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Asymmetric Synthesis of Functionalized Cyclopentanones via a Multicatalytic Secondary Amine/*N*-Heterocyclic Carbene Catalyzed Cascade Sequence

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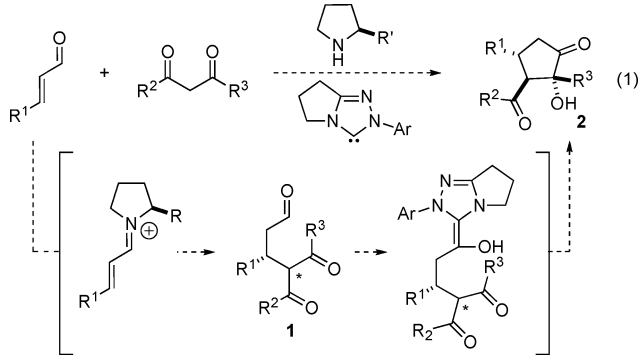
Increased focus has recently been placed on the development of organic transformations that allow for the rapid construction of densely functionalized molecules from simple readily available starting materials. One approach in which these demands can be achieved is through the expanding field of cascade catalysis.[1] Although a number of examples of asymmetric cascade catalysis have been developed, most rely on a single catalyst[1a,d−g,2] to perform two sequential operations. More recently, multiple catalyst systems for cascade reactions have been realized.[1b,c,3] Although these reactions showcase the potential power in this field, relatively few asymmetric examples exist.[4] The major challenge in developing multiple catalyst systems for cascade catalysis is that each catalyst must be compatible with all reagents, intermediates, and other catalysts present from the onset of the reaction. This circumstance is occasionally avoided by addition of reagents and/or catalysts at the midpoint of a given reaction.

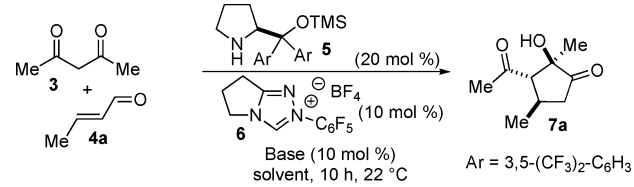
Stimulated by the inherent basicity of many common organic catalysts, most notably secondary amines,[5] Cinchona alkaloids,[6] and nucleophilic carbenes,[7] we speculated that these catalysts could coexist in a single flask to exert their influence over complementary bond-forming events without mutual interference. Indeed, we have already revealed this by utilizing carbene and acyl transfer cocatalysis in the synthesis of amides.[8] To generalize this concept, we initiated a research program to develop multicatalytic asymmetric processes.

At the outset of our studies, we considered the use of active methylene compounds and α,β-unsaturated aldehydes as the first opportunity to test our hypothesis. A number of examples involving the enantioselective secondary-amine-catalyzed conjugate addition of malonates and β-ketoesters to α,β-unsaturated aldehydes[9] and ketones[10] have been described. Reaction between a 1,3-diketone and an enal generates aldehyde **1** bearing a tethered ketone (eq 1). We envisioned that this intermediate would undergo an intramolecular crossed benzoin[11] reaction in the presence of a carbene catalyst to afford highly functionalized cyclopentanone **2** via a formal [3+2] process in a multicatalytic cascade sequence.



While both secondary amines and carbenes are inherently basic, initiation of the sequence by carbene reaction could be detrimental given the possibility of the carbene-catalyzed benzoin,[12] Stetter,[13] and redox[14,15] pathways. The test reaction involved treatment of acetylacetone with crotonaldehyde, 3,5-bistrifluoromethyl diphenyl prolinol TMS ether catalyst **5**,[16] and triazolium salt **6**[17] (Table 1). Combining the two catalysts in the absence of exogenous base yields trace amounts of the desired cyclopentanone (entry 1). However, intermediate **1** is observed by crude ^{1}H NMR, suggesting that the Michael addition occurs but the carbene is not being generated under the reaction conditions. To alleviate this problem, catalytic triethylamine was added to the reaction. In the presence of base, the desired cyclopentanone **7a** is formed in moderate yield and excellent enantioselectivity (entry 2). A brief screen of the reaction conditions revealed sodium acetate to be the optimal base, while chloroform gives the highest level of diastereoselectivity (entries 3−6). Increasing the concentration in the presence of 2 equiv of dicarbonyl **3** provides optimal yields without loss of enantioselectivity or diastereoselectivity (entry 7).

