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An Organocatalytic Asymmetric Nazarov Cyclization

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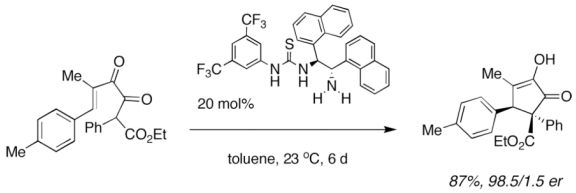
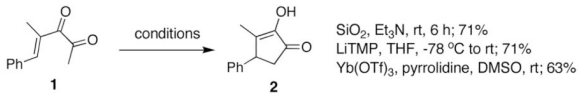
Abstract



An organocatalytic asymmetric Nazarov cyclization of diketoesters has been developed that proceeds by means of a dual activation mechanism. Screening of a number of catalysts led to a new thiourea that incorporates a primary amino group. The method gives rise to cyclic products with two adjacent quaternary asymmetric carbon atoms, one of which is an all carbon atom stereocenter, with complete or nearly complete diastereoselectivity, and in high or very high enantiomeric excess. A brief and very convenient synthesis of the acyclic diketoester starting materials through nucleophilic addition to a ketene has been described.

In earlier work we have described cyclizations of α-ketoenones under a variety of mild reaction conditions. For example, ketoenone **1** can be converted to α-hydroxycyclopentenone **2** in 71% yield by exposure to silica gel and triethylamine in the absence of solvent at room temperature (eq 1).1 Alternatively, treatment of **1** with lithium tetramethylpiperidide or with $Yb(OTf)_3$ and pyrrolidine leads to **2** in 71% and 63% yield, respectively.2 There are earlier examples of diketone cyclizations that lead to α-hydroxycyclopentenones that may may proceed through a similar mechanism. For example, in 1975 Weinreb and Auerbach, inspired by an observation published in 1965 by Muxfeldt and coworkers,3 described the cyclization of diketone **3** to **4** under the influence of $Mg(OMe)_2$ during their synthesis of cephalotaxine (eq 2).4,5 Both Muxfeldt and



[1]

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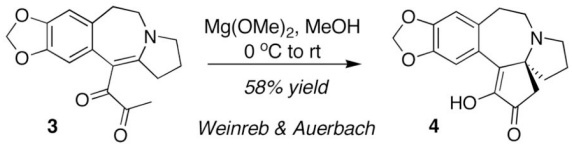
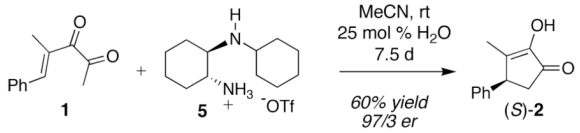
Supporting Information Available: Detailed experimental and spectroscopic data and reproductions of ^1H and ^{13}C NMR data for **18**–**30**, and of the intermediates leading to **18**–**30**. X-ray structure of the (−)-camphanic acid derivative of **19**. This material is available free of charge via the Internet at http://pubs.acs.org.



[2]

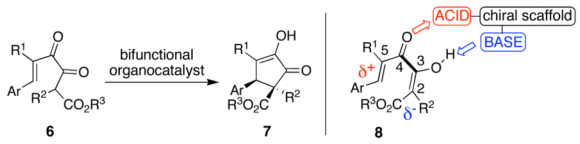
Weinreb described the cyclization as an intramolecular Michael reaction of a chelated magnesium enolate. Moreover, both groups noted that the cyclization did not proceed in the absence of Lewis acidic metal species. Although we cannot rule out the intramolecular Michael addition, we have described our reactions as Nazarov cyclizations6 for two reasons. First, the intramolecular Michael addition is a forbidden 5-*endo-trig* process7 and second, many of our cyclizations are favored by enolate substitution, whereas steric encumbrance of the nucleophile would be expected to inhibit a Michael reaction.

A longstanding goal in our group has been to develop a useful asymmetric organocatalytic Nazarov cyclization of α-ketoenones.8,9 Many Nazarov cyclizations require strongly acidic conditions, but the mild conditions for the cyclizations of **1** gave us reason to believe that an organocatalytic process could be developed. Our first iminium ion-mediated Nazarov cyclization of α-ketoenones proceeded via exposure of **1** to stoichiometric diamine triflate **5** to give (*S*)-**2** in 60% yield and 97/3 er (eq 3).10 The reaction was slow (7.5 d) and a catalytic cycle was not established, presumably due to the exceptional stability of a covalent intermediate.



