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Catalytic, Asymmetric Preparation of Ketene Dimers from Acid Chlorides

Michael A. Calter,* Robert K. Orr, and Wei Song

Department of Chemistry, University of Rochester, Rochester, New York 14627-0216

calter@chem.rochester.edu

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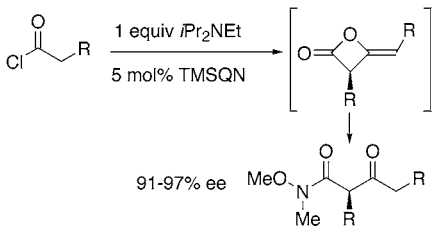
ABSTRACT



The cinchona alkaloid-catalyzed dimerization of monosubstituted ketenes generated in situ from the reaction of acid chlorides and diisopropylethylamine yields ketene dimers in high yields and enantioselectivities. This reaction tolerates sterically demanding and functionally diverse substituents. Kinetic studies suggest that the rate-determining step for the reaction is the deprotonation of the acid chloride by the tertiary amine to form ketene and that the stereochemistry-forming step is addition of an ammonium enolate with ketene.

Ketenes have served as key intermediates in a number of important reactions, particularly those involving asymmetric catalysis.[1] However, the general instability of ketenes has complicated methods for their generation. Fortunately, several groups recently reported catalytic, asymmetric reactions of ketenes generated in situ from the reaction of acid halides with tertiary amines.[2] We previously reported that the cinchona alkaloid-catalyzed dimerization of pyrolytically generated methylketene efficiently and enantioselectively afforded a highly useful intermediate for the synthesis of polypropionates.[3] We now report the first examples of catalytic, asymmetric dimerization of in situ generated ketenes, along with the dramatically expanded scope possible with the new conditions. We also show that this reaction is mechanistically distinct from other, nucleophile-catalyzed reactions of in situ generated ketenes.

Our design of conditions for the target reaction started with precedents for the two basic steps: base-promoted formation of ketenes from acid chlorides and ketene dimerization. Dimerization of pyrolytically formed methylketene required nucleophilic catalysis by cinchona alkaloid derivatives. This requirement necessitated the choice of a stoichiometric base that would not catalyze the formation of racemic dimer.[4] Several groups have described the use of cinchona alkaloid catalysts and non-nucleophilic, stoichiometric amines to limit stoichiometric amine-catalyzed reactions. In one of the examples most relevant to the desired reaction, Lectka and co-workers reported that acid chlorides condense with reactive imines at −78 °C using catalytic benzoylquinine (BzQN) and stoichiometric proton sponge (PS) in toluene (Scheme 1).[2d] In related work, Romo et al. used quinidine (QD) and diisopropylethylamine (Hünig's base, HB) in toluene at −20 °C for the addition of acetyl chloride to reactive aldehydes.[2c] However, neither of these precedents offered compelling evidence for the intermediacy of a ketene.

Based on the precedents of Scheme 1, we assayed conditions for the in situ generation and dimerization of methylketene, starting with propionyl chloride (Scheme 2, Table 1). For the purposes of determining yield and enantiomeric purity, we immediately converted volatile and unstable methylketene dimer **1** into β-ketoamide **2**.[5] Treat-

(1) For a recent review of asymmetric reactions involving ketenes, see: Orr, R. K.; Calter, M. A. *Tetrahedron* **2003**, *59*, 3545−3565.

(2) (a) Nelson, S. G.; Peelen, T. J.; Wan, Z. *J. Am. Chem. Soc.* **1999**, *121*, 9742−9743. (b) Yoon, T. P.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2001**, *123*, 2911−2912. (c) Tennyson, R. L.; Romo, D. *J. Org. Chem.* **2000**, *65*, 7248−7252. (d) Taggi, A. E.; Hafez, A. M.; Wack, H.; Young, B.; Drury, W. J., III; Lectka, T. *J. Am. Chem. Soc.* **2000**, *122*, 7831−7832.

(3) Calter, M. A.; Liao, W. *J. Am. Chem. Soc.* **2002**, *124*, 13127−13129 and references therein.

