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Oxidatively Initiated NHC-Catalyzed Enantioselective Synthesis of 3,4-Disubstituted Cyclopentanones from Enals

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Supporting Information

ABSTRACT: An unprecedented N-heterocyclic carbene (NHC)-catalyzed annulation of enals to form 3,4-disubstituted cyclopentanones has been discovered. Aryl enals undergo dimerization in the presence of a single-electron oxidant to form C_2 symmetric cyclopentanones. A cross-reaction has also been developed, allowing for the synthesis of differentially substituted cyclopentanones. Mechanistically, the reaction is thought to proceed through radical intermediates, further establishing the synthetic utility of this class of reactivity.

Over the past decade, N-heterocyclic carbene (NHC)-catalyzed reactions of the homoenolate equivalent have been the focus of intense investigation.[1] Glorius and Bode reported the first examples of NHC-generated homoenolate equivalents in 2004 independently and concurrently.[2] These seminal reports showed the synthetic utility of the homoenolate in the context of synthesizing 2,3-disubstituted γ-lactones (Figure 1, eq 1). Soon after these reports Bode and He showed that γ-lactams are easily accessed via this pathway through the coupling of an enal and an imine (Figure 1, eq 2).[3] In 2006 Nair et al. demonstrated the coupling of enals with chalcones to furnish 1,3,4-trisubstituted cyclopentene (Figure 1, eq 3).[4] Further developments in this field have broadened the partners that participate in these annulations and investigated asymmetric version of the reaction.[5] These annulation reactions are all presumed to proceed via two-electron pathways.

In 2014, we described the NHC-catalyzed conversion of enals to aldols using nitroarenes as oxidants in methanol. The net transformation converts enals and nitroarenes to β-hydroxy esters. Evidence points to one-electron oxidation of the homoenolate equivalent[6] by an electron-deficient nitroarene oxidant.[7,8] During our investigations, we observed the formation of cyclopentanone products[9] when the reaction is conducted in a non-nucleophilic solvent. For example, the reaction of 4-methoxycinnamaldehyde **1a** with 4-nitropyridine N-oxide **2** in dichloromethane at room temperature in the presence of NHC **3a** forms cyclopentanone **4a** in 49% yield as a single diastereomer. Intrigued by this previously unknown reactivity, we began to explore the reaction parameters.

An initial screen of chiral NHC catalysts at room temperature proved discouraging with only backbone-fluorinated NHC **3b** providing any desired product in a meager 12% ee.[10] Switching the solvent to toluene afforded an increase to 60% ee (Table 1). Increasing in the reaction temperature to 70 °C improved the reactivity and allowed us to screen a variety of chiral catalysts.

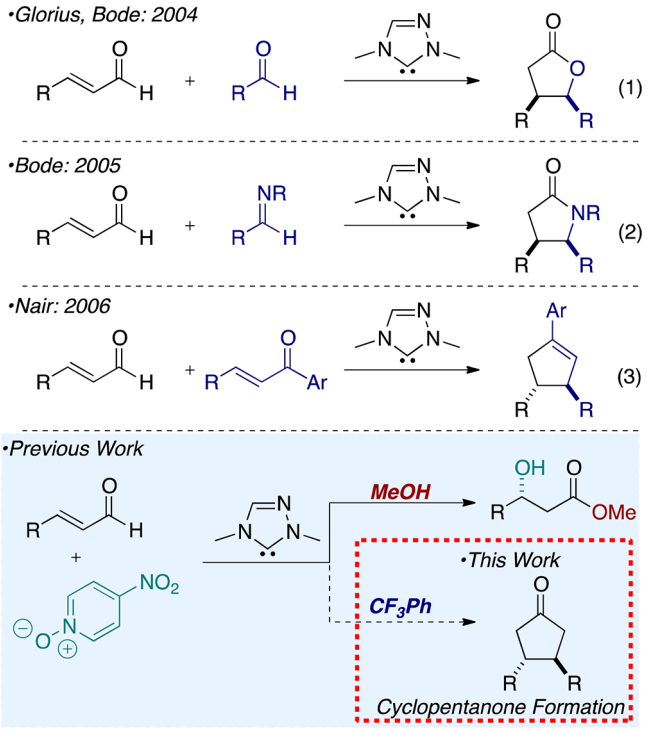

Figure 1. Background.

