Catalytic, Asymmetric Dimerization of Methylketene

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We hope to develop quick, inexpensive routes to biologically important classes of molecules using catalytic, asymmetric transformations. Toward this goal, we are exploring reactions catalyzed by chrial tertiary amines. Tertiary amines are attractive catalysts, as these compounds are generally stable, inexpensive, and less toxic than most transition metals. Although the asymmetric variants of some tertiary amine-catalyzed processes are known,[1] many such reactions have not been attempted with chiral catalysts. One example of the latter case is the tertiary amine-catalyzed dimerization of methylketene (Scheme 1).[2,3] We report here that cinchona alkaloids and their derivatives catalyze the dimerization of methylketene with high enantioselectivity, yielding a product that easily transforms into a useful synthon for polypropionate synthesis.

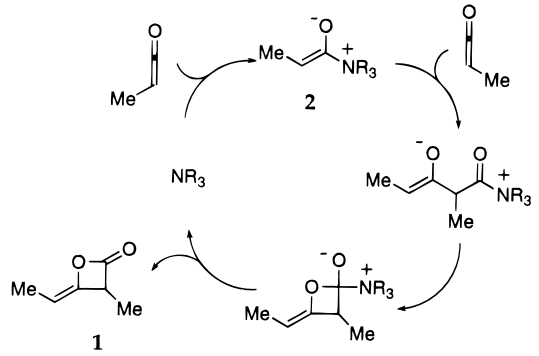
The tertiary amine-catalyzed dimerization of methylketene yields β-lactone **1** *via* a formal Claisen condensation (Scheme 1). We reasoned that a chiral tertiary amine might impose a facial bias on ammonium enolate **2**, eventually producing β-lactone **1** in an optically enriched form. We were encouraged in this respect by the high enantioselectivity (98% ee) realized by Wynberg in the related cycloaddition of ketene to chloral catalyzed by cinchona alkaloids.[4] We also assumed that **1** would be a useful polypropionate precursor. Accordingly, we studied the dimerization of methylketene catalyzed by various chiral, nonracemic tertiary amines.

We used Ward's procedure to prepare a −78 °C solution of methylketene in tetrahydrofuran (THF).[5] In this procedure, the ketene distilled away from the reaction pot as it formed, yielding a reactant solution free of any starting materials or byproducts. We then added the ketene solution to 1 mol % of the amine catalyst in THF at −78 °C (Scheme 2). The volatility and instability to silica gel of **1** hampered the isolation of this compound, so we added $LiAlH_4$ to the reaction mixture to produce primary alcohol **3** (Table 1).[6]

Either enantiomer of **3** is produced with high enantiocontrol from the dimerization of methylketene with readily available catalysts. Quinidine and its derivatives afford uniformly high enantioselectivities, while quinine and propionylquinine are notably less selective catalysts. This trend is similar to trends observed in numerous processes utilizing cinchona alkaloids as catalysts or ligands.[1]

The overall yield for this reaction sequence is 20% based on bromopropionyl bromide, regardless of the identity of the catalyst. The following results indicate

Scheme 1



Scheme 2

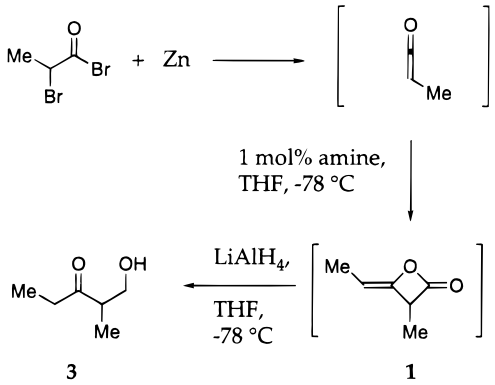


Table 1. Catalysts and Enantioselectivies for the Production of 3

entry	catalyst	% ee of **3**
1	quinidine	98 (*R*)
2	propionylquinidine	97 (*R*)
3	(trimethylsilyl)quinidine	98 (*R*)
4	quinine	70 (*S*)
5	propionylquinine	54 (*S*)
6	(trimethylsilyl)quinine	93 (*S*)

that the dimerization reaction is quantitative; reaction of the methylketene with aniline afforded approximately 30% of the corresponding amide, and reduction of purified **1** afforded a 70% yield of **3**. While the yield for this reaction sequence is lower than that for the existing route to **3**,[7] the low cost of the starting material (100 g/$18.25 for 2-bromopropionyl bromide from Aldrich) and the lack of intermediate isolations make this route attractive. We are currently exploring the asymmetric dimerization of methylketene generated by alternative means[8] and also different methods for reduction.

