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Enantioselective, Cyclopentene-Forming Annulations via NHC-Catalyzed Benzoin−Oxy-Cope Reactions

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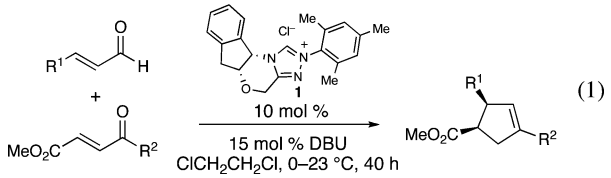
N-Heterocyclic carbene (NHC)-catalyzed redox transformations of functionalized aldehydes[1] enable the catalytic generation of reactive intermediates including activated carboxylates,[2,3] enolates,[4,5] and homoenolates.[6,7] Recently, Nair described the synthesis of racemic *trans*-1,3,4-triarylcyclopentenes by a remarkable annulation of enals and chalcones catalyzed by achiral imidazolium-derived carbenes, reportedly via a homoenolate equivalent.[8] As part of our own ongoing studies aimed at developing NHC-catalyzed annulation reactions, we now document a highly enantioselective *cis*-cyclopentene-forming annulation[9] mediated by chiral triazolium precatalyst **1** (eq 1 in Table 1). Mechanistic and stereochemical

Table 1. Catalytic Enantioselective Annulations of 4-Oxoenoates



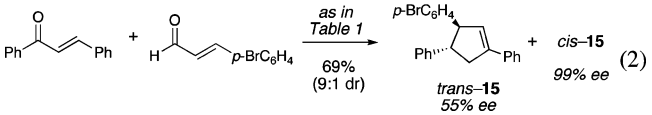
(1)

entry	R^1	R^2	% yield[a]	*cis*:*trans*[b]	% ee[c]
1	Ph	Ph	78	11:1	99 (68)[d]
2[e]	Ph	*p*-$MeOC_6H_4$	58	5:1	99 (68)[d]
3	Ph	*p*-BrC_6H_4	50	11:1	99 (79)[d]
4	Ph	2-furyl	93	>20:1	98
5	*p*-BrC_6H_4	Ph	58	6:1	99 (67)[d]
6	*p*-$CF_3C_6H_4$	Ph	68	4:1	98 (67)[d]
7	2-furyl	Ph	53	5:1	99 (82)[d]
8	*n*-Pr	Ph	25	14:1	96 (32)[d]

[a] Isolated yield after chromatography. [b] Approximate ratio of *cis*:*trans* cyclopentene diastereomers as determined by HPLC analyses at several wavelengths. In most cases, the diastereomers cannot be distinguished by ^{1}H NMR analysis. [c] Determined by HPLC analysis. [d] The % ee of the minor diastereomer. [e] The ethyl ester was used as the 4-oxoenoate substrate.

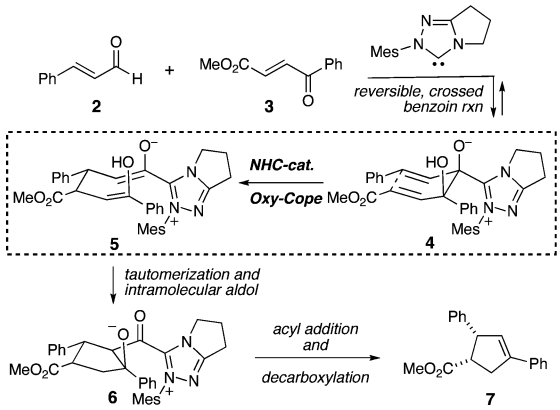
evidence supports a cascade sequence involving a catalytic, asymmetric intermolecular aldehyde−ketone crossed benzoin reaction and a novel NHC-promoted oxy-Cope rearrangement (Scheme 1).

A study of reaction conditions for enantioselective, cyclopentene-forming annulations with cinnamaldehyde and 4-oxoenone **3** identified 10 mol % of triazolium precatalyst **1**,[5] 15 mol % of DBU, dichloroethane (0.1 M), and a reaction temperature of 0 °C to room temperature as optimal. In contrast to the use of chalcone derivatives, which provided the *trans*-cyclopentene products (eq 2), **3** and related enones gave the *cis*-cyclopentenes selectively (Table 1). In all cases examined, *cis*-cyclopentenes were obtained with a high degree of enantioselectivity (>96% ee), while the formation of the



(2)

Scheme 1. Cyclopentenes via NHC-Catalyzed Oxy-Cope RAR



trans-diastereomers occurred with considerably less enantioinduction. In accord with Nair's findings, the substrate scope presently appears to be limited to enones bearing an aromatic substituent, as only these lead to intermediates that undergo facile decarboxylation.[10]

The incongruity between the optimized conditions for the cyclopentene-forming annulations and the usual protocols employed for NHC-catalyzed homoenolate generation invited further consideration of the reaction pathway. Triazolium-derived NHCs are known to be outstanding catalysts for benzoin-forming reactions. Although the intermolecular crossed aldehyde−ketone benzoin is thought to be disfavored,[11] an intramolecular variant is catalyzed by both thiazolium and triazolium salts.[12] Crossed benzoin reaction between cinnamaldehyde (**2**) and enone **3** would lead to an intermediate (**4**) poised for an oxy-Cope rearrangement that would give **5** (Scheme 1), the identical product invoked in the proposed conjugate addition of a homoenolate to the enone. As previously suggested by Nair, **5** would undergo tautomerization, stereoselective intramolecular aldol addition, lactonization, and decarboxylation to afford cyclopentene product **7**. Indeed, a similar cyclopentanone-forming aldol cascade initiated by an anionic oxy-Cope reaction has been reported,[13] and formal conjugate additions of allylic anions to enones that proceed via 1,2-addition/oxy-Cope rearrangement are well-known.[14]

