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N-Heterocyclic Carbene-Catalyzed Enantioselective Mannich Reactions with α-Aryloxyacetaldehydes

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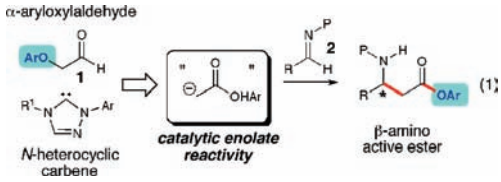
The catalytic generation of enolates is a crucial enterprise due to the broad utility of these nucleophiles in synthesis.[1] Direct access to enolates employing transition metals as catalysts has been reported by many groups over the past decade.[2] A complementary strategy using secondary amines as catalysts has undergone a resurgence of activity and become a powerful, general method for enantioselective enolate additions.[3] Most recently, *N*-heterocyclic carbenes (NHCs) have emerged as a different class of small molecules which catalyze and control new enolate reactions.[4] In addition to investigating carbene-catalyzed reactions to access Umpolung reactivity patterns (e.g., acyl anions), we have been developing access to new enolate reactions by the protonation of homoenolate intermediates and oxidation of NHC−aldehyde adducts.[5] An intriguing possibility for these carbene-catalyzed approaches is to have an activating group on the aldehyde induce enolate formation and then rebound, regenerating the catalyst and creating a useful activated ester in the process.[5e,6] Herein, we report a new enantioselective Mannich reaction using this strategy (eq 1).



We explored additions to activated imines (Mannich reaction) to investigate this new reaction and capture the enolate generated in this process. The products would be β-amino carbonyl compounds which are important in chemistry, biology, and medicine.[7] Our idea for this reaction focused on accessing a particular Breslow intermediate (**I**) from the initial tetrahedral intermediate (Scheme 1).[8] With a properly tuned leaving group (OAr), this would induce an elimination, generating aryloxy anion **III** and enol **II**. In the presence of the imine, the Mannich reaction occurs and generates acyl azolium **IV**. If properly balanced in terms of leaving group ability vs nucleophlicity, the aryloxy anion could undergo acylation which would (a) result in the formation of the β-amino ester (**V**) and (b) allow the NHC to reenter the catalytic cycle. Several challenges needed to be addressed for this pathway to be operative. First, the leaving group must be competent in an elimination step to generate the enol. Once ejected, this anion must be nucleophilic enough to regenerate the catalyst after the desired C−C bond forming process. Lastly, carbene addition to the secondary electrophile (in this case, the imine) must be reversible.

We began by surveying α-substituted acetaldehydes with azolium salts and bases. The stable, easy to prepare 4-nitrophenoxyacetaldehyde emerged as a competent substrate for facile formation of the enolate in the presence of carbenes. Azolium salt **A** with Et_3N and CH_2Cl_2 led to formation of amide **3** in poor yield (37%) but

Scheme 1. Proposed Catalytic Pathway

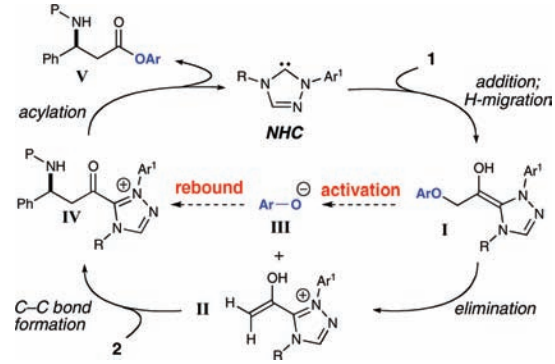
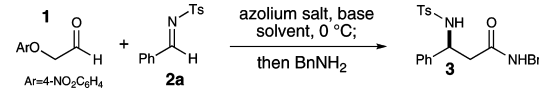
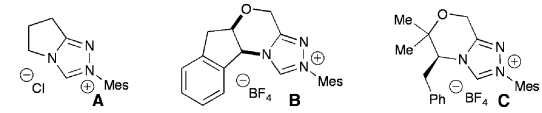


Table 1. Optimization of Conditions[a]



entry	azolium salt	base	solvent	yield (%)[b]	ee (%)[c]
1	**A**	Et_3N	THF	6	–
2	**A**	Et_3N	CH_2Cl_2	30	–
3	**B**	Et_3N	CH_2Cl_2	37	68
4	**C**	Et_3N	CH_2Cl_2	31	88
5[d]	**C**	NaH[e]	CH_2Cl_2	24	85
6[d,f]	**C**	$NaOC_6H_4NO_2$[g]	THF/CH_2Cl_2[h]	59	95
7[i]	**C**	$NaOC_6H_4NO_2$[g]	THF/CH_2Cl_2[h]	72	94

[a] Reactions run with 10 mol % of azolium salt and base and 0.07 M in solvent unless otherwise noted. [b] Isolated yields. [c] Determined by HPLC. [d] 2 equiv of **1**. [e] 1 equiv of NaH. [f] 4 Å MS used as additive. [g] 1 equiv of base. [h] 1:4 THF/CH_2Cl_2 (0.1 M). [i] 3 equiv of **1** and 4 Å MS used as an additive.



encouraged us to investigate the stereoselectivity of this process (Table 1). Due to isolation issues with the corresponding aryl ester, benzyl amine was added to the reaction after consumption of **2a**, leading to higher yields of the amide (**3**). Employing aminoindanol-derived precatalyst **B** facilitated product formation in a similar yield but led to an enantioenrichment of 68% (entry 3).

