Communication

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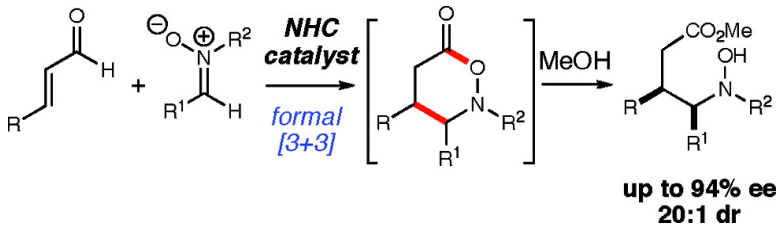

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Highly Diastereo- and Enantioselective Additions of Homoenolates to Nitrones Catalyzed by *N*-Heterocyclic Carbenes

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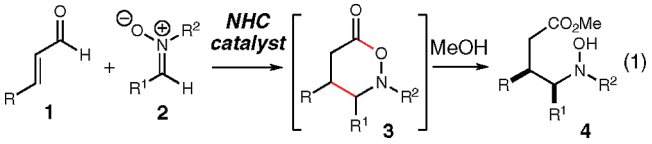
Harnessing unconventional reactivity for new bond-forming processes provides unusual avenues for the synthesis of target molecules. Non-traditional cycloadditions outside the venerable [4 + 2] and [3 + 2] processes also facilitate access to desired compounds in a highly convergent manner by combining at least two simple starting materials.[1] A relatively unexplored class of powerful transformations utilizes unusual reactivity patterns, such as homoenolates, in the context of non-traditional, formal cycloadditions. In this communication, we report the highly diastereo- and enantioselective combination of α,β-unsaturated aldehydes (**1**) with nitrones (**2**) catalyzed by *N*-heterocyclic carbenes to afford γ-amino esters, such as **4**, upon the addition of an alcohol (eq 1). A unique aspect of this process is the rare six-membered heterocycle that is generated as the initial product of the reaction (**3**).

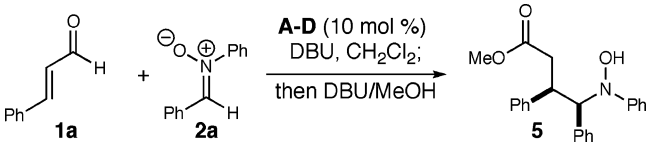


The successful addition of homoenolate species to nitrones would be a significant transformation since the products are potentially γ-amino acids. These molecules are used clinically as modulators of neurotransmission,[2] and the related γ-lactam structure is a key constituent of many natural products (e.g., lactacystin)[3] as well as pharmaceutical agents. To our knowledge, there are no reports of homoenolate additions to nitrones under either catalytic or stoichiometric conditions.[4]

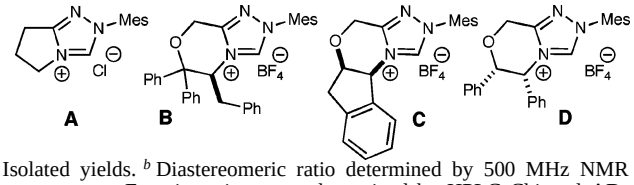
Our efforts[5] and those of others[6] investigating the area of *N*-heterocyclic carbene (NHC) catalysis have recently yielded innovative methods to access unique homoenolate reactivity. In these processes, an α,β-unsaturated aldehyde possesses nucleophilic character at the β-carbon which upon addition to an electrophile yields an activated ester. In light of our experience with these atypical nucleophiles, we envisioned that nitrones should be productive in a formal [3 + 3] reaction since they are useful reactants in a variety of cycloaddition reactions.[7]

