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Organocatalytic Iminium Ion/Carbene Reaction Cascade for the Formation of Optically Active 2,4-Disubstituted Cyclopentenones

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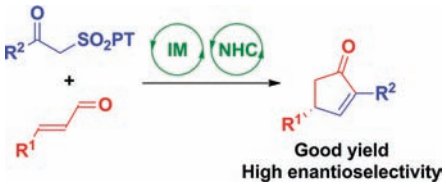
ABSTRACT



An organocatalytic iminium ion/N-heterocyclic carbene (NHC) cascade reaction between β-keto phenyltetrazolesulfones and α,β-unsaturated aldehydes, providing direct access to optically active 2,4-disubstituted cyclopent-2-enones, has been developed. The products are isolated in good yields with high enantioselectivities.

The utilization of organocatalytic cascade reactions in the development of complex reaction sequences has been explored significantly in recent years.[1] Combinations of enamine and iminium ion catalysis are well-studied examples among these developments.[2] Recently, the catalytic activities of secondary amines and N-heterocyclic carbenes (NHCs) have been combined in the synthesis of complex structures.[3]

The application of easily accessible β-keto heteroarylsulfones[4,5] as nucleophiles in the enantioselective organocatalytic introduction of alkenyl and alkynyl

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(2) For selected recent examples, see: (a) Simmons, B.; Walji, A. M.; MacMillan, D. W. C. *Angew. Chem., Int. Ed.* **2009**, *48*, 4349. (b) Galzerano, P.; Pesciaioli, F.; Mazzanti, A.; Bartoli, G.; Melchiorre, P. *Angew. Chem., Int. Ed.* **2009**, *48*, 7892. (c) Quintard, A.; Alexakis, A. *Chem. Commun.* **2011**, *47*, 7212. (d) Xiang, S.; Zhang, B.; Cui, Y.; Hiao, N. *Chem. Commun.* **2011**, *47*, 5007. (e) Appayee, C.; Brenner-Moyer, S. E. *Org. Lett.* **2010**, *12*, 3356. (f) Hong, B.; Sadani, A. A.; Nimje, R. Y.; Dange, N. S.; Lee, G. *Synthesis* **2011**, *12*, 1887.

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(7) For reviews on the synthesis of cyclopentenones, see: (a) Gibson, S. E.; Lewis, S. E.; Mainolfi, N. *J. Organomet. Chem.* **2004**, *689*, 3873. (b) Lee, H.; Kwong, F. *Eur. J. Org. Chem.* **2010**, 789. For recent examples of enantioselective formations of cyclopentenones illustrating different approaches, see: (c) Tanaka, K.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 10296. (d) Tanaka, K.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 8078. (e) Schelwies, M.; Dübon, P.; Helmchen, G. *Angew. Chem., Int. Ed.* **2006**, *45*, 2466. (f) Cao, P.; Deng, C.; Zhou, Y.; Sun, X.; Zheng, J.; Xie, Z.; Tang, Y. *Angew. Chem., Int. Ed.* **2010**, *49*, 4463. (g) Schultz-Fademrecht, C.; Tius, M. A.; Grimme, S.; Wibbeling, B.; Hoppe, D. *Angew. Chem., Int. Ed.* **2002**, *41*, 1532. (h) Nunes, J. P. M.; Veiros, L. F.; Vaz, P. D.; Afonso, C. A. M.; Caddick, S. *Tetrahedron* **2011**, *67*, 2779. (i) Dickmeiss, G.; Sio, V. D.; Udmark, J.; Poulsen, T. B.; Marcos, V.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2009**, *48*, 6650. (j) Shi, X.; Gorin, D. J.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 5802. (k) Dübon, P.; Schelwies, M.; Helmchen, G. *Chem.—Eur. J.* **2008**, *14*, 6722.

