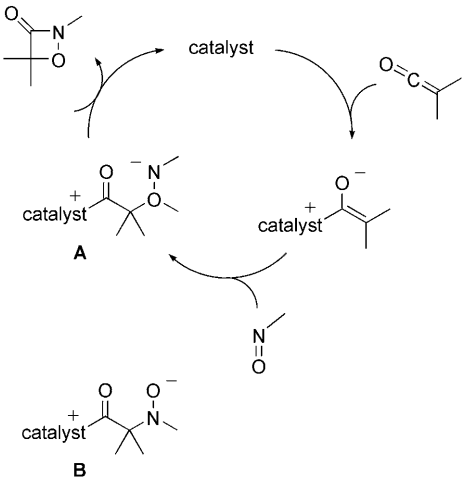
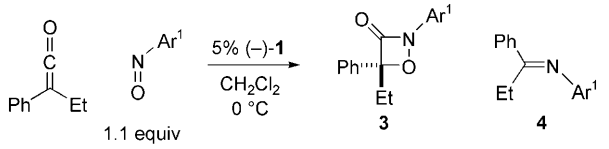


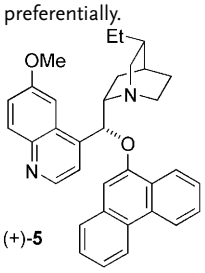
Figure 1. Possible mechanism for the nucleophile-catalyzed cycloaddition of a ketene with a nitrosoarene.

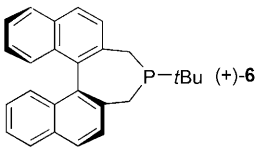
Table 1: Effect of reaction parameters on the nucleophile-catalyzed cycloaddition of a ketene with a nitrosoarene.



Entry	Change from "standard" conditions	Yield of **3** [%][a]	*ee* of **3** [%][b]	Yield of **4** [%][a]
1	none	90	79	3
2	no (−)-**1**	9	–	30
3	5% (−)-**2**, instead of (−)-**1**	16	−22	33
4	5% (+)-**5**, instead of (−)-**1**	19	−35	61
5	5% (+)-**6**, instead of (−)-**1**	33	<2	17
6	toluene, instead of CH_2Cl_2	89	66	2
7	THF, instead of CH_2Cl_2	71	78	1
8	−20°C	81	73	6
9	RT	89	76	4

[a] Determined by ^{1}H NMR spectroscopy with an internal standard; [b] a negative *ee* value signifies that the opposite enantiomer of **3** was formed preferentially.

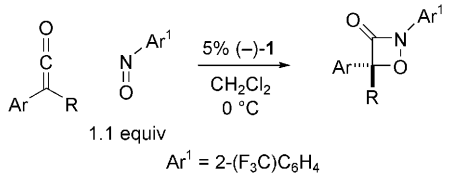




less effective than **1** (Table 1, entries 3–5). Cycloadditions in toluene and THF proceeded with slightly diminished yield or *ee* value compared to CH_2Cl_2 (Table 1, entries 6 and 7), as did reactions conducted at lower or higher temperatures (Table 1, entries 8 and 9).

We examined the scope of the catalytic asymmetric [2+2] cycloaddition of ketenes with a nitrosoarene (Table 2). In the case of aryl methyl ketenes wherein the aryl group is unhindered, enantioselectivity was poor (Table 2, entries 1 and 2). Otherwise, the 1,2-oxazetidin-3-ones were produced with good to excellent *ee* values (Table 2, entries 3–18).

Table 2: Nucleophile-catalyzed asymmetric cycloaddition of ketenes with a nitrosoarene.