We initiated these investigations by combining cinnamaldehyde (**1a**) and diphenyl nitrone (**2a**) while surveying different triazolium salts and reaction conditions (Table 1). While thiazolium and imidazolium salts did not produce desired products, the use of achiral triazolium salt **A** at 10 mol % afforded complete consumption of the nitrone (entry 1). Initially, a challenging aspect of this processes was the characterization and manipulation of the first product formed in the reaction (i.e., **3**). This unusual heterocycle was unstable to chromatography, but by adding methanol and DBU to the reaction after consumption of the nitrone, the γ-hydroxyl amino ester (**5**) could be isolated in 75% yield. With this protocol, a screen of chiral triazolium salts revealed that azolium **D**, originally developed in our laboratory,[5c] generated **5** with high levels of stereoselectivity (8:1 dr, 87% ee) but only moderate yield (entry 4). Lowering the temperature provided increased selectivity (20:1 dr, 93% ee) and yield of **5** with 20 mol % of **D** necessary for consumption of **1a** (entry 6). Last, changing the MeOH/DBU addition at the end of the reaction to NaOMe provided the methyl ester products in consistently higher yield.[8]

Table 1. Optimization of Conditions



entry	azolium salt	temp (°C)	yield[a] (%)	dr[b]	ee[c] (%)
1	**A**	0	75[d]	4:1	
2	**B**	0	46[d]	8:1	−65
3	**C**	0	52[d]	8:1	−33
4	**D**	0	51[d]	8:1	87
5	**D**	−25	49[d]	20:1	93
6	**D**[e]	−25	70[f]	20:1	93



[a] Isolated yields. [b] Diastereomeric ratio determined by 500 MHz NMR spectroscopy. [c] Enantiomeric excess determined by HPLC Chiracel AD-H. [d] 2:1 ratio of **1a** to **2a**. [e] 20 mol % of **D**, Et_3N used instead of DBU. [f] 2:1 ratio of **2a** to **1a**, NaOMe/MeOH used in place of DBU/MeOH.

Our current model for this reaction (Scheme 1) involves the addition of the homoenolate equivalent (**I**, formed in situ from the combination of the NHC and unsaturated aldehyde) to the nitrone (**2**). After this stereochemical-determining step, catalyst turnover is promoted by an intramolecular acylation after the tautomerization of enol **II** to acyl azolium **III**. As in a majority of recent carbene-catalyzed processes, the success of this pathway relies on (a) a *nonproductive* interaction between the secondary electrophile in the reaction (nitrone) and the in situ generated catalyst, and (b) a *productive* interaction between the catalyst and primary electrophile (α,β-unsaturated aldehyde).

We first examined the scope of this reaction with regard to nitrone substituents (Table 2). The reaction accommodates both electron-withdrawing and -donating aromatic substitution on the carbon (R1) with high levels of dr and %ee (entries 1−5).[9] Nitrones derived from saturated aldehydes were not suitable substrates. An electron-withdrawing aromatic ring (4-chlorophenyl) on the nitrogen of the nitrone provided the methyl ester in moderate yield with high selectivity (entry 7). Electron-donating groups on the nitrogen, such as 4-methoxyphenyl or 4-methylphenyl, resulted in no product formation (not shown).

We then varied the aldehyde component of this new reaction (Table 3). Electron-withdrawing and -donating groups on the aromatic ring of the aldehyde are tolerated well (entries 1 and 2). Importantly, α,β-unsaturated aldehydes with alkyl groups in the

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Scheme 1. Reaction Pathway

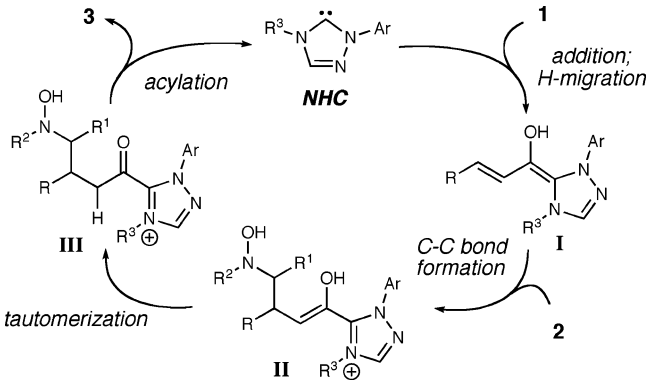
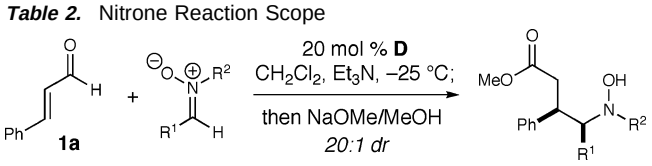