(4) Sauer, J. C. *J. Am. Chem. Soc.* **1947**, *69*, 2444−2448.

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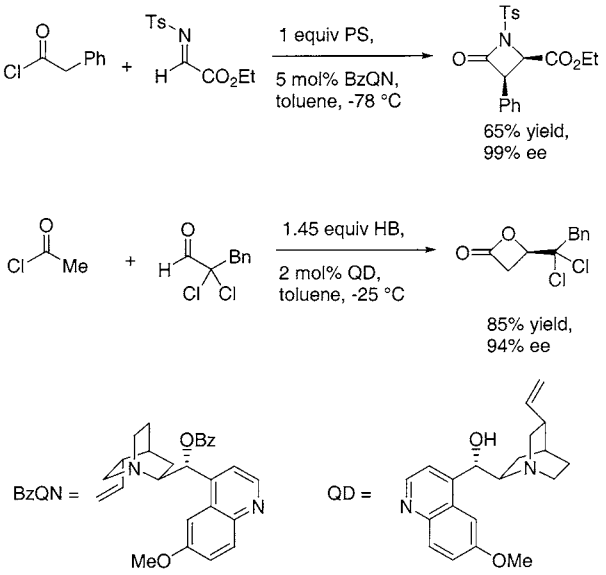
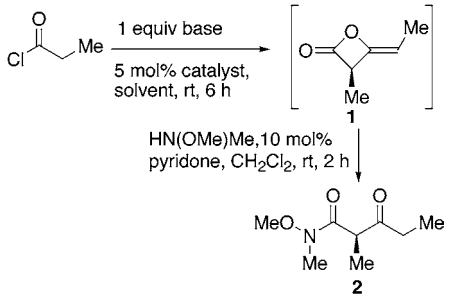
Scheme 1



ment with stoichiometric PS or HB in toluene did not lead to product in the absence of cinchona alkaloid catalyst

Scheme 2



(entries 1 and 2). Lectka's conditions from Scheme 1 also failed to produce significant quantities of **2** (entry 3). However, these workers have shown that pathways not involving ketene intermediates predominate under these conditions.[6] Conditions similar to those of Romo did afford minor amounts of product (entry 4), but the key to high levels of conversion was the use of CH_2Cl_2 as solvent (entry 5). We had previously demonstrated that trimethylsilylquinine (TMSQN) was superior to the parent alkaloid or acyl derivatives in the dimerization of preformed methylketene. The same held true in the present reaction, as the nonsilylated alkaloids afforded lower selectivities and conversions (entries 7 and 8). Conveniently, the use of trimethylsilylquinidine (TMSQD) gave high enantioselectivity for the opposite enantiomer (entry 9). One could also isolate **1** in relatively

(5) Previous experiments demonstrated that the conversion of **1** into **2** proceeds in high yield and without epimerization. See: Calter, M. A.; Guo, X. *J. Org. Chem.* **1998**, *63*, 5308−5309.

(6) Taggi, A. E.; Hafez, A. M.; Wack, H.; Young, B.; Ferraris, D.; Lectka, T. *J. Am. Chem. Soc.* **2002**, *124*, 6626−6635.

Table 1. Yields and Selectivities for the Formation of **2**[a]

entry	catalyst[b]	solvent	base	% yield of **2**	% ee **2** (config)
1		PhMe	PS	0	
2		PhMe	HB	0	
3	BzQN	PhMe	PS	0	
4	TMSQN	PhMe	HB	19	93 (*R*)
5	TMSQN	CH_2Cl_2	HB	79	94 (*R*)
6	QN	CH_2Cl_2	HB	56	70 (*R*)
7	BzQN	CH_2Cl_2	HB	64	80 (*R*)
8	PropQN	CH_2Cl_2	HB	65	69 (*R*)
9	TMSQD	CH_2Cl_2	HB	79	97 (*S*)
10	TBSQN	CH_2Cl_2	HB	72	94 (*R*)
11	TMSQN[c]	CH_2Cl_2	HB	71	96 (*R*)
12	TMSQN[c,d]	CH_2Cl_2	HB	71	97 (*R*)

[a] All reactions run starting with 2 mmol of propionyl chloride at a concentration of 0.1 M, unless otherwise noted. [b] PropQN = propionyl quinine. [c] Filtered through silica gel prior to formation of **2**. [d] Run starting with 115 mmol of propionyl chloride in 460 mL of CH_2Cl_2 (0.25 M).

pure form and reduced yield by rapid filtration of the unpurified reaction mixture through a small plug of silica gel, a finding that has importance for other reactions of **1** (entry 11). Finally, increasing the scale and concentration did not effect the yield or enantioselectivity of the reaction (entry 12).

