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Organocatalytic Synthesis of *N*-Phenylisoxazolidin-5-ones and a One-Pot Synthesis of β-Amino Acid Esters

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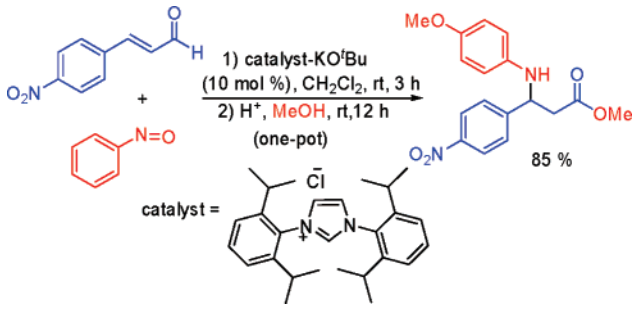
ABSTRACT



A novel *N*-heterocyclic carbene (NHC)-catalyzed C–N bond formation by the reaction of α,β-unsaturated aldehydes and nitrosobenzene to *N*-phenylisoxazolidin-5-ones, followed by an acid-catalyzed esterification and Bamberger-like rearrangement in a mild one-pot protocol leads to *N*-*p*-methoxyphenyl (*N*-PMP) protected β-amino acid esters.

New catalytic methods for carbon−nitrogen (C−N) bond formation are important for their broad applications in organic synthesis, especially for pharmaceuticals and natural products.[1] Organocatalytic C−N bond formations that avoid the use of toxic and expensive metal catalysts are of particular interest. Proline-catalyzed direct α-aminations of carbonyl compounds developed independently by List[2] and Jørgensen and co-workers[3] are the first examples of organocatalytic C−N bond formation. Yamamoto et al.[4] and Maruoka and co-workers[5] subsequently reported *N*-nitroso aldol reaction of enamines selectively forming *N*-hydroxyaminoketones. The recent enantioselective conjugate addition of *N*-silyloxycarbamates to enals using imidazolidinone catalysts developed by MacMillan and co-workers[6] is an elegant method for enantio-enriched β-amino aldehydes. Another recent interesting example is the reaction of enals and *N*-protected hydroxylamine in the presence of chiral pyrrolidine catalysts, forming 5-hydroxyisoxazolidines that were further converted to the corresponding β-amino acids or γ-amino alcohols.[7] We report here a novel method for C−N

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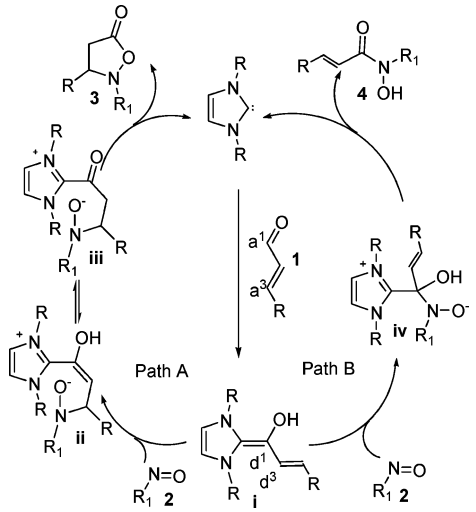
bond formation by the reaction of α,β-unsaturated aldehydes with nitrosobenzene using *N*-heterocyclic carbene (NHC) catalysis, forming *N*-phenylisoxazolidin-5-ones[8] that are converted to the corresponding *N*-*p*-methoxyphenyl (*N*-PMP)-protected β-amino acid esters in a mild one-pot synthetic protocol. β-amino acids possess biologically important properties, occur in natural products, and are key building blocks to several bioactive compounds.[9]