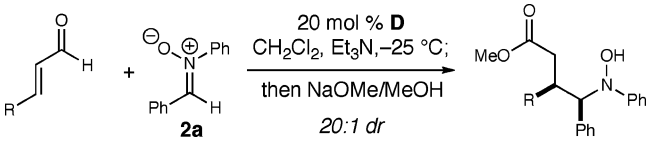
Table 2. Nitrone Reaction Scope



entry	R^1	R^2	yield[a] (%)	ee[b] (%)
1	Ph	Ph	70 (**5**)	93
2	4-Me−C_6H_4	Ph	71 (**6**)	90
3	4-Br−C_6H_4	Ph	68 (**7**)	84
4	4-MeO−C_6H_4	Ph	62 (**8**)	90
5	2-naphthyl	Ph	69 (**9**)	81
6	cyclohexyl	Ph	0	
7	Ph	4Cl-Ph	80 (**10**)	93

[a] Isolated yields. [b] Enantiomeric excess determined by HPLC Chiracel OD-H or AD-H. Diastereomeric ratio determined by ^{1}H NMR spectroscopy (500 MHz).

Table 3. Aldehyde Reaction Scope

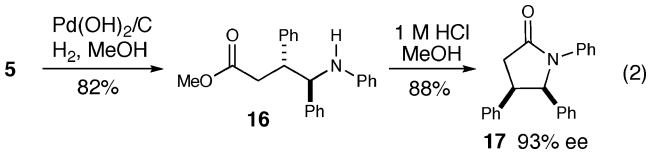


entry	R	yield[a] (%)	ee[b] (%)
1	4-Cl−C_6H_4	78 (**11**)	90
2	4-MeO−C_6H_4	72 (**12**)	89
3	2-naphthyl	73 (**13**)	94
4	Me[c]	73 (**14**)	94
5	C_3H_7[c]	64 (**15**)	92

[a] Isolated yields. [b] Enantiomeric excess determined by HPLC Chiracel OD-H or AD-H. [c] DBU used in place of Et_3N.

β-position afford the desired γ-hydroxy amino esters with high selectivity and good yields (entries 4 and 5).

With an efficient pathway to γ-hydroxy amino methyl esters, we envisaged that cleavage of the N−O bond would facilitate clean access to γ-amino esters (eq 2). The N−O bond is easily cleaved under a hydrogen atmosphere in the presence of $Pd(OH)_2$, and subsequent exposure of the amino ester to aqueous HCl in methanol provides the corresponding lactam **17** in 88% yield and 93% ee.[10]



In summary, we have developed the first highly diastereo- and enantioselective homoenolate addition to nitrones catalyzed by chiral *N*-heterocyclic carbenes. This formal [3 + 3] addition delivers γ-amino ester derivatives and is the first general and highly selective strategy for the addition of homoenolate nucleophiles to nitrones. Electron-rich and electron-poor aryl groups are suitable substituents on the carbon of the nitrone, and alkyl and aryl groups are tolerated on the α,β-unsaturated aldehyde. Scission of the N−O bond under mild conditions results in the formation of γ-amino esters that quickly close in the presence of acid to form γ-lactams in good yields. *N*-Heterocyclic carbene catalysis is a powerful approach that provides new directions for synthesis through innovative bond construction.

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

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(8) The hydroxyl amine products are stable when stored at −20 °C, but slowly decompose at 23 °C.

(9) Relative and absolute configuration of **7** was determined by X-ray crystallography; see Supporting Information for details. Additional stereochemistry assigned by analogy.

(10) For a racemic synthesis of **17**, see ref 4c.

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