[3]

Our strategy toward overcoming this problem was the use of weaker non-covalent catalysts in combination with diketoesters, shown in eq 4. During the course of our studies we accumulated evidence that more highly enolic diketones underwent cyclization with greater facility. Moreover, enolic diketoesters are attractive substrates because either the *E* or



[4]

the *Z* enol isomer can be formed selectively,11 sparing us the labor of controlling the geometry of a tetrasubstituted alkene. These substrates also have the potential to generate two adjacent stereogenic carbon atoms diastereoselectively, one of which is an all-carbon stereocenter. Our catalytic system was designed to induce complementary polarization at the two terminal carbon atoms12 as indicated in **8** (eq 4), consequently a bifunctional organocatalyst combining Bronsted acidic and Lewis basic groups was developed (see Figure 1).

It remained for us to develop the general and convenient diketoester synthesis that is summarized in Scheme 1. Lithiated cyanohydrin silyl ether13 **14** was added to ketene **15** leading to ketoester **16** in 65% yield. Exposure of **16** to CsF led to **17** in 88% yield. The ketene was formed conventionally, by treating the malonate *mono*-acid chloride with Hünig's base in ether at −78° C.14 The commercial availability of several chiral thiourea catalysts allowed us to prove principle quickly.15,16 Exposure of **17** to 20 mol% of thiourea **9** led to the desired product **18** in 68/32 er. However, catalyst **10** that lacks a basic amino group was completely ineffective and did not lead to cyclization of **17**. Addition of 0.2 equiv Hünig's base to the reaction mixture of **17** and **10** induced catalytic activity and led to **18** in 70/30 er. In all cases the relative stereochemistry indicated a conrotatory process that had taken place from the *E* enol of **17**. The absolute stereochemistry was assigned on the basis of X-ray crystallographic analysis. These data provide strong support for the dual activation mechanism that is implicit in **8** (eq 4) and are consistent with the observations of both Muxfeldt and Weinreb referred to above that also suggest dual activation.

A fairly extensive screening of bifunctional catalysts led to our choice of **11**. A few trends revealed themselves during this work. For example, catalyst **12** that bears a tertiary amino group led to **18** in only 56/44 er, whereas **13** bearing a secondary amine led to product in 74/26 er. The optimal catalyst **11** led to **18** in 90.5/9.5 er (67%, 14 d). Since the cyclization of **17** to **18** could be induced by base alone, these results may reflect a competitive background reaction with more hindered amines.

A number of examples of the cyclization of diketoesters under optimized conditions (20 mol % **11**, 0.1 M in toluene, 23°C) are summarized in Figure 2. Reaction yields were generally good (58% to 95%) and er's were good to excellent (90/10 to 98.5/1.5). The reactions were slow, requiring between 4 and 21 d for completion. This may reflect product inhibition, since the product is likely to engage the catalyst in a similar way to the enol form of the acyclic starting material. Support for this hypothesis was provided by **7** (Ar=R^1=R^2=Ph, R^3=Et; 87%, 75/25 er, 2d) that precipitated from the reaction mixture and which was formed in the fastest reaction of the ones examined. In only four examples (**7, 21**, **25**, **29**) were we able to detect ca. 5% of the diastereomeric cyclopentenone product derived from the *Z* enol. In the absence of a C6 aryl group cyclization does not take place. The cyclization requires an aryl group at C6 but tolerates alkyl or phenyl groups at C2.17