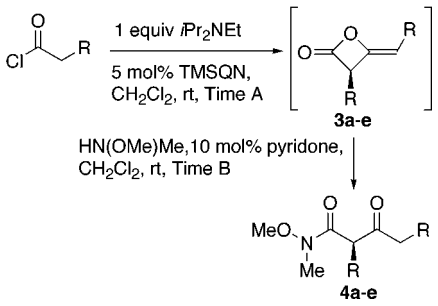
Table 2. Yields and Selectivities for the Formation of **4a**−**e**

compd	R	time A (h)	time B (h)	% yield	% ee
4a	Et	6	2	82	92
4b	*i*Pr[a]	24	24	65	96
4c	*t*Bu[a]	96	24	58	92
4d	CH_2OTIPS	3	2	88	91
4e	CH_2CO_2Me[b]	3	2	64	92

[a] Reaction performed at 0.5 M concentration of acid chloride. [b] Dimer filtered through silica gel before opening.

The conditions developed for **1** also allowed the preparation of dimers **3a**-**e**, bearing a variety of more highly functionalized side chains not compatible with pyrolytic methods for ketene generation (Scheme 3, Table 2). Again, the dimers were converted without isolation into the corre-

Scheme 3



sponding β-ketoamides **4a**−**e**. The reaction tolerated increasing steric bulk, although adequate conversion to the isopropyl and *tert*-butylketene dimers required an initial concentration of 0.5 M for the acid chloride and longer times for the opening reaction. Substrates bearing convenient functional groups for further elaboration, such as β-siloxy or ester groups, afforded dimers in reasonable yields and high enantioselectivities.

We next determined the rate- and stereochemistry-determining step of the reaction. A simple ^{1}H NMR study showed that the rate of generation of **1** from propionyl chloride depended linearly on the concentration of propionyl chloride and HB, but not on catalyst concentration (Figure 1).[7] These results were consistent with ketene formation

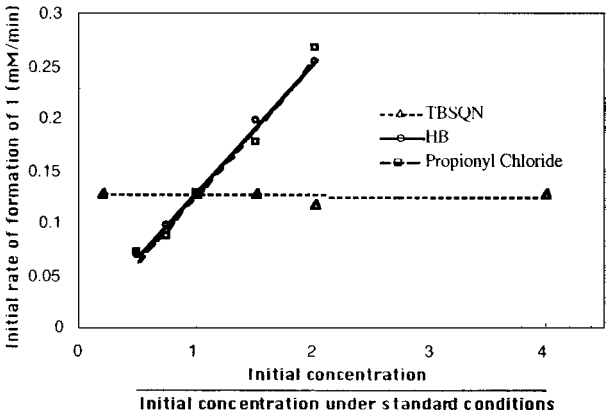
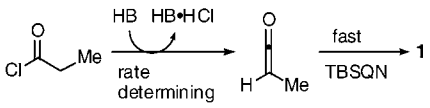


Figure 1. Initial rates for the formation of **1** at various concentrations of propionyl chloride, HB, and TBSQN. Standard conditions refer to starting concentrations of 0.1 M for both propionyl chloride and HB and 0.005 M for TBSQN. The reactions were monitored by ^{1}H NMR at 25 °C in CD_2Cl_2, and the amount of **1** was quantified by comparison of the integration of the signal at 4.75 ppm with that of the signal at 5.82 ppm for an internal standard, 2,5-dimethylfuran.

being rate-determining for the in situ dimerization reaction and the rate-determining step for ketene formation being deprotonation of acid chloride by HB (Scheme 4). The large

