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Enantioselective Nucleophilic β-Carbon-Atom Amination of Enals: Carbene-Catalyzed Formal [3+2] Reactions

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Abstract: *An enantioselective β-carbon amination for enals is disclosed. The nitrogen atom from a protected hydrazine with suitable electronic properties readily behaves as a nucleophile. Addition of the nitrogen nucleophile to a catalytically generated N-heterocyclic-carbene-bound α,β-unsaturated acyl azolium intermediate constructs a new carbon–nitrogen bond asymmetrically. The pyrazolidinone products from our catalytic reactions are common scaffolds in bioactive molecules, and can be easily transformed into useful compounds such as β^3-amino-acid derivatives.*

Carbon–nitrogen (C–N) bonds are ubiquitous in natural products, pharmaceutical compounds, and other functional molecules which include polymeric materials. The development of efficient methods for asymmetric construction of C–N bonds continues to be an important objective in organic synthesis. In particular, the direct installation of a nitrogen atom at the β-carbon atom of aldehydes and esters can provide a most efficient access to useful β-amino acids and their derivatives.[1,2] N-heterocyclic carbene (NHC) organic catalysts have been explored to activate aldehydes and carboxylic esters to generate intermediates with reactive β-carbon atoms. For example, the NHC-mediated reaction of enals[3] or saturated esters[4] can generate a homoenolate intermediate (**I**) with a nucleophilic β-carbon atom (Figure 1 a). The nucleophilic β-carbon atom of **I** has been widely studied with regard to the formation of new carbon–carbon bonds.[5] The formation of C–N and C–O bonds using the homoenolate intermediate has also appeared in several studies. Specifically, reaction of **I** with electrophilic nitrogen atoms to form C–N bonds has been reported by the groups of Scheidt,[6a] Ying,[6b] Zhong,[6c] Ma,[6d] and She.[6e] The group of Rovis as well as our group have realized β-carbon C–O bond formation of **I** by radical pathways.[7] In contrast, addition of an NHC catalyst to α,β-unsaturated esters[8] or oxidation of the NHC-bound homoenolate intermediate[9] can effectively generate an α,β-unsaturated acyl azolium intermediate[10] **II** (Figure 1 b). This activation mode (via **II**) provides a complimentary approach for β-carbon-atom functionalizations of aldehydes or esters, as the electrophilic β-carbon atom (of **II**) can in principle react with a large set of nucleophiles. Somewhat unfortunately, to date, nearly all reactions involving the electrophilic β-carbon atom of **II** are limited to carbon–carbon bond formation. To the best of our knowledge, there is only one example of the addition of an aryl amine unit to **II** in a cascade reaction, as reported by Hui and coworkers.[11] Some of the intrinsic challenges for the β-amination of **II** include: 1) the relatively weak electrophilicity of the β-carbon atom of **II**,[9g] and 2) the competing amide bond formation between a nitrogen nucleophile and the acyl azolium moiety of **II**.

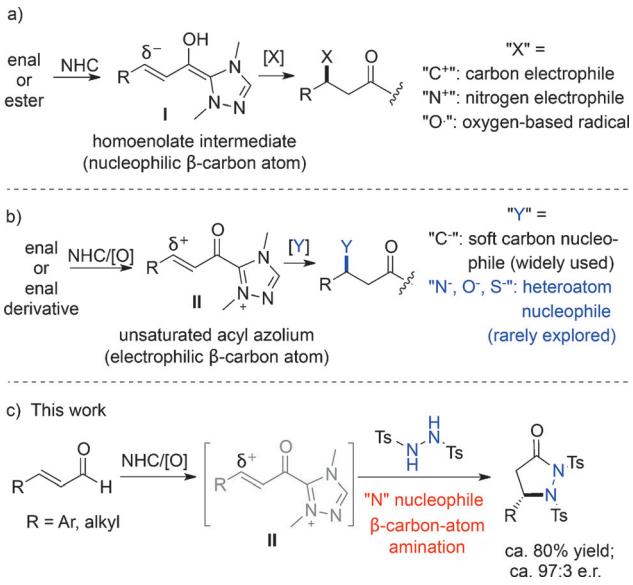

Figure 1. NHC-catalyzed β-carbon-atom functionalization of enals and carboxylic acid derivatives. Ts = 4-methylbenzenesulfonyl.