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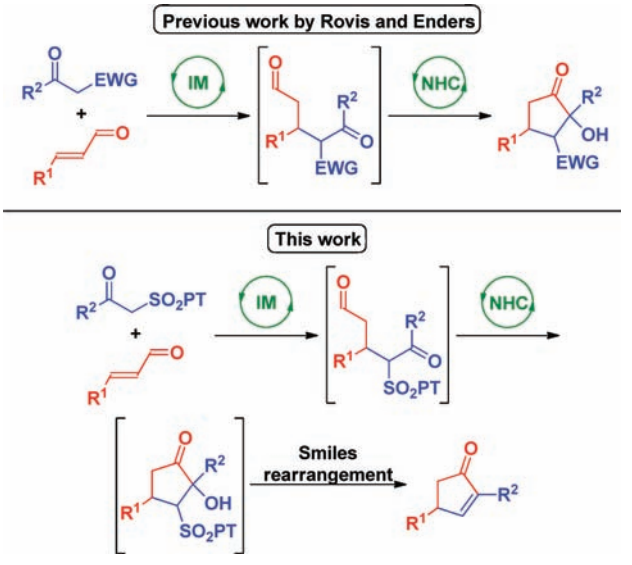
moieties into organic molecules has recently been described.[6] Inspired by the seminal work of Rovis[3a] and Enders,[3b] which affords polysubstituted cyclopentanones (Scheme 1, top), we envisioned that β-keto phenyltetrazolesulfones could be employed in an iminium ion/NHC-catalyzed reaction sequence for the formation of optically active 2,4-disubstituted cyclopent-2-enones (Scheme 1, bottom),[7] as the NHC-catalyzed benzoin condensation leads to a Smiles rearrangement (vide infra).[8] The cyclopentenone motif is present in numerous natural products and bioactive molecules and serves as a useful intermediate in synthesis.[9] Therefore, enantioselective organocatalytic[10] approaches toward these compounds are of interest.

Herein, we wish to disclose the synthesis of optically active 2,4-disubstituted cyclopent-2-enones by a one-pot organocatalytic iminium ion/NHC reaction sequence. The products are formed in high enantioselectivities and isolated in good yields. Moreover, selected transformations illustrate the synthetic versatility of the products obtained.

We initially focused on having both aminocatalyst **3** and carbene catalyst precursor **4** (Table 1) present from the beginning of the reaction; however, we realized that the NHC-catalyzed step does not occur at the lowered temperature required to obtain satisfying enantiomeric excess in the initial organocatalytic Michael addition step. Consequently, carbene precursor **4** was added in a sequential one-pot manner at elevated temperature after the completion of the addition.

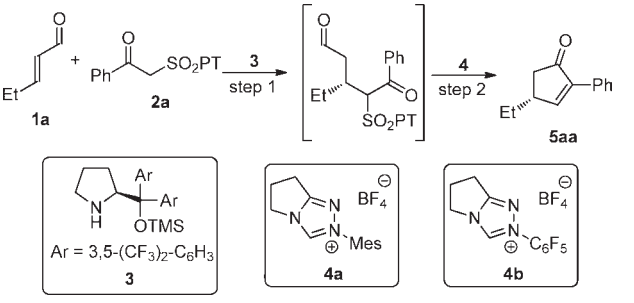
Scheme 1. Previous Work for the Synthesis of Enantioenriched Cyclopentanones (Top) and the Present Organocatalytic Approach toward Optically Active 2,4-Disubstituted Cyclopent-2-enones (Bottom) (PT = Phenyltetrazole)



Having established the optimal reaction conditions for the initial iminium ion catalyzed step,[11] we turned our attention toward developing the entire one-pot cascade sequence (Table 1). Commencing with an optimization of the isolated yield of product **5aa**, employing the carbene precursor **4a**, we were unable to obtain any conversion from the Michael-adduct to the desired product (entry 1). The more electron-withdrawing perfluorinated moiety in catalyst **4b** partly solves the conversion problem, and **5aa** was isolated in 27% yield employing 50 mol % of DIPEA as base (entry 2). Changing the base to the weaker NaOAc has an advantageous effect on the isolated yield (entry 3). To obtain the desired product in an acceptable yield, it is necessary to increase the carbene and base loadings, and product **5aa** was isolated in 60% yield employing 25 mol % of **4b** and 200 mol % of NaOAc (entry 4). Subsequent investigations showed that the enantioselectivity is virtually unaffected by the temperature employed in the carbene-catalyzed step (entries 5 and 6). However, the enantioselectivity can be improved to 93% ee by lowering the aminocatalyst loading in the initial addition step (entries 6 and 7).

With the optimized reaction conditions for the cascade sequence in hand, we next investigated the scope of the reaction (Scheme 2). Commencing with the scope of the α,β-unsaturated aldehydes **1**, it was found that a variety of aliphatic aldehydes can be employed. The optically active products **5aa**–**5ca** were formed in good yields (61–63%) and high enantioselectivities (90–96% ee) independent of the length of the aldehyde substituent. The formation of the products **5da**, **5ea**, and **5dd** demonstrates that double bonds in the aldehyde chain are also tolerated. Moreover, the presence of a heteroatom is accepted, as illustrated by

Table 1. Optimization of the One-Pot Cascade Sequence[a]



entry	carbene (mol %)	base (mol %)	temp (°C), step 1/step 2	yield[b] (%)	ee[c] (%)
1	**4a** (50)	DIPEA (50)	rt/40	no conversion	
2	**4b** (13)	DIPEA (50)	rt/rt	27	
3	**4b** (13)	NaOAc (50)	rt/rt	37	
4	**4b** (25)	NaOAc (200)	rt/rt	60	
5	**4b** (25)	NaOAc (200)	−30/20	57	85
6	**4b** (25)	NaOAc (200)	−30/40	57	86
7[d]	**4b** (25)	NaOAc (200)	−30/40	63	93

[a] All reactions performed one-pot as follows. Step 1: **1a** (0.20 mmol), **2a** (0.10 mmol), **3** (10 mol %), and *o*-NO_2-benzoic acid (10 mol %) in toluene (1.0 mL) at the designated temperature. Step 2: As reported in the table. [b] Isolated yield. [c] Enantiomeric excess determined by CSP-HPLC. [d] Performed with **3** (5 mol %) and *o*-NO_2-benzoic acid (10 mol %).

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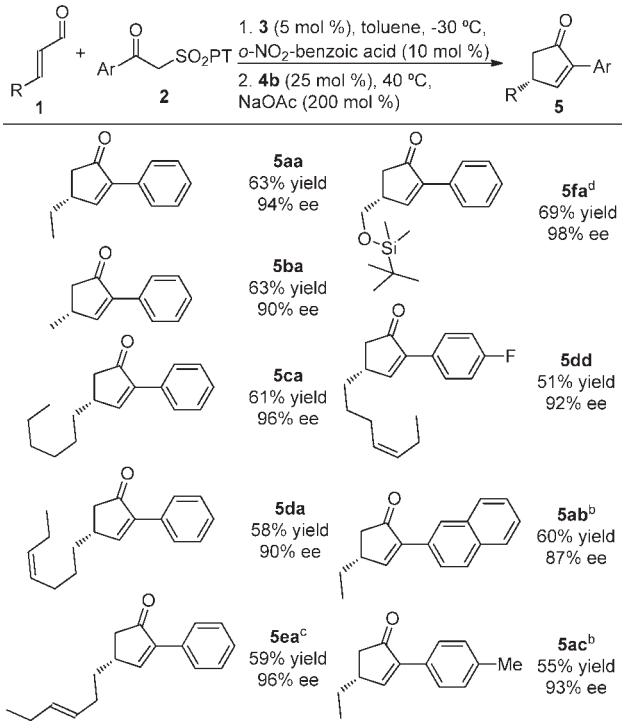
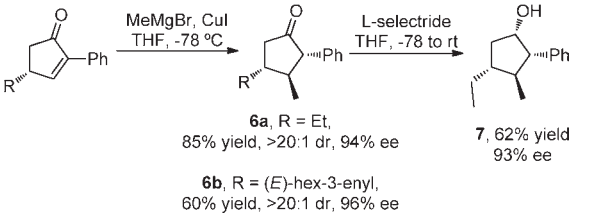
Scheme 2. Scope of the Organocatalytic Formation of 2,4-Disubstituted Cyclopent-2-enones **5**[a]



[a] All reactions performed one-pot as follows. Step 1: **1** (0.40 mmol), **2** (0.20 mmol), **3** (5 mol %), and *o*-NO_2-benzoic acid (10 mol %) in toluene (2 mL) −30 °C. Step 2: **4b** (25 mol %) and NaOAc (200 mol %) added at 40 °C. Isolated yields by FC. Enantiomeric excess determined by CSP-HPLC. [b] With **3** (10 mol %) and *o*-NO_2-benzoic acid (20 mol %) employed. [c] Enantiomeric excess determined after methyl cuprate addition (see Supporting Information for details). [d] Performed on 0.10 mmol scale.