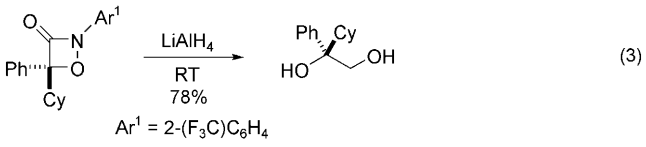


Entry	Ar	R	Yield [%][a]	*ee* [%]
1	Ph	Me	72	13
2	4-(MeO)C_6H_4	Me	60	3
3	*o*-tolyl	Me	90	90
4	2-(MeO)C_6H_4	Me	92	97
5	2-BrC_6H_4	Me	93	94
6	Ph	Et	88	80
7	*m*-tolyl	Et	86	78
8	1-naphthyl	Et	86	78
9	*o*-tolyl	Et	90	96
10	2-(MeO)C_6H_4	Et	93 (88[b])	>98 (>98[b])
11	Ph	CH_2CH_2*i*Pr	86	79
12	Ph	*i*Bu	90	91
13	Ph	*i*Pr	85	92
14	4-ClC_6H_4	*i*Pr	84	92
15	4-(MeO)C_6H_4	*i*Pr	81	90
16	3-thienyl	*i*Pr	78	84
17	Ph	cyclopentyl	81	91
18	Ph	cyclohexyl	84	93

All data are the average of two experiments. [a] Yield of purified product; [b] 1% catalyst loading.

For example, for aryl methyl ketenes in which the aryl group is *ortho*-substituted, highly enantioenriched product was generated (Table 2, entries 3–5). In the case of aryl ethyl ketenes, approximately 80% *ee* was obtained with less hindered aryl substituents (Table 2, entries 6–8), whereas enantioselectivity was very good with larger aromatic groups (Table 2, entries 9 and 10). For *o*-anisyl ethyl ketene, use of a lower catalyst loading (1%) led to only a small loss in yield (Table 2, entry 10).[14] Although branching in the γ position of the alkyl group did not result in enhanced enantioselectivity (Table 2, entry 11 vs. entry 6), branching in the β position furnished a significant increase in the *ee* value (Table 2, entry 12). A range of aryl alkyl ketenes that bear a secondary alkyl substituent also underwent cycloaddition with very good enantioselectivity (Table 2, entries 13–18).

The enantioenriched 1,2-oxazetidin-3-ones could then be converted into synthetically useful compounds, such as 1,2-diols [Eq. (3)] and α-hydroxycarboxylic acids [Eq. (4)].[15] The sequence depicted in Equation (4) illustrates a way to avoid the poor enantioselectivity that is observed in the [2+2] cycloaddition of phenyl methyl ketene (Table 2, entry 1): incorporation of the 2-bromo substituent led to formation of the 1,2-oxazetidin-3-one in excellent yield and *ee* value (Table 2, entry 5), and the bromide "auxiliary" was then removed by hydrogenolysis.



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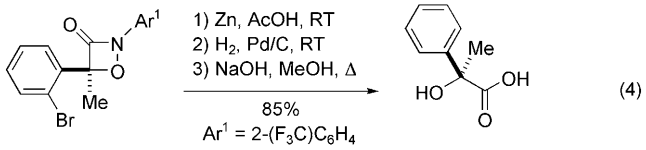

(4)

In analogy to other [2+2] cycloadditions of ketenes that are catalyzed by planar-chiral DMAP derivatives,[9] we hypothesize that this new method for the asymmetric synthesis of 1,2-oxazetidin-3-ones proceeds along the pathway outlined in Figure 1. We have determined that the resting state of catalyst **1** during the reaction is the free catalyst, and that the rate law is first order in catalyst, ketene, and nitroso compound, which suggests that the addition of **1** to the ketene is not the turnover-limiting step of the catalytic cycle.[16]

In summary, we have provided the first examples of catalyzed cycloadditions of ketenes with nitroso compounds to form 1,2-oxazetidin-3-ones. Through the appropriate choice of chiral catalyst and nitroso compound, the synthesis of these intriguing heterocycles was achieved with very good regioselectivity and enantioselectivity. In addition to serving as potentially bioactive target molecules, 1,2-oxazetidin-3-ones were transformed into other important classes of compounds, such as α-hydroxycarboxylic acid derivatives. The versatility of the present method compares favorably with other catalytic asymmetric approaches to the synthesis of α-hydroxycarboxylic acids that bear tertiary alcohols.