Herein we report the addition of a nucleophilic nitrogen center of hydrazide to the catalytically generated α,β-unsaturated acyl azolium intermediate (Figure 1 c). The reactivity of the nitrogen nucleophile is tuned by using hydrazines with proper protecting groups. Our reaction installs a nitrogen atom at the β-carbon atom of an enal and affords a pyrazolidinone adduct with good yield and excellent enantioselectivity. The pyrazolidinone adduct with a nitrogen–nitrogen (N–N) bond in a five-membered ring is widely

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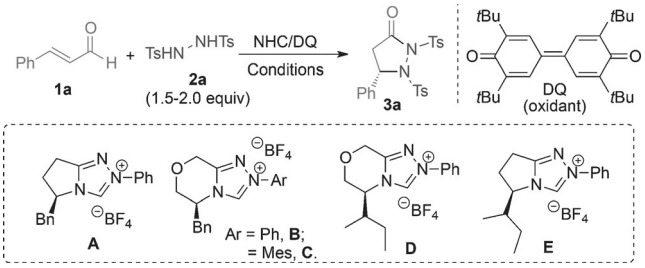
found as a core scaffold in natural products and bioactive molecules[12] such as azapropazone[12a] and phendione.[12c] Notably, similar compounds in optically enriched forms were previously obtained by either chiral resolutions or an additional oxidation step of the optical pyrazolidin-3-ols.[13] The N–N bond of our products can be readily cleaved, thus leading to β^3-amino-acid derivatives with high optical purity.

Our initial studies used the enal **1a** as the substrate to generate an α,β-unsaturated acyl azolium intermediate under oxidative NHC catalysis utilizing quinone (DQ) as the oxidant (Table 1).[9a–c] A survey of potential nitrogen nucleophiles revealed that tosyl-protected hydrazine (**2a**) could react effectively, thus leading to the β-amination product **3a** in an encouraging yield and e.r. value (entry 1). The high acidity of the NH proton (pK_a around 17.1 in DMSO from Bordwell pK_a table) of **2a** promotes the aza-Michael addition step under basic conditions. Several amino-acid-derived triazolium NHC precatalysts (**B**–**E**; entries 2–5) were found to be effective in this reaction, and **B** proved to be superior in terms of both yield and enantioselectivity (entry 2). The effects of bases were also examined (entries 6–10). Under the influence of strong bases such as Cs_2CO_3 (entry 6) and DBU (entry 9), unproductive consumption of **2a**, because of decomposition,[14] led to lower yields. We finally found that by increasing the amount of **2a** from 1.5 to 2.0 equivalents, **3a** could be obtained in 88% yield and 97:3 e.r. (entry 10). The model reaction could be easily scaled up without affecting the enantioselectivity (entry 12).

Table 1: Screening of reaction conditions for the reaction of **1a** with **2a**.[a]