Table 1. Catalyst and Solvent Screen



entry[a]	solvent	base	yield (%)	dr[b]	ee (%)[c,d]
1	CH_2Cl_2	none	trace	nd	nd
2	CH_2Cl_2	Et_3N	31	80:20:<1:<1	84
3	CH_2Cl_2	NaOAc	55	80:20:<1:<1	86
4	EtOH	NaOAc	<20	80:20:<1:<1	70
5	PhMe	NaOAc	53	80:20:<1:<1	84
6	$CHCl_3$	NaOAc	60	85:15:<1:<1	86
7[e]	$CHCl_3$	NaOAc	93	85:15:<1:<1	86

[a] All reactions conducted using 20 mol % **5**, 10 mol % **6**, and 10 mol % base at 22 °C (0.06 M) unless otherwise stated. [b] Diastereomeric ratio determined by GC analysis of unpurified reaction mixture. [c] Enantiomeric excess determined by GC analysis on chiral stationary phase. [d] Major diastereomer. [e] 20 mol % **5**, 10 mol % **6**, 10 mol % NaOAc, and 2 equiv of **3** (0.2M) at 22 °C.

In all cases, only two of the four possible diastereomers are observed by GC/MS analysis. The relative configuration of the major diastereomer was assigned on the basis of NOE studies, confirmed by analogy to X-ray crystal structures of major and minor diastereomers (**13** and **10d**, respectively). The absolute configuration is based on previous work by Jørgensen and co-workers.[9d]

A series of α,β-unsaturated aldehydes with varying substitution was subjected to the optimized reaction conditions (Table 2). Alkyl as well as aromatic substitution is tolerated in the reaction (entries

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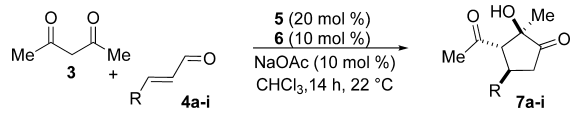
Table 2. α,β-Unsaturated Aldehyde Scope



entry[a]	aldehyde (**4**)	product	yield (%) (dr[b])	ee[c,d]
1	**4a**	**7a**	93 (85:15:<1<1)	86
2	**4b**	**7b**	77 (85:15:<1<1)	93
3	**4c**	**7c**	60 (80:20:<1:<1)	85
4	**4d**	**7d**	70 (85:15:<1<1)	80
5	**4e**	**7e**	59 (80:20:<1:<1)	95
6	**4f**	**7f**	71 (75:25:<1:<1)	92
7	**4g**	**7g**	72 (80:20:<1:<1)	95
8	**4h**	**7h**	60 (85:15:<1:<1)	90
9	**4i**	**7i**	32 (67:33:<1:<1)	82

[a] See footnote e, Table 1. [b] See Table 1. [c] Enantiomeric excess determined by GC or HPLC analysis on a chiral stationary phase. [d] See Table 1.

1−5). Protected alcohols and amines participate in the desired reaction to give products readily amenable to further functionalization (entries 6−8). The sterically larger *iso*-propyl enal **4i** provides reduced yields and diastereoselectivity while maintaining good levels of enantioselectivity (entry 8).

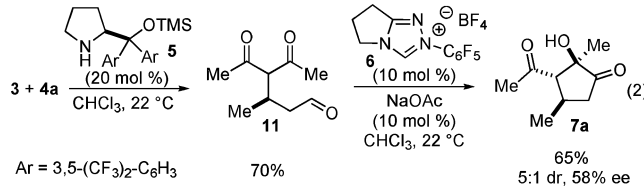
Next we examined unsymmetrical 1,3-dicarbonyls under the optimized reaction conditions (Table 3). Methyl, ethyl, *tert*-butyl, and benzyl acetoacetate provide the desired products with alkyl and aromatic enals giving high levels of enantioselectivity (entries 1−4). β-Ketothioester **8e** also gives the desired product with good selectivity (entry 3). However, these unsymmetrical dicarbonyls afford all four possible diastereomers with moderate selectivity. Cyclic β-ketoesters also react under the optimized conditions to give both [3.3.0] and [4.3.0] bicyclic systems (entries 6−7). Benzyl protected nitrogen is tolerated in the cyclic β-ketoester backbone to afford the highly functionalized bicyclic structure **10g** (entry 5).

Table 3. β-Ketoester Scope

entry[a]	R^2	β-ketoester	product	yield (%) (dr[b])	ee[c,d]
1	Me **4a**	**8a**	**10a**	90 (64:33:3:<1)	91
2	*n*-Pr **4b**	**8b**	**10b**	80 (60:30:8:2)	93
3	Ph **4c**	**8c**	**10c**	86 (60:35:5:<1)	97
4	Me **4a**	**8d**	**10d**	90 (58:39:2:<1)	82
5	*n*-Pr **4b**	**8e**	**10e**	56 (69:22:6:3)	81
6	Me **4a**	**8f**	**10f**	79 (80:20:<1:<1)	94
7	Me **4a**	**8g**	**10g**	76 (85:15:<1:<1)	90

[a−d] See Table 2.