Ultimately, NHC **3c** proved optimal, providing the desired product in 51% yield, 84% ee, as a single diastereomer. A high-throughput experimentation (HTE) screen revealed that trifluorotoluene was the best solvent and the beneficial effect of lithium chloride on yield.[11]

With optimized conditions identified, we explored the scope of the dimerization. Electron-rich and electron-deficient aryl enals are tolerated in the reaction. Electron-rich substrates proved to provide higher yields than their electron-poor counterparts. The heteroaromatic 2-furylcinnamaldehyde works in the reaction as well. Unfortunately, aliphatic enals do not participate. To our delight, 4-bromocinnamaldeyde provides product in reasonable yield and contains a potential handle for cross coupling reactions. In all cases, the cyclopentanone products are formed as a single diastereomer. The remainder of the mass balance in these reactions is the α,β-unsaturated acid, the result of a two-electron oxidation of

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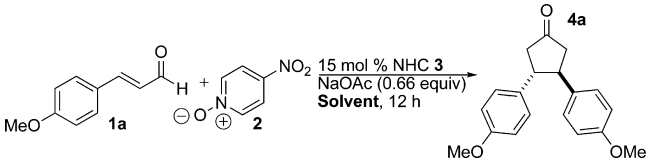
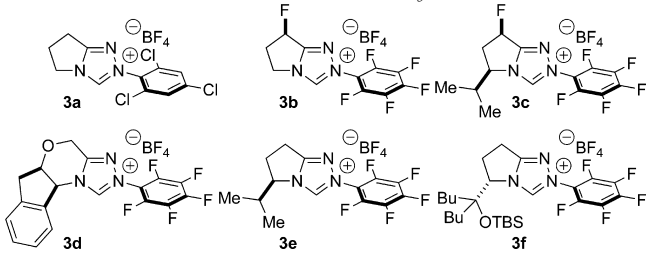
Table 1. Reaction Optimization[a]



entry	NHC	additive	temp (°C)	solvent	yield (%)[b]	ee (%)[c]
1	**3a**	–	23	CH_2Cl_2	49	–
2	**3b**	–	23	CH_2Cl_2	25	12
3	**3b**	–	23	PhMe	28	60
4	**3c**	–	23	CH_2Cl_2	<5	–
5	**3d**	–	23	CH_2Cl_2	<5	–
6	**3e**	–	23	CH_2Cl_2	<5	–
7	**3b**	–	70	PhMe	46	50
8	**3c**	–	70	PhMe	51	84
9	**3d**	–	70	PhMe	30	50
10	**3e**	–	70	PhMe	44	76
11	**3f**	–	70	PhMe	26	−78
12	**3c**	–	70	$PhCF_3$	64	84
13	**3c**	LiCl	70	$PhCF_3$	79	84



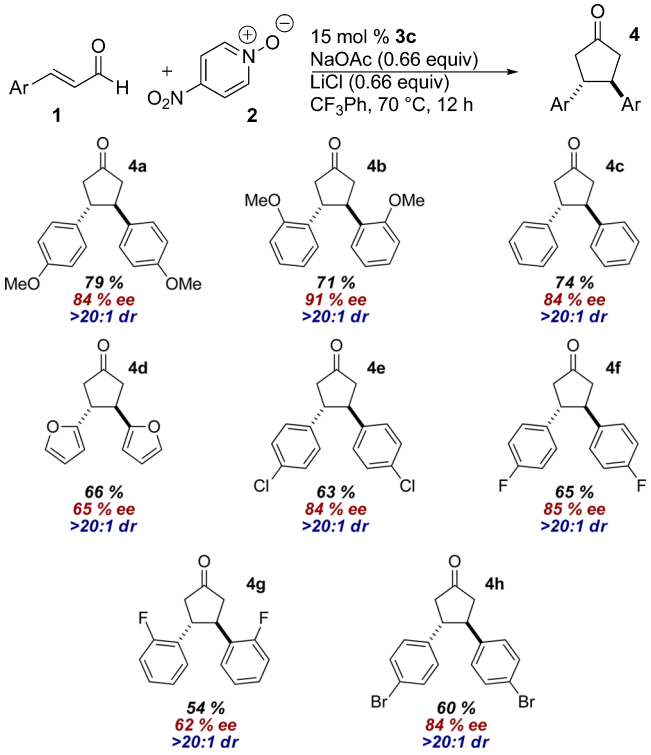
[a]Reactions were conducted with 1.0 equiv of **1** and 0.66 equiv of **2**. [b]Isolated yields after chromatography. [c]Enantiomeric excess was determined by HPLC analysis on a chiral stationary phase.

the Breslow intermediate to form the acyl azolium, followed by attack by adventitious water (Table 2).

