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An Organocatalytic Asymmetric Nazarov Cyclization

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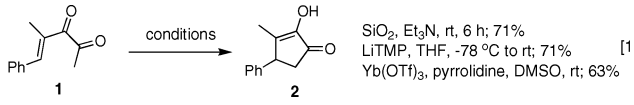
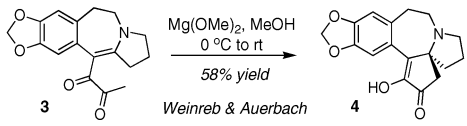
In earlier work, we described cyclizations of α-ketoenones under a variety of mild reaction conditions. For example, ketoenone **1** can be converted to α-hydroxycyclopentenone **2** in 71% yield by exposure to silica gel and triethylamine in the absence of solvent at room temperature (eq 1).[1] Alternatively, treatment of **1** with



[1]

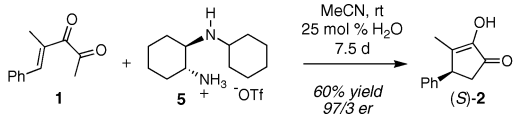
lithium tetramethylpiperidide or with $Yb(OTf)_3$ and pyrrolidine leads to **2** in 71 or 63% yield, respectively.[2] There are earlier examples of diketone cyclizations that lead to α-hydroxycyclopentenones that may proceed through a similar mechanism. For example, in 1975 Weinreb and Auerbach, inspired by an observation published in 1965 by Muxfeldt and co-workers,[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



[2]

and 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 cyclizations[6] for two reasons. First, the intramolecular Michael addition is a forbidden 5-endo-trig process,[7] 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 iminium ion-mediated Nazarov cyclization of α-ketoenones proceeded via exposure of **1** to a stoichiometric amount of diamine triflate **5**, giving (*S*)-**2** in 60% yield and 97/3 er (eq 3).[10] The



[3]

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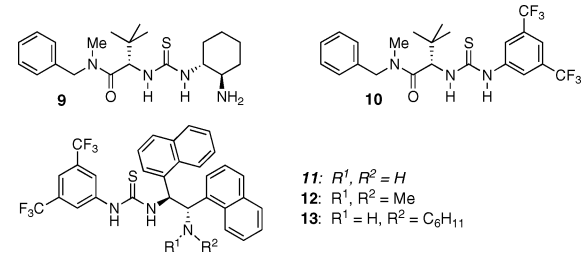
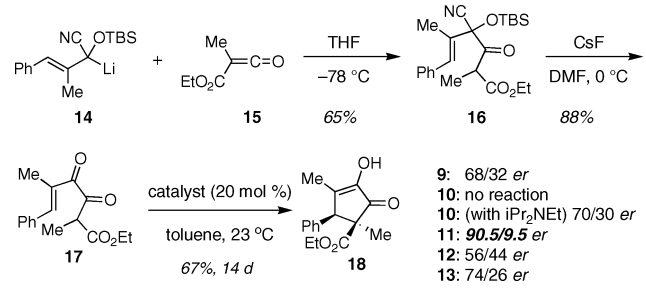


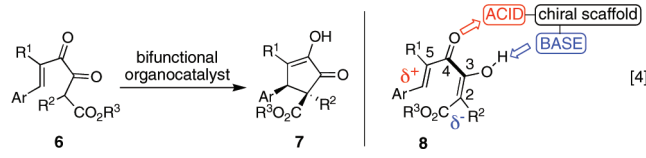
Figure 1. Organocatalysts.

Scheme 1. Synthesis of Diketoesters and Cyclization



reaction was slow (7.5 d) and a catalytic cycle was not established, presumably because of the exceptional stability of a covalent intermediate.

Our strategy for overcoming this problem was the use of weaker noncovalent catalysts in combination with diketoesters, as shown in eq 4. During the course of our studies, we accumulated evidence



[4]

that more highly enolic diketones underwent cyclization with greater facility. Moreover, enolic diketoesters are attractive substrates because either the *E* or *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 atoms,[12] 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 ether[13] **14** was added to ketene **15**, leading to ketoester **16** in 65% yield. Exposure of **16** to CsF led to **17** in 88%

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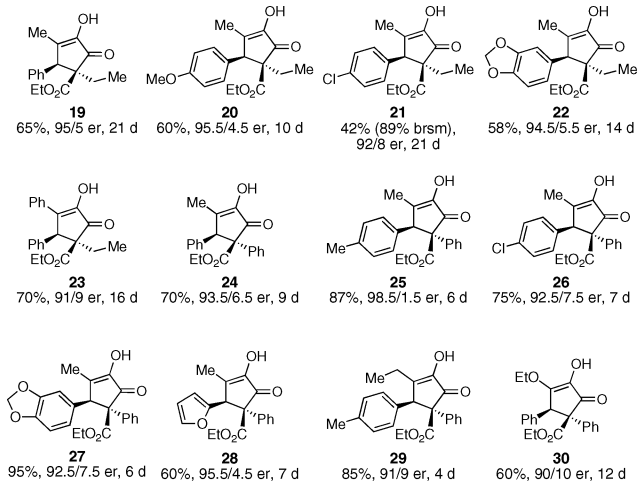

Figure 2. Examples of the organocatalytic cyclization.

yield. The ketene was formed conventionally by treating the malonate monoacid chloride with Hünig's base in ether at −78 °C.[14] The commercial availability of several chiral thiourea catalysts allowed us to provide a proof of principle quickly.[15,16] Exposure of **17** to 20 mol % thiourea **9** led to the desired product **18** in 68/32 er. However, catalyst **10**, which lacks a basic amino group, was completely ineffective and did not lead to cyclization of **17**. Addition of 0.2 equiv of 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 mentioned 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** bearing 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, the cooperative mechanism may be suppressed with more hindered amines.

A number of examples of the cyclization of diketoesters under the optimized conditions (20 mol % **11**, 0.1 M in toluene, 23 °C) are summarized in Figure 2. Reaction yields were generally good (58−95%), and er's were good to excellent (90/10 to 98.5/1.5). The reactions were slow, requiring between 4 and 21 days for completion. This may reflect product inhibition, since the product is likely to engage the catalyst in a similar way as 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, 2 days), which precipitated from the reaction mixture and was formed in the fastest reaction of the ones examined. In only four examples (**7**, **21**, **25**, **29**) were we able to detect the diastereomeric cyclopentenone product derived from the *Z* enol (∼5% yield). In the absence of a C6 aryl group, cyclization was extremely slow. The cyclization requires an aryl group at C6 but tolerates alkyl or phenyl groups at C2.[17]

If the mechanistic hypothesis implicit in eq 4 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 the imposition of 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 also address the problem of product inhibition.

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

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