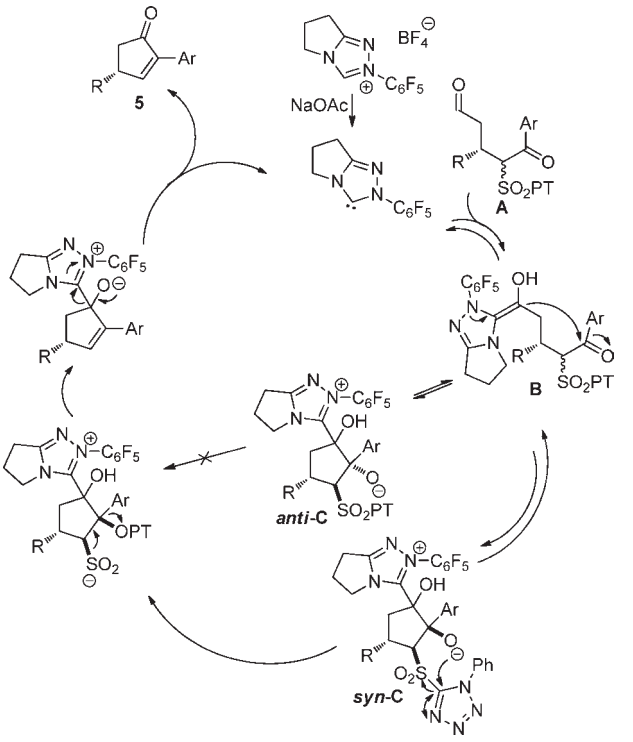
the employment of aldehyde **1f** containing an TBDMS-protected alcohol substituent, thereby providing another site for functionalization. This entry shows also that more sterically demanding substituents are tolerated in the aldehyde side chain.[12]

Scheme 3. Transformation of the Obtained Products **5**[a]



[a] See Supporting Information for detailed reaction conditions.

Scheme 4. Proposed Mechanism for the NHC-Catalyzed Benzoin Condensation and Subsequent Smiles Rearrangement



Next, the scope of the nucleophiles **2** was examined. Nucleophiles with both electron-withdrawing and electron-donating substituents on the aromatic moiety can be employed, as demonstrated by the formation of products **5dd** and **5ac** in 51 and 55% yields and 92 and 93% ee, respectively. Moreover, substituents can be placed in either the *para*- or *meta*-positions, as shown by the synthesis of products **5ab** and **5ac**. A *meta*-chloro-substituted nucleophile **2** was also attempted, resulting in a low yield of 33% and moderate enantioselectivity of 43% ee (not shown). Finally, nucleophiles bearing larger ring systems are also viable substrates for the developed catalytic sequence, as illustrated by the employment of 2-naphthyl-substituted

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(11) The initial addition step was performed as described in ref 6a with *o*-NO_2-benzoic acid as cocatalyst.

(12) Aromatic and heteroaromatic aldehydes were found to be unreactive in the initial addition step.

(13) The absolute configuration was assumed to be *R* by analogy to previous published results (see ref 6a).

2b.[13] Nucleophiles bearing an aliphatic ketone substituent were found to be inapplicable, presumably because they form a stable pyranose intermediate.[4a]

To demonstrate the potential of the obtained products **5**, selected transformations forming more complex structures were performed (Scheme 3). Methyl cuprate addition furnishes the products **6a**,**b** as single diastereomers in good yields, while maintaining the high enantioselectivities. An L-selectride reduction of product **6a** afforded **7** containing four adjacent stereocenters and isolated in 62% yield as a single diastereomer.[14]

The proposed mechanism for the benzoin condensation initiated Smiles rearrangement is outlined in Scheme 4. Following the initial iminium ion-catalyzed Michael addition of nucleophiles **2** to α,β-unsaturated aldehydes **1** forming intermediate **A**, the carbene adds to the aldehyde moiety, forming the Breslow intermediate **B**. This sets the stage for the crucial step, namely, the intramolecular attack on the aromatic ketone. The resultant five-membered ring **C** must have the alkoxide and sulfone moiety positioned in a *syn*-relationship to facilitate the Smiles rearrangement. Should *anti*-**C** be formed, thus placing the substituents too far from each other to react, equilibration back to the Breslow intermediate might furnish the correct diastereomer. Both epimers of **A** exist in a ca. 1:1 ratio due to rapid equilibration of the stereocenter carrying the sulfone moiety; however, it is assumed that *syn*-**C** is formed in large excess from the most reactive epimer of **B**.[3b]

In conclusion, we have presented an organocatalytic enantioselective iminium ion/NHC-catalyzed reaction sequence affording optically active 2,4-disubstituted cyclopent-2-enones. The products are formed in good yields and high enantioselectivities. Moreover, selected transformations leading to more complex structures illustrate the synthetic usefulness of this new reaction concept.

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Supporting Information Available. Detailed experimental procedures and compound characterizations. This material is available free of charge via the Internet at http://pubs.acs.org.

(14) The relative configuration was assigned by a selective 1D NOESY experiment on **7** (see Supporting Information).