The phenylalanine-derived azolium salt **C**[5b] significantly improved the enantioselectivity but led to no improvement of the yield. At this point, a survey of bases was conducted. Interestingly, sodium 4-nitrophenoxide increased the yield to 59% (entry 6). Finally, 3 equiv of **1** with sodium 4-nitrophenoxide provided a good yield (72%) of **3** with high selectivity (94% ee, entry 7).[9] This anion is (a) surprisingly basic enough to generate the active carbene catalyst from the azolium precursor and (b) nucleophilic enough to *re-enter*

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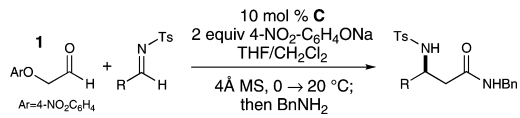
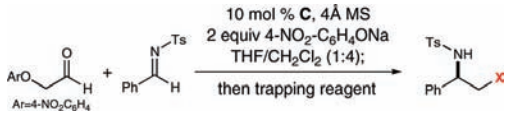
Table 2. Substrate Scope[a]

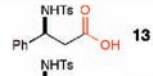
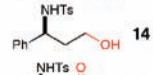
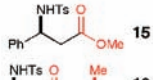
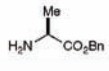
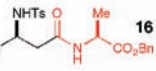


entry	R	product	yield (%)[b]	ee (%)[c]
1	Ph	**3**	72	94
2	4-Me-C_6H_4	**4**	70	95
3	2-naphth	**5**	66	92
4	1-naphth	**6**	61	90
5	3-Br-C_6H_4	**7**	75	91
6	4-Cl-C_6H_4	**8**	69	91
7	2-Cl-C_6H_4	**9**	64	88
8	3,4-Cl-C_6H_3	**10**	71	90
9	4-F-C_6H_4	**11**	56	95
10	3-MeO-C_6H_4	**12**	64	92

[a] 3 equiv of **1** in 0.1 M THF/CH_2Cl_2 (1:4). [b] Isolated yields. [c] Determined by HPLC with a chiral stationary phase.

Table 3. Synthetic Transformations



entry	trapping reagent	product		yield (%)[a]	ee (%)[b]
1	MeOH/ aq. NaOH		**13**	71	92[c]
2	$LiBH_4$		**14**	70	98
3	MeONa		**15**	61	94
4			**16**	51	20:1 *dr*

[a] Isolated yields. [b] Determined by HPLC with a chiral stationary phase. [c] See Supporting Information for absolute configuration determination.

the catalytic cycle and facilitate turnover by adding to the acyl azolium intermediate (**IV**).[10]

4-Nitrophenoxyacetaldehyde with several aromatic imines affords products with good yields and excellent enantioselectivity (Table 2). Electron-withdrawing groups are accommodated in different positions with a minimum 88% ee for the products (entries 6−9). Naphthyl derivatives are also tolerated with good yields and excellent enantioselectivity (entries 3 and 4). Halogen substitution is allowed with varying positions and types of substitution. Imines derived from aliphatic aldehydes are not successful coupling partners.

To demonstrate the value of this rebound catalysis strategy, we intercepted the initial amino ester formed in situ (**V** in Scheme 1) with a variety of nucleophiles (Table 3). Once the starting material is consumed, several reagents can be added directly to the reaction to furnish useful compounds. Basic conditions (MeOH/aq. NaOH) furnished *N*-tosyl β-amino acid **13** in good yield (71%),[11] while the addition of sodium methoxide promoted facile transesterification to the corresponding methyl ester in 61% yield. The reduction of the phenyl ester was achieved with $LiBH_4$ to yield 1,3-amino alcohols without loss of the stereochemical integrity (70% yield, 98% ee). Since peptides containing β-amino acids are useful, the initial 4-nitrophenyl ester provided the impetus for us to investigate the synthesis of these compounds using this new reaction.[12] The peptide coupling with benzyl protected alanine is successful and forms a new β-amino acid, C−C bond, and amide linkage in a single operation (51% yield).

In summary, we have developed a highly selective and versatile Mannich reaction using a new concept in carbene catalysis. Beginning from an α-aryloxyacetaldehyde, the addition of a carbene initiates the elimination of an aryloxy anion with concomitant enol/enolate formation. In the presence of activated imines, a Mannich reaction occurs to afford β-amino acyl azolium intermediates. The aryloxy anion can "rebound" by re-entering the catalytic cycle, regenerating the catalyst, and delivering a useful activated intermediate. These β-amino esters can be intercepted in situ to yield valuable nitrogen-containing compounds. Current investigations are focused on enhancing and exploring this rebound strategy in carbene catalysis which will be reported in due course.

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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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(10) β-Lactams have not been observed in these reactions, even prior to addition of external nucleophile. For complete conversion of the imine, 3 equiv of **1** are required. Further studies to understand this process are underway.

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