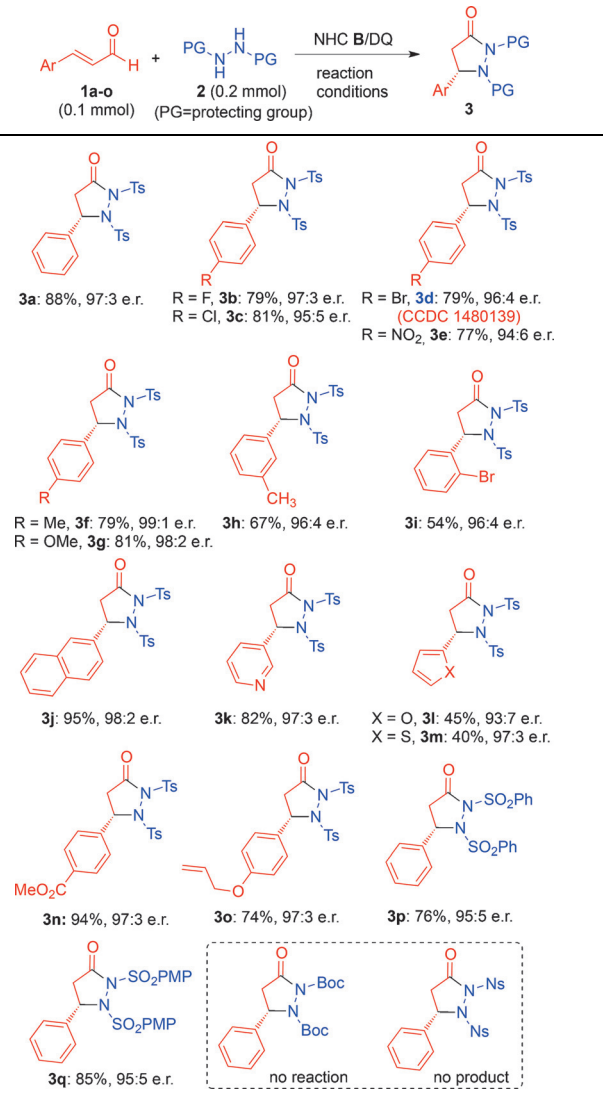


Entry	NHC	Base	Yield [%][b]	e.r.[c]
1	**A**	K_2CO_3	45	88:12
2	**B**	K_2CO_3	71	97:3
3	**C**	K_2CO_3	66	95:5
4	**D**	K_2CO_3	61	96:4
5	**E**	K_2CO_3	61	92:8
6	**B**	Cs_2CO_3	45	88:12
7	**B**	K_3PO_4	53	96:4
8	**B**	DIEA	51	94:6
9	**B**	DBU	25	92:8
10	**B**	DABCO	42	95:5
11	***B***	*K_2CO_3 (2.0 equiv. **2a**)*[d]	*92 (88)*[e]	*97:3*
12	**B** (12 mol%), K_2CO_3, 2.0 equiv. **2a**		78 (2.9 g)[f]	97:3

[a] Reaction conditions: **1a** (0.05 mmol, 1.0 equiv), **2a** (0.075 mmol, 1.5 equiv), NHC (20 mol%), base (2 equiv) and **DQ** (1.2 equiv), 4 Å M.S. (50 mg) in THF (0.05 M) at RT for 16 h. [b] Yield determined by NMR spectroscopy, based on **1a**, by using 1,3,5-trimethoxybenzene as an internal standard. [c] Determined by chiral-phase HPLC analysis. [d] 2 equiv of **2a** was used. [e] Yield of isolated product given within parentheses. [f] Prepared on 2.9 gram scale. DABCO = 1,4-diazabicyclo-[2.2.2]octane, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, DIEA = diiso-propylethylamine, M.S. = molecular sieves.

With optimized reaction conditions in hand (Table 1, entry 11), the generality of the reaction was explored (Tables 2 and 3). We first examined β-aryl enals reaction with hydrazides (Table 2). With tosyl-protected hydrazide **2a** as a model nitrogen nucleophile, different substituents and substituent patterns on the β-aryl group of enals were well tolerated (**3a**–**j**). Replacing the β-phenyl group of **1a** with a pyridine unit also led to the product **3k** with excellent yield and e.r. value. When enals with either a β-furyl or thienyl group were used, the corresponding products were obtained with excellent e.r. values, albeit with moderate yields (**3l**,**m**). Readily convertible functional groups on the enal substrates, such as ester and allyl units, are compatible with the reaction conditions (**3n**,**o**). The tosyl protecting group of **2a** could be

Table 2: Formal [3+2] annulations of the aromatic-enal with hydrazide.[a]

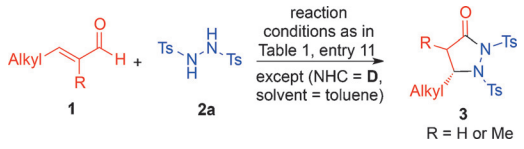


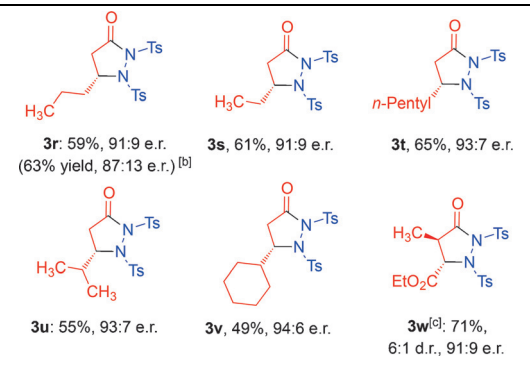
[a] Reaction conditions as in Table 1, entry 11. Yields (after SiO_2 chromatography purification) based on the enal **1**. PG = protecting group, Ns = 4-nitrobenzenesulfonyl, PMP = *p*-methoxyphenyl.

replaced with other sulfonyl units (**3p**,**q**). When Boc-protected (Boc = *tert*-butyloxycarbonyl) hydrazide was used, no β-amination product was obtained and most of the two substrates remained unreacted. The hydrazide with Ns (4-nitrobenzenesulfonyl) as the protecting group tended to decompose easily under basic reaction conditions and no β-amination adduct was observed.