Mechanistically, we believe that this transformation is related to the β-hydroxylation of enals that we previously reported.[7] We postulate that the reaction proceeds by formation of Breslow intermediate **I**,[12] which transfers a single electron to 4-nitropyridine N-oxide **2** to generate a radical cation **II** and radical anion **III** (Scheme 1). Radical cation **II** is then attacked at the β-carbon by a second, native, Breslow intermediate **I** to form **IV**.[13] **IV** then undergoes a second single electron transfer to radical anion **III** to form acyl azolium **V**. The acyl azolium is then attacked intramolecularly by the pendant enolate azolium to liberate one equivalent of NHC and form cyclopentanone **VI**. This cyclopentanone is attacked by water to liberate the second equivalent of NHC and form β-ketoacid **VII**. This β-ketoacid then undergoes decarboxylation to furnish cyclopentanone product **4**.[14] Once radical anion **III** abstracts the second electron from **IV**, intermediate **VIII** is formed, which decomposes to nitroso **IX** (observed by LCMS). This reactivity represents a rare example of carbon turnover of the acyl azolium.[15] Typically, exogenous alcohol, a tethered alcohol, or a tethered amine attacks the acyl azolium. Even in the case of the cyclopentene forming reactions[1] the acyl azolium is turned over by a tethered alcohol to form a β-lactone, which then extrudes CO_2.

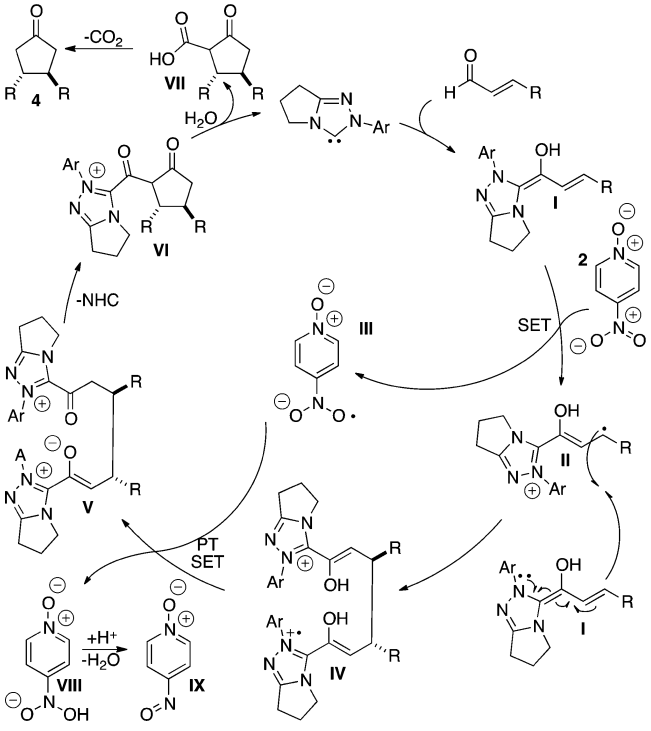
We also entertained the idea that the reaction proceeds by one Breslow intermediate undergoing a two-electron oxidation to form an acyl azolium which is in turn attacked via a [1,4] addition by a native Breslow intermediate (Scheme 2). To test this hypothesis, we subjected 3-phenylpropiolaldehyde **5**, a precursor

Table 2. Dimerization Scope[a]



[a]See footnotes a–c in Table 1.

Scheme 1. Proposed Catalytic Cycle



for the acyl azolium, and 4-methoxycinnamaldehyde **1a** to reaction with carbene **3c** but observed no cyclopentanone products.[16] Further, employing the known 2-electron oxidant phenazine **7** in the reaction also does not lead to cyclopentanone products.[17]

In an effort to broaden the synthetic utility of the transformation, we investigated the use of a heterocoupling partner