Several control experiments support the viability of this pathway, at least when triazolium precatalysts are utilized. Exposure of acyloin **8** to the reaction conditions resulted in facile retro-benzoin reaction, demonstrating both the feasibility and reversibility of a benzoin-type process (Scheme 2a). When *O*-TMS-protected ketone **10** was allowed to react with the catalyst in the presence of a nucleophile, such as ethanol, oxy-Cope reaction followed by formation and trapping of the catalyst-bound activated carboxylate occurred (i.e., **11** in Scheme 2b), leading to acyclic ester **12**.[15] In contrast, coupling of cinnamaldehyde and chalcone under identical conditions (1:1 DCE/EtOH) provided only the cyclopentene product,

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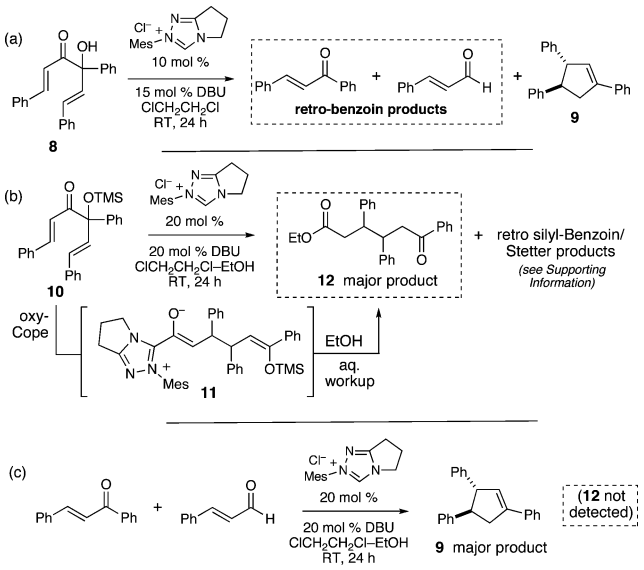
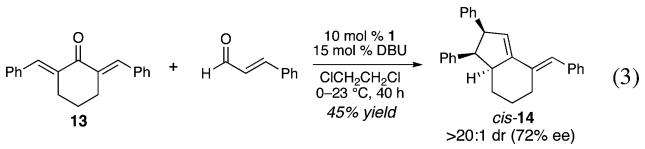
Scheme 2



demonstrating that the reaction shown in Scheme 2b does not occur simply by retro-benzoin followed by catalytic homoenolate addition (Scheme 2c). At the present time, we cannot distinguish between a stepwise benzoin reaction followed by oxy-Cope rearrangement of intermediate **4** (Scheme 1) and a concerted pathway that leads directly to **5** without the intermediacy of **4**.[16]

The seemingly disparate stereochemical outcomes between chalcones and the 4-oxoenoates, coupled with the diminished levels of enantioinduction in the *trans*-diastereomers, provide a mechanistically revealing insight that strongly supports a benzoin−oxy-Cope pathway. Enones, including chalcone and related structures, are known to exist as equilibrating mixtures of s-*cis* and s-*trans* conformers.[17] The 4-oxoenoates apparently prefer to react with the catalyst-bound Breslow intermediate as the s-*cis* conformation shown in Figure 1a. Benzoin-type addition leads to an intermediate poised for oxy-Cope rearrangement via a boat transition state that gives rise to the *cis*-stereochemistry observed in the cyclopentene products.[18] In contrast, chalcones appear to react from the s-*trans* conformation (Figure 1b), which leads to an intermediate poised for oxy-Cope reaction via a chair transition state that predicts the stereochemical outcome observed in the *trans*-products.[19]

To test our hypothesis that the reactive conformation of the enone determined the relative stereochemistry of the annulation products, we prepared chalcone-type enone **13**, which is locked into an s-*cis* conformation. Upon treatment of **13** with cinnamaldehyde under the standard catalytic conditions, cyclopentene **14** was obtained in moderate yield but in >20:1 dr, favoring the *cis*-diastereomer (eq 3).



(3)

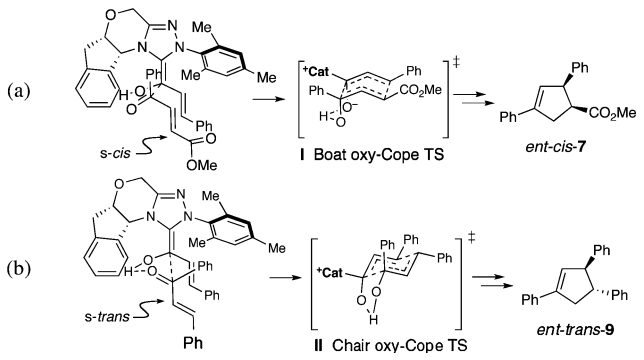


Figure 1. Transition states for NHC-promoted oxy-Cope rearrangements predicting the observed relative and absolute stereochemical outcomes. For clarity, *ent*-**1** is shown as the catalyst.

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

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