We next examined enals having a β-alkyl substituent (Table 3). When the standard reaction conditions (Table 1, entry 11) were used for β-aryl enals, the corresponding product **3r**, from a β-alkyl enal, was obtained in 63% yield and 87:13 e.r. (Table 3). With a slight modification of the reaction conditions by using **D** as the NHC precatalyst and toluene as the solvent, the reaction enantioselectivities could be improved to 91:9 e.r. We then used the modified reaction conditions to examine the generality of the β-alkyl enal reactions. Notably, enals bearing relatively bulky alkyl substituents led to better stereoselectivities (e.g., **3v**). When an α,β-disubstituted enal (**1w**) was used, both the standard and modified reaction conditions with catalyst **D** were not effective (only trace amounts of product were observed). Additional investigations revealed that the precatalyst **E** led to **3w** in 71% yield with 6:1 d.r. and 91:9 e.r.

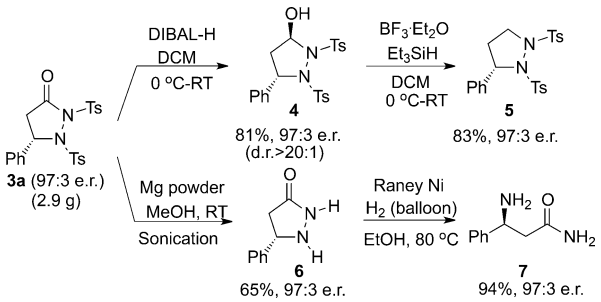
Table 3: Formal [3+2] annulations of the alkyl-enal with **2a**.[a]





[a] **1** (0.10 mmol), **2a** (0.20 mmol), NHC **D** (20 mol%), K_2CO_3 (0.2 mmol), **DQ** (1.2 equiv) and 4 Å M.S. (100 mg) in toluene (2 mL) at RT for 16 h. Yields (after SiO_2 chromatography purification) based on the enal **1**. [b] Reaction conditions as in Table 1, entry 11. [c] Catalyst **E** was used instead of **D**.

The optically enriched pyrazolidinone products prepared in our catalytic reaction can readily undergo further transformations, as illustrated in Scheme 1. The carbonyl group of **3a** can be reduced to the corresponding alcohol to give the pyrazolidin-3-ol **4** in 81% yield without erosion of the e.r. value. The compound **4** could be further reduced to the pyrazolidine **5**. Both **4** and **5** are privileged heterocyclic structures in natural and synthetic bioactive compounds.[15] Deprotection of **3a** with Mg/MeOH furnishes the compound **6**, which was further converted into the β^3-amino-acid derivative **7** by reductive cleavage of the N–N bond using Raney Ni. β^3-Amino acids and their derivatives have been widely found in drugs,[16] bioactive molecules,[17] and building blocks for non-natural peptidic foladmers.[18]



Scheme 1. Synthetic transformations of the pyrazolidinone **3a**. DCM = dichloromethane, DIBAL-H = diisobutylaluminum hydride

In summary, we have developed a highly efficient approach for the β-carbon amination of unsaturated aldehydes. Our method involves the addition of a nucleophilic nitrogen atom to the catalytically generated α,β-unsaturated acyl azolium intermediate, having an electrophilic β-carbon atom, as the key step. This C–N bond-forming reaction enabled by NHC catalysts readily provides pyrazolidinone products with good to excellent yields and enantioselectivities. The products, easily prepared on gram scale, can be converted into useful molecules, such as β-amino amides. Most of the reactions mediated by NHC organocatalysts have focused on carbon–carbon bond formations. We expect that this study and future developments on carbon–heteroatom bond constructions shall significantly expand the utility of NHC organocatalysis.

Experimental Section

General procedure for the β-amination of enals: A dry 10 mL Schlenk tube with stir bar was charged with hydrazide **2** (0.20 mmol, 2.0 equiv), NHC **B** (7.6 mg, 20 mol%), K_2CO_3 (27.6 mg, 0.2 mmol, 2 equiv), **DQ** (48.9 mg, 0.12 mmol, 1.2 equiv) and molecular sieves (100 mg). The tube was evacuated, and refilled with nitrogen. Then enal **1** (0.10 mmol, 1.0 equiv) was added and the mixture was dissolved with newly distilled solvent THF (2.0 mL). The mixture was stirred at room temperature for 16 h when the substrate was consumed completely (monitored by TLC). The reaction mixture was concentrated under vacuum and purified by column chromatography on silica gel (hexane/ethyl acetate) to afford desired product **3**.

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