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[2] For an overview, see: O. Riant, J. Hannedouche, *Org. Biomol. Chem.* **2007**, *5*, 873–888.

[3] For a pioneering example, see: Y. Hamashima, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2000**, *122*, 7412–7413.

[4] For two seminal studies, see: a) E. F. DiMauro, M. C. Kozlowski, *J. Am. Chem. Soc.* **2002**, *124*, 12668–12669; b) K. Funabashi, M. Jachmann, M. Kanai, M. Shibasaki, *Angew. Chem.* **2003**, *115*, 5647–5650; *Angew. Chem. Int. Ed.* **2003**, *42*, 5489–5492.

[5] T. Ooi, K. Fukumoto, K. Maruoka, *Angew. Chem.* **2006**, *118*, 3923–3926; *Angew. Chem. Int. Ed.* **2006**, *45*, 3839–3842.

[6] For example, previously described catalytic asymmetric processes do not generally provide access to enantioenriched α-hydroxycarboxylic acids wherein the tertiary alcohol bears a secondary alkyl substituent or a hindered aromatic group (see Table 2).

[7] a) H. Staudinger, S. Jelagin, *Ber. Dtsch. Chem. Ges.* **1911**, *44*, 365–374; b) S. P. Makarov, V. A. Shpanskii, V. A. Ginsburg, A. I.; Shchekotikhin, A. S. Filatov, L. L. Martynova, I. V. Pavlovskaya, A. F. Golovaneva, A. Y. Yakubovich, *Dokl. Akad. Nauk SSSR* **1962**, *142*, 596–599; c) G. Kresze, A. Trede, *Tetrahedron* **1963**, *19*, 133–136; d) R. C. Kerber, M. C. Cann, *J. Org. Chem.* **1974**, *39*, 2552–2558; e) D. Moderhack, K. Stolz, *Chem. Zeit.* **1990**, *114*, 5–7.

[8] To our knowledge, there are no reports of the synthesis of an enantioenriched 1,2-oxazetidin-3-one. This heterocycle has a structural similarity to a β-lactam and to cycloserine.

[9] a) Imines: E. C. Lee, B. L. Hodous, E. Bergin, C. Shih, G. C. Fu, *J. Am. Chem. Soc.* **2005**, *127*, 11586–11587; B. L. Hodous, G. C. Fu, *J. Am. Chem. Soc.* **2002**, *124*, 1578–1579; b) Aldehydes: J. E. Wilson, G. C. Fu, *Angew. Chem.* **2004**, *116*, 6518–6520; *Angew. Chem. Int. Ed.* **2004**, *43*, 6358–6360; c) Azo compounds: J. M. Berlin, G. C. Fu, *Angew. Chem.* **2008**, *120*, 7156–7158; *Angew. Chem. Int. Ed.* **2008**, *47*, 7048–7050.

[10] For excellent overviews of ketene chemistry, including investigations by others of catalytic asymmetric [2+2] cycloadditions, see: a) T. T. Tidwell, *Eur. J. Org. Chem.* **2006**, 563–576; b) R. K. Orr, M. A. Calter, *Tetrahedron* **2003**, *59*, 3545–3565.

[11] The 1,2-oxazetidin-3-one is the major product of the uncatalyzed process.

[12] For a discussion, see Reference [7d].

[13] For uncatalyzed [2+2] cycloadditions of ketenes with nitrosoarenes, the electronic nature of the nitrosoarene can have a moderate impact upon product distribution (Reference [7d]).

[14] When conducted on a 5 mmol scale (2% catalyst loading), the cycloaddition depicted in Table 2, entry 10 proceeded in 96% yield (1.6 g product) and with 98% *ee*.

[15] Ring openings of 1,2-oxazetidin-3-ones (with $Ar^1 \neq 2$-$(F_3C)C_6H_4$) by $LiAlH_4$ and Zn/AcOH have previously been described (Reference [7c]). Additional derivatizations are described in the Supporting Information.

[16] We do not detect a nonlinear effect: product *ee* value correlates linearly with catalyst *ee* value.