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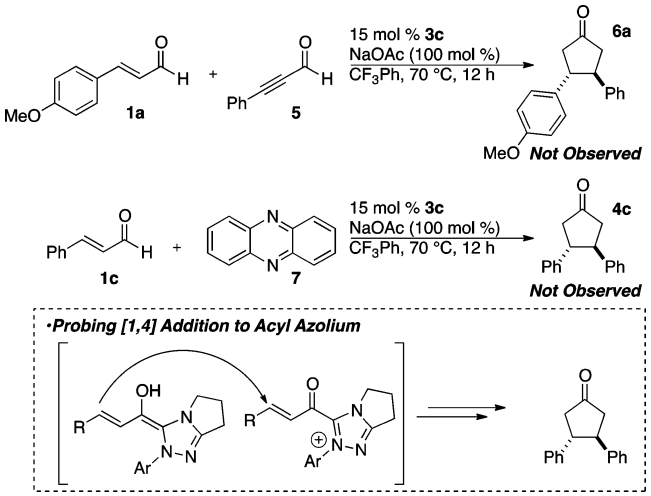
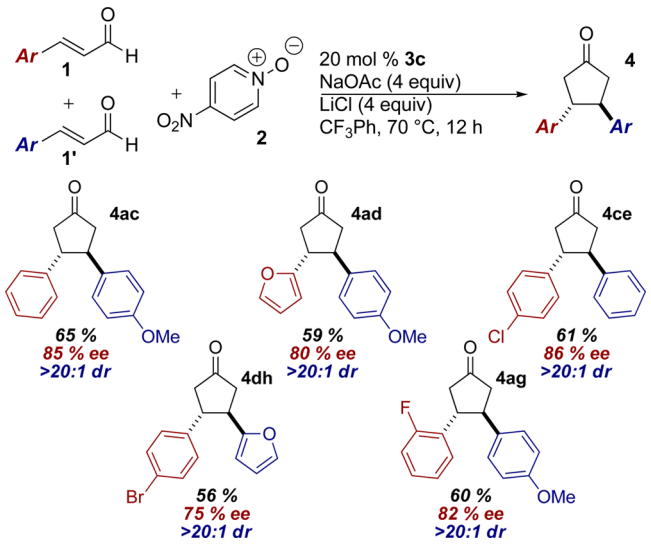
Scheme 2. Control Experiments



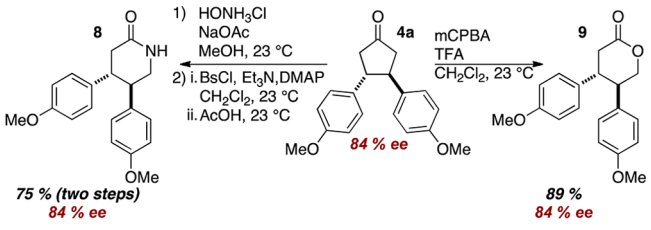
that would deliver unsymmetrical adducts. All attempts at using other electron-deficient alkenes (such as nitroalkenes, enoates, enones) met with failure; the reaction appears to require an enal on both sides. As a partial solution, we found that biasing the reaction with an excess of one of the enals delivers the cross product in good yields. Best results are achieved when the more electron-rich (more reactive) enal is used in excess. In these reactions, the dimer of the more reactive enal is always formed, but the dimer of the limiting enal is observed in only trace amounts (Table 3).

Table 3. Cross-Reaction[a,b]



[a]Reactions were carried out with 1.0 equiv of **1**, 4.0 equiv of **1′**, and 4.0 equiv of **2**. [b]See footnotes b–c in Table 1.

Scheme 3. Derivatization



To demonstrate the utility of the cylopentanone products, a Baeyer–Villager oxidation and a Beckman rearrangement were carried out. In both cases, retention of stereochemistry was observed and lactone **8** and lactam **9** products were formed in good yields (Scheme 3).

In conclusion, we have developed a methodology for the enantioselective synthesis of 3,4-disubstituted cyclopentanones. The protocol allows for the dimerization of aryl enals[18] to form C-2 symmetric cyclopentanones. Further, a cross reaction has been developed to synthesize nonsymmetric 3,4-disubstituted cyclopentanones. The proposed reaction mechanism invokes radical intermediates. Furthering the substrate scope and investigating new modes of reactivity enabled by these intermediates is the subject of ongoing investigations.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b06390.

Experimental procedures and compound characterization (PDF)

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Notes

The authors declare no competing financial interest.

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(11) See Supporting Information.
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(13) An alternate hypothesis raised by a reviewer involves dimerization of radical cation **II** to form a protonated form of **V** (Scheme 1). The use of a substoichiometric amount of oxidant (0.66 equiv relative to enal) suggests we only need to oxidize one of the two enal-derived partners prior to dimerization. However, given that we have seen overreduction of the nitroarene in our hydroxylation chemistry (ref 7), we cannot rigorously exclude this possibility.
(14) Analysis of the headspace of a reaction conducted under N_2 atmosphere reveals 120,000 ppm CO_2.
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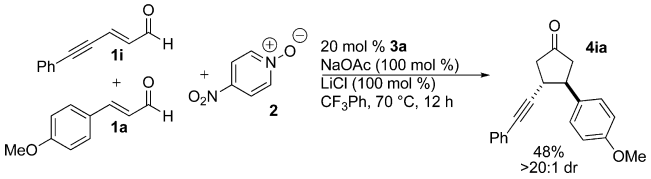
(18) Under these conditions, aliphatic enals and dienals do not afford dimer product. An yne-enal participates in the cross-reaction with achiral catalyst, but not with chiral catalyst.



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