Since methylketene rapidly acylates alcohols, we sought to determine whether the active catalysts in the quinine- or quinidine-catalyzed reactions are the free alcohols or the propionylated alkaloids. Propionyl quinidine afforded the same induction as quinidine (entries 1 and 2), indicating that the ester was probably the active catalyst in both these reactions. However, propionyl quinine was a less enantioselective catalyst than quinine (entries 4 and 5), suggesting that the free alcohol accounted for at least some of the product in the quinine-catalyzed reaction.[9]

We propose the following structure for the putative ammonium enolate derived from quinidine and meth-

(1) Wynberg, H. *Top. Stereochem.* **1986**, *16*, 87.
(2) Sauer, J. C. *J. Am. Chem. Soc.* **1947**, *69*, 2444.
(3) Samtleben, R.; Pracejus, H. *J. Prakt. Chem.* **1972**, *314*, 157.
(4) (a) Wynberg, H.; Staring, E. G. J. *J. Am. Chem. Soc.* **1982**, *104*, 166. (b) Wynberg, H.; Staring, E. G. J. *J. Org. Chem.* **1985**, *50*, 1977.
(5) McCarney, C. C.; Ward, R. S. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1600.
(6) The enantiomeric excess of **3** was assayed by conversion to the corresponding Mosher ester followed by GC analysis. The configuration of the major enantiomer produced was established by comparison of the rotation of this compound to the rotation of **3** derived from methyl (*S*)-(+)-3-hydroxy-2-methylpropionate (see ref 7).
(7) Luke, G. P.; Morris, J. *J. Org. Chem.* **1995**, *60*, 3013.
(8) Masters, A. P.; Sorensen, T. S.; Ziegler, T. *J. Org. Chem.* **1986**, *51*, 3559.

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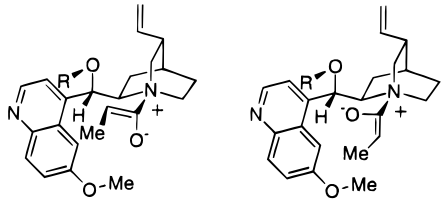

Figure 1. Possible conformations of ammonium enolate **2**.

ylketene (Figure 1). The enolate geometry and the quinidine conformation are based on literature precedent.[10,11] The observed facial selectivity indicates that rotamer A is favored over rotamer B. Rotamer B might be destabilized by the steric interaction between the enolate methyl group and the aromatic moiety of the catalyst. Inspection of rotamer A indicates that one face of the enolate is relatively open toward electrophilic attack by another molecule of methylketene, while the other is quite hindered.

The results indicate that the oxygen substituent in quinine and its derivatives rotates further away from shielding a face of the enolate than in the corresponding quinidine diastereomers. Therefore, a larger group (TMS) is required for the quinine diastereomers to afford a high facial bias.

The product of this reaction, **3**, is a useful synthon for polypropionate synthesis. The titanium enolate of this compound undergoes a stereoselective aldol addition with isobutyraldehyde.[6] Derivatives of **3** are used as dipropionate equivalents in the construction of oleandolide and portions of the siphonarins and the baconipyrones.[12] Compound **1** has not been used as a chiral synthon as it has not previously been available in an optically enriched form. We are exploring the *in situ* reactions of this novel dipropionate equivalent with nucleophiles and electrophiles to produce tripropionates.

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Supporting Information Available: Experimental procedures for the preparation of **3** and all the quinine and quinidine derivatives used as catalysts; full characterization of quinine and quinidine derivatives (5 pages).

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(9) These results are similar to Wynberg's results with acylated catalysts in the addition of ketene to chloral (ref 4a).

(10) There are numerous examples of nucleophiles adding to aldoketenes opposite the larger substituent. For example, see: Dondoni, A.; Fantin, G.; Fogagnolo, M.; Mastellari, A.; Medici, A.; Pedrini, P. *J. Org. Chem.* **1984**, *49*, 3478.

(11) Dijkstra, G. D. H.; Kellog, R. M.; Wynberg, H.; Svendsen, J. S.; Marko, I.; Sharpless, K. B. *J. Am. Chem. Soc.* **1989**, *111*, 8069.

(12) (a) Paterson, I.; Norcross, R. D.; Ward, R. A.; Romera, P.; Lister, M. A. *J. Am. Chem. Soc.* **1994**, *116*, 11287. (b) Paterson, I.; Franklin, A. S. *Tetrahedron Lett.* **1994**, *35*, 6925.