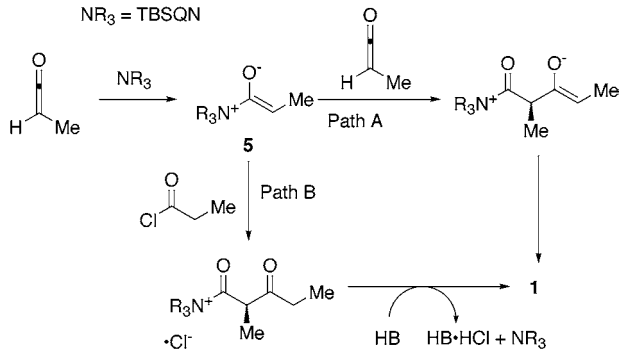
Scheme 4



kinetic isotope effect, 5.1, observed starting with propionyl chloride-*2*,*2*-d_2 supported these conclusions. This mechanism differed dramatically from that for the Lectka example in Scheme 1, in which formation of an acylammonium intermediate between acid chloride and BzQN was the rate-determining step.[6]

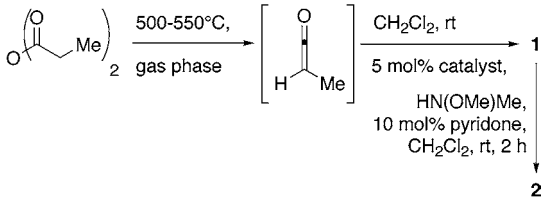
We next sought to determine whether the nature stereochemistry-determining step of the dimerization depended on whether the methylketene was pregenerated or generated in situ. All evidence from our work and the work of others indicated that the stereochemistry-determining step involved the reaction of an ammonium enolate, such as **5**, with an electrophile (Scheme 5).[8] In the case of the dimerization of

Scheme 5



pregenerated methylketene (Scheme 6), the electrophile must be another molecule of methylketene (path A, Scheme 5).[9] However, the use of in situ generated methylketene opens the possibility of a reaction between **5** and propionyl chloride (path B).

Scheme 6



In an attempt to distinguish between paths A and B for the dimerization of in-situ-generated methylketene, we compared the optical activity of **1** produced under these conditions with that produced from thermolytically generated methylketene (Schemes 2 and 6, Table 3). Using several catalysts with a range of enantioselectivies, the optical activities were identical within experimental error. This result suggested a common stereochemistry-determining step for both reactions, and therefore, that the dimerization of in situ-generated methylketene proceeded by path A. This conclusion implies that methylketene was significantly more electrophilic toward **5** than propionyl chloride, as the results from the rate study indicated that concentration of methylketene was generally much lower than that of propionyl chloride.

(7) The kinetics experiments were conducted using TBSQN as catalyst, as this compound demonstrated optimal stability under the reaction conditions.

(8) Pracejus, H. Mätje, H. *J. Prakt. Chem.* **1964**, *24*, 195−205.
(9) Samtleben, R.; Pracejus, H. *J. Prakt. Chem.* **1972**, *314*, 157−169.

Table 3. Yields and Selectivities for the Formation of **2**[a]

reaction[a]	catalyst	% ee of **2**
Scheme 2	TMSQN	96
Scheme 6	TMSQN	97
Scheme 2	BzQN	80
Scheme 6	BzQN	81
Scheme 2	PropQN	69
Scheme 6	PropQN	69

[a] Results for Scheme 2 from Table 1, entries 7, 8, and 11.

In conclusion, we have developed conditions for the in situ generation and dimerization of ketenes from acid halides. These conditions allowed a fundamental expansion in the scope of the dimerization. The mechanism of the reaction differs dramatically from that of previously studied, nucleophile-catalyzed reactions of in situ generated ketenes. The discovery of these conditions should impact the use of in situ generated ketenes in other catalytic, asymmetric processes.

Acknowledgment. We acknowledge the NIH for support and Prof. Joseph Dinnocenzo for helpful conversations.

Supporting Information Available: Complete experimental procedures and characterization data for compounds **2** and **4a**−**e**. This material is available free of charge via the Internet at http://pubs.acs.org.

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