To shed light on the observed reactivity, we conducted a control experiment leaving the azolium catalyst out of the reaction (eq 2). Prolinol catalyst **5** mediates the asymmetric Michael reaction furnishing aldehyde **11** in 70% yield. Surprisingly, subjection of this intermediate to the azolium catalyst and base generates the desired product in only 58% ee again with diminished yield.[18] Experiments aimed at elucidating the source of this variance revealed that aldehyde **11** undergoes a retro-Michael in the presence of prolinol **5**, thus eroding ee. This situation is exacerbated in the presence of silica gel.[19] The carbene catalyst serves to shuttle the intermediate aldehyde on to product thus limiting the prolinol-mediated retro-Michael.



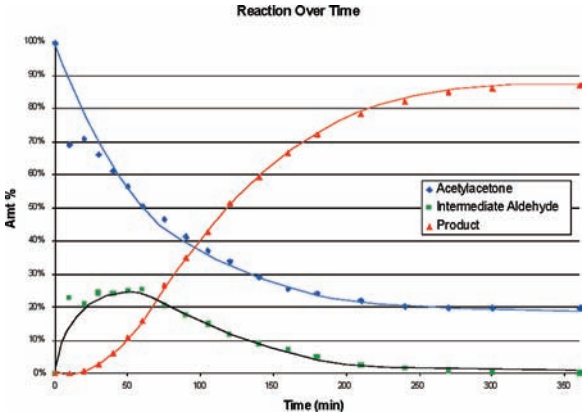
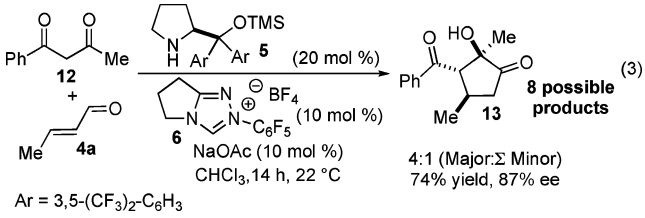


Figure 1. One-pot cascade reaction monitored by GC analysis utilizing 20 mol % **5**, 10 mol % **6**, 10 mol % NaOAc, with 1 equiv of acetylacetone **3** and crotonaldehyde **4a** in $CHCl_3$ (0.2 M) at 22 °C.

To lend further credence to this hypothesis, we monitored the reaction between acetylacetone and crotonaldehyde by withdrawing aliquots at regular intervals (Figure 1). The GC data reveal only moderate buildup of intermediate aldehyde **11** and continuous formation of product, indicating both catalytic cycles are operating concurrently. The lower yield observed for cyclopentanone **7a** obtained from the stepwise process (46% vs 93% in the one-step process) suggests a symbiotic relationship between the two catalysts wherein both catalysts function more efficiently in the presence of each other than they do independently. This type of reactivity highlights the power of the multicatalytic cascade process wherein the one-pot reaction actually outperforms the sequential process, allowing for reactivity that is otherwise not easily accessible.

Finally, in an effort to probe the possibility of controlling the regioselectivity of unsymmetrical 1,3-diketones, 1-benzoyl-acetone **12** was subjected to the reaction conditions (eq 3). To our delight the desired product was obtained in 74% yield, 87% ee in a ratio of 4:1 (major: the sum of all other potential regioisomers and diastereomers). It seems that sterics play a more significant role than eletronics in the carbene catalyzed intramolecular benzoin reaction, since the sterically smaller methyl ketone reacts preferentially over the larger yet more electrophilic phenyl ketone.



In conclusion, we have developed an operationally simple single step multicatalytic cascade process[20,21] for the preparation of α-hydroxycyclopentanones containing three contiguous stereocenters. The highly functionalized products are obtained from cheap, readily available reagents in high enantioselectivities and moderate diastereoselectivities. We further provide conclusive evidence that both catalysts are mutually compatible and are operating concurrently. Experiments aimed at extending the scope of these types of transformations are currently underway.

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Supporting Information Available: Experimental procedures, characterization $^1H/^{13}C$ NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) Addition of 10 mol % sodium acetate to the first step results in similar yield and enantioselectivity. We also observed that carrying out the reaction in a stepwise manner led to more complex reaction mixtures.

(19) See Supporting Information.

(20) General Procedure: a 1 dram vial was equipped with a magnetic stir bar under argon and charged with catalyst **6** (0.024 mmol). $CHCl_3$ (1 mL), 1,3-dicarbonyl (0.448 mmol), and enal (0.224 mmol) were added sequentially followed by catalyst **5** (0.044 mmol) and NaOAc (0.024 mmol) in one portion. The reaction was allowed to stir at room temperature for 14 h at which point the reaction mixture was filtered through a short pad of silica gel, eluted with Et_2O (~10 mL), and then concentrated in vacuo. The resulting crude product was purified by flash silica gel chromatography.

(21) Reaction of **4a** and **8a** was conducted on 2.4 mmol scale using 10 mol % **5**, 5 mol % **6**, and 5 mol % NaOAc to afford 90% yield, 91% ee, and identical diastereomer ratio of **10a**.

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