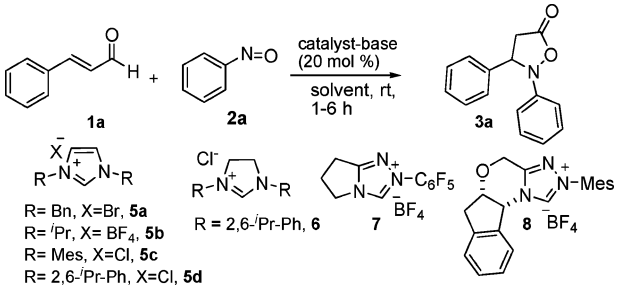
NHC-catalyzed activation of carbonyl compounds has evolved as a potential method for metal-free C−C bond-forming reactions via the nucleophilic "Breslow intermediate"[10] or the homoenolate equivalent species **i**.[11] We envisioned that nitroso compounds could act as potential electrophiles for such reactions, forming the corresponding C−N bonds[12] leading to amides or β-amino acid derivatives. The coupling of the nitroso compound with the homoenolate equivalent **i** (d^3 nucleophile)[13] would form intermediate nitroxide species **ii** and **iii** (Path A, Scheme 1). The nitroxide **iii** can then attack the carbonyl group of the activated carboxylate intramolecularly, leading to isoxazolidin-5-ones, returning the carbene catalyst back for further turnovers. Potential competing reactions would be the reaction of the d^1 nucleophile with the nitroso compound to form the *N*-hydroxycinnamamide (Path B, Scheme 1) and the self-condensation of enal.[11b] The ability of thiamine-dependent enzymes to convert aromatic nitroso compounds into hydroxamic acids has been investigated by Corbett et al.[14]

Scheme 1. NHC Catalysis: Nitrosobenzene as an Electrophile



In our initial experiments, cinnamaldehyde and nitrosobenzene were found to rapidly react in the presence of NHC catalysts generated from imidazolium salts (**5**−**6**), forming 2,3-diphenylisoxazolidin-5-one (**3a**). Optimization studies using different imidazolium and triazolium salts indicated that sterically more demanding imidazolium catalyst **5d** provided the highest selectivity toward **3a**. On the other hand, use of sterically less hindered catalysts such as **5c** also formed *N*-hydroxy-*N*-phenylcinnamamide (**4a**)[15] (Table 1). The NHCs derived from the triazolium salts **7**[16] and **8**[17] produced

Table 1. NHC-Catalyzed Synthesis of 2,3-Diphenylisoxazolidin-5-one: Catalyst Optimization



entry	catalyst	solvent	base	yield (%)[a]
1	**5a**	THF	KO^{t}Bu	14
2	**5b**	THF	KO^{t}Bu	5
3	**5c**	THF	KO^{t}Bu	60
4	**5d**	THF	KO^{t}Bu	80
5	**6**	THF	KO^{t}Bu	10
6	**7**	THF	KO^{t}Bu	-[b]
7	**8**	THF	KO^{t}Bu	-[b]
8	**5d**	CH_2Cl_2	KO^{t}Bu	82
9	**5d**	C_6H_6	KO^{t}Bu	50
10	**5d**	CH_2Cl_2	DBU[c]	48

[a] Yields determined by ^{1}H NMR. [b] Over 95% formation of *N*-hydroxy-*N*-phenylcinnamamide (**4a**) was observed. [c] DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

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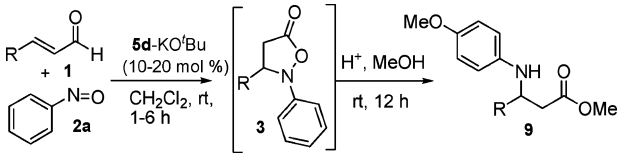
4a exclusively, irrespective of the steric bulk. The only other observable side product was a small amount of azoxybenzene, which was effectively minimized by optimizing the reaction parameters.

In attempts to cleave the N−O bond of the 2,3-diphenylisoxazolidin-5-one (**3a**), we have developed an acid-catalyzed esterification, followed by a Bamberger-like rearrangement[18] to form *N*-*p*-methoxyphenyl *β*-phenethylamino acid ester **9a**.[19] This is an excellent method to create a nitrogen-protecting group (PMP), which has been known to be deprotected under mild oxidative conditions.[20] More interