Communication

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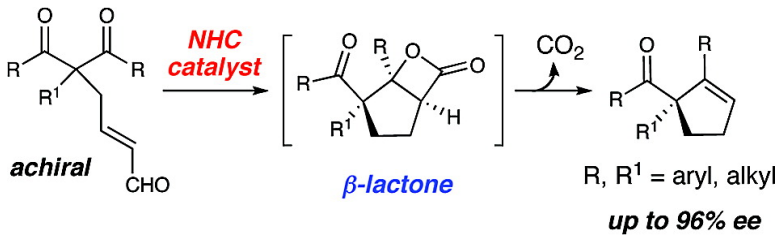

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Enantioselective Synthesis of α,α-Disubstituted Cyclopentenes by an *N*-Heterocyclic Carbene-Catalyzed Desymmetrization of 1,3-Diketones

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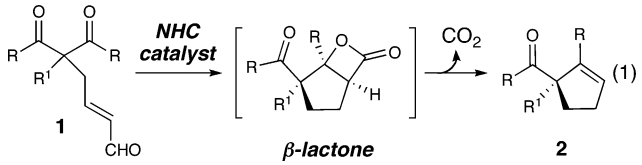
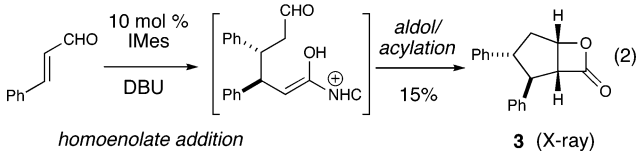
The conversion of simple precursors into optically active products is a continuing goal in chemistry to efficiently access complex architectures for use in total synthesis and medicinal chemistry.[1] An especially important substitution pattern is a carbon atom bonded to four other carbon substituents (i.e., quaternary), and the generation of these congested centers is a significant challenge.[2] The desymmetrization of achiral molecules is a powerful strategy for the synthesis of optically active materials and presents a distinct method for the construction of stereogenic quaternary carbon centers.[3] In this Communication, we report the enantioselective synthesis of α,α-disubstituted cyclopentenes (**2**) by an intramolecular aldol reaction of achiral tricarbonyl compounds (**1**) catalyzed by chiral *N*-heterocyclic carbenes (eq 1).



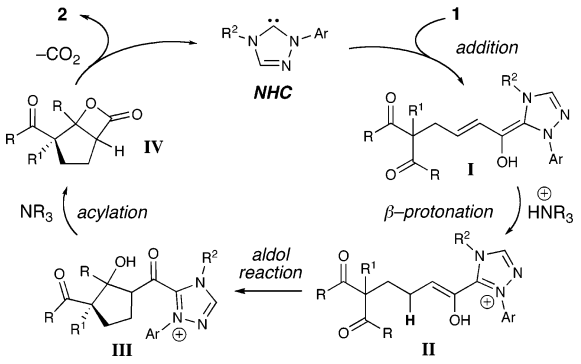
In 2006, Nair demonstrated that *N*-heterocyclic carbenes (NHCs) catalyze the formation of cyclopentenes from unsaturated aldehydes and chalcones.[4] A premise in this elegant work is that, after the homoenolate addition, a β-lactone intermediate is formed which undergoes liberation of carbon dioxide to generate the alkene product.[5,6] Recently, Bode reported a route to optically active cyclopentenes using an NHC-catalyzed crossed benzoin/oxy-Cope sequence.[7] Our investigations of new NHC-catalyzed reactions[8] have involved the use of these unique nucleophilic catalysts to access homoenolate and enolate/enol reactivity from the *same* unsaturated aldehyde starting material.[9,10] We had observed this interesting duality in our early investigations with NHC-derived homoenolates in which IMes[11] promoted the unusual dimerization of cinnamaldehyde to afford the β-lactone **3**, as determined by X-ray analysis (eq 2).



This finding, combined with our recently developed NHC-catalyzed enantioselective Michael reaction,[12] prompted us to examine the possibilities of carbene-catalyzed aldol reactions. Our objective was to couple a decarboxylation event to a symmetry breaking operation (e.g., an aldol reaction) in order to generate optically active alkenes.[13]

Our proposed reaction pathway (Scheme 1) involves initial addition of the NHC to the aldehydes. As in our Michael reaction, the key protonation of **I** generates an enol (**II**) in situ which is poised to undergo productive bond formation. By employing a chiral NHC catalyst with substrates such as **1**, an enantioselective aldol

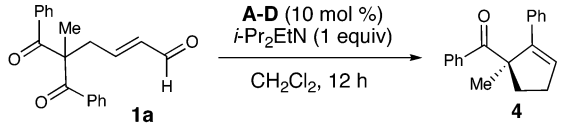
Scheme 1. Proposed Reaction Pathway



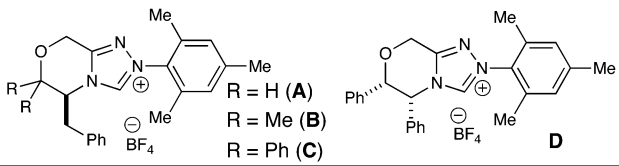
reaction ensues to produce β-hydroxy ketone intermediate **III**. Intramolecular acylation of this tertiary alcohol releases the NHC catalyst, and the resulting β-lactone (**IV**) undergoes loss of CO_2 to generate **2**.