If the mechanistic hypothesis implicit in **8** is valid, it raises the interesting question of how stereochemical information is transmitted to the developing C-C bond that is remote from the stereogenic carbon atoms of the catalyst. Since asymmetric induction in **18** requires imposing helicity in **17**, it is plausible that coordination with the catalyst results in torsion of the C3–C4 bond. The other elements of novelty in this work are the synthesis of the starting materials and the discovery of an unusual organocatalytic process that generates two adjacent stereogenic carbon atoms, one of which is an all-carbon stereocenter.18 The acyclic substrates will likely prove to be versatile starting materials for several other variants of the Nazarov cyclization. We will explore these and will also address the problem of product inhibition.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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17. The C2 phenyl group increases the reaction rate (compare **21** and **26**, **22** and **27**) whereas aliphatic groups larger than ethyl (isopropyl, *n*-propyl) sharply decrease the reaction rate.
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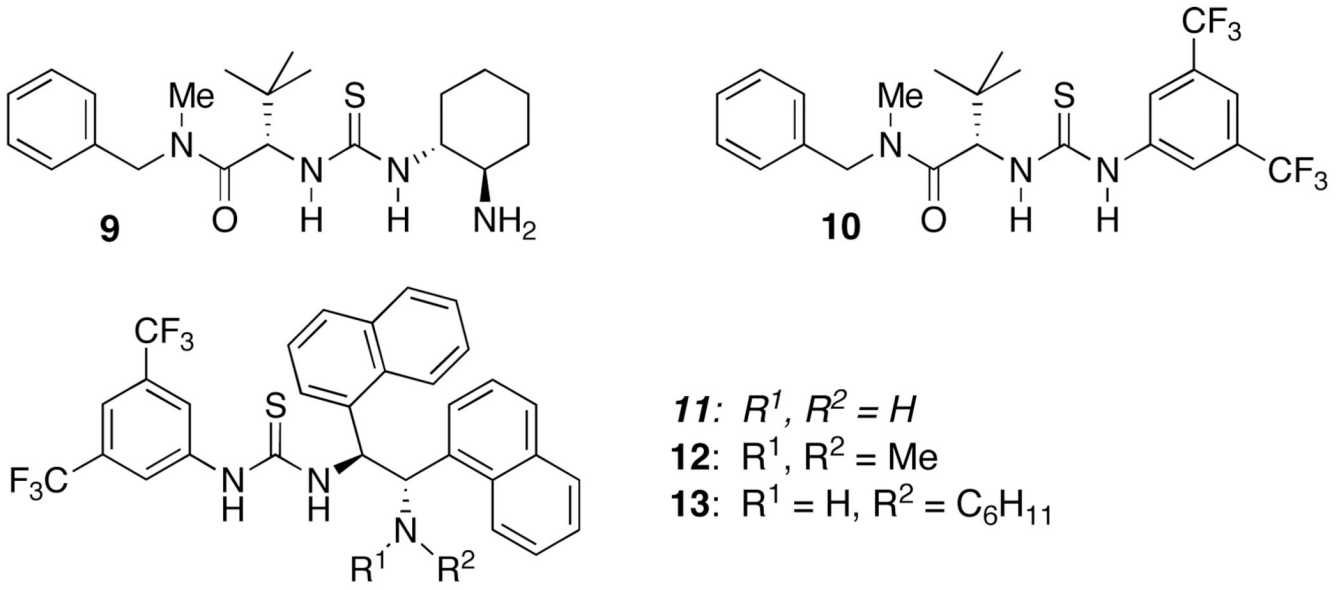


Figure 1.
Organocatalysts.

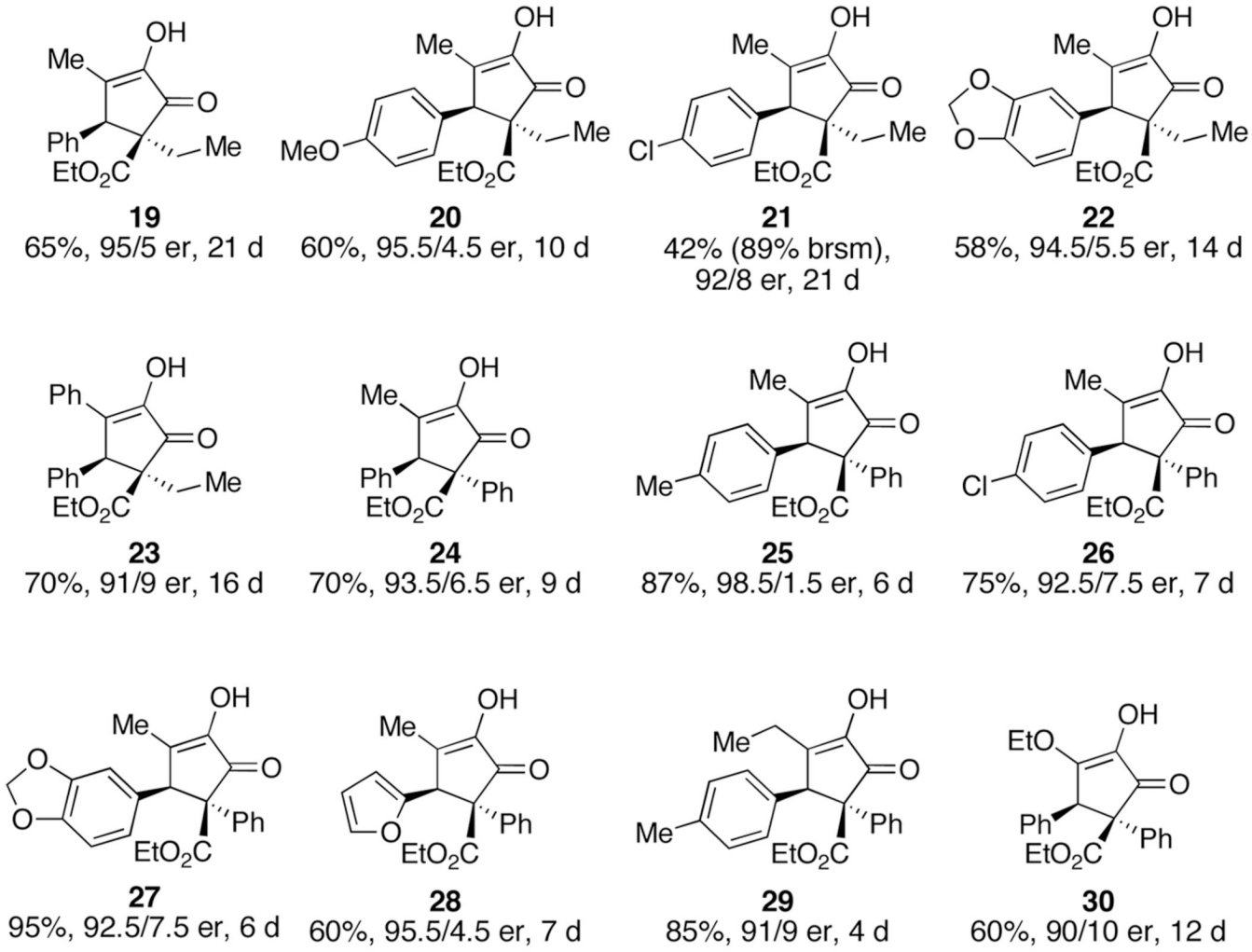
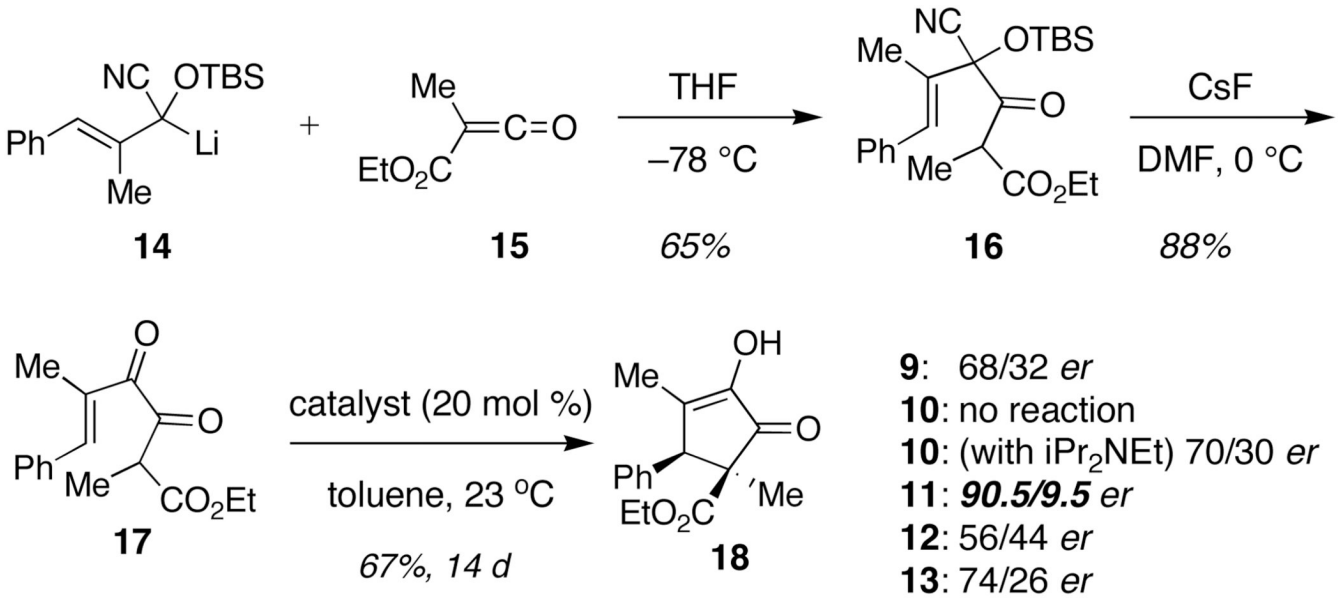


Figure 2.
Examples of the organocatalytic cyclization.



Scheme 1.
Synthesis of diketoesters and cyclization.