The combination of chiral triazolium salt **A** derived from L-phenylalanine with unsaturated aldehyde **1a** and *i*-Pr_2EtN as base led to a selective reaction (−83% ee) with only moderate yield of cyclopentene **4** (Table 1, entry 1).[14] Interestingly, the substitution on the six-membered ring of the catalyst significantly impacts the stereochemical outcome of the reaction. For example, using the geminal dimethyl catalyst **B** from L-phenylalanine affords −76% ee of **4** (entry 2), yet the diphenyl catalyst **C** with the same absolute stereochemistry as **B** generates **4** in 51% ee (entry 3). By switching to azolium **D**[9c] and elevating the temperature of the reaction (40 °C) to ensure complete decarboxylation, an 80% yield of **4** is obtained in excellent enantioselectivity with 10 mol % of **D** (entries

Table 1. Optimization of Conditions[a]



entry	temperature (°C)	azolium salt	yield (%)[b]	ee (%)[c]
1	23	**A**	47	–83
2	23	**B**	38	–76
3	23	**C**	45	51
4	23	**D**	40	94
5[d]	23	**D**	66	94
6[d]	40	**D**	80	93
7[d,e]	40	**D**	70	93



[a] See Supporting Information for reaction details. [b] Isolated yield. [c] Determined by HPLC using Chiracel AD-H column. [d] Careful exclusion of oxygen. [e] 5 mol % of **D**.

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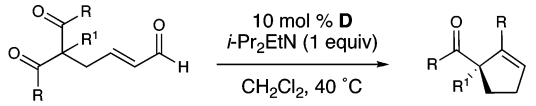
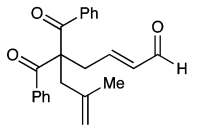
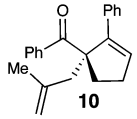
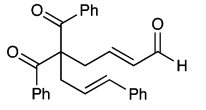
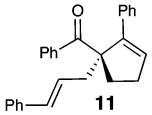
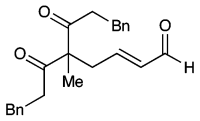
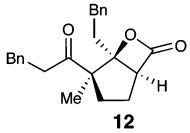
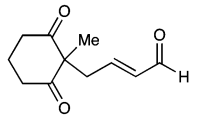
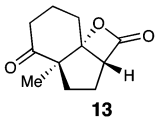
Table 2. Substrate Scope

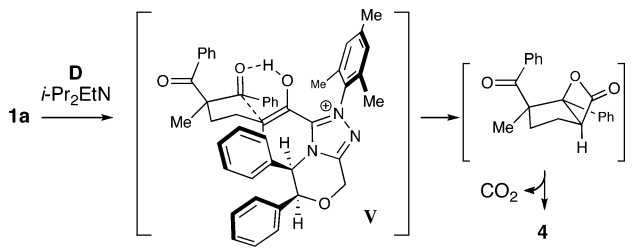


entry	R	R^1	cyclopentene	yield (%)	ee (%)[a]
1	Ph	Me	**4**	80	93
2	4-Cl-Ph	Me	**5**	76	94
3	4-Me-Ph	Me	**6**	60	94
4	3-Me-Ph	Me	**7**	65	93
5	Ph	Et	**8**	73	90
6	Ph	allyl	**9**	70	83
7			 **10**	69	83
8[b]			 **11**	64	82
9[b]			 **12**	65[c]	93
10[b]			 **13**	51[c]	96

[a] Determined by HPLC Chiracel AD-H. [b] 20 mol % of **D**. [c] Diastereomeric ratio = 20:1. Relative stereochemistry of **12** and **13** determined by NOE and X-ray crystallography, respectively. See Supporting Information for details.

6 and 7).[15] Notably, the exclusion of oxygen in the reaction increases the overall yields (entry 4 vs 5). For entry 4, we observe the unsaturated acid derived from **1** (not shown), apparently from oxidation of the homoenolate intermediate **I**. Studies to capitalize on this observation are in progress.

Once the optimal catalyst and conditions were identified, we investigated the scope of this desymmetrization (Table 2). Different aryl ketones are good substrates for the reaction (entries 1−4). Replacing the methyl group with other alkyl groups causes a slight decrease in enantioselectivity for substituents larger than ethyl (entries 6−8). Aliphatic diketones deliver the β-lactone products (**12**, **13**) instead of alkenes. In these systems, the relative stereochemistry of the methyl group and lactone in the products depends on whether the diketone moiety is locked in a ring.



Our current model for this reaction involves the Z(*O*)-enol intermediate **V**. A six-membered hydrogen-bonded aldol reaction occurs which minimizes the nonbonding interactions between the phenyl substituents on the catalyst and the phenyl ketone not undergoing attack. The ensuing liberation of carbon dioxide from the resulting β-lactone affords optically active **4**.[16]

In summary, we have developed a highly selective route to α,α-disubstituted cyclopentenes catalyzed by *N*-heterocyclic carbenes. This new process combines an enantioselective aldol reaction with a decarboxylation of a β-lactone intermediate to afford functionalized carbocycles containing a quaternary carbon stereocenter. The use of chiral triazolium salts generates chiral nucleophilic enols capable of promoting a desymmetrization event. The investigation and applications of nucleophiles generated in situ from the combination of unsaturated aldehydes and NHCs are ongoing.

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Supporting Information Available: Experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) Absolute configuration of **4** determined by X-ray crystallographic analysis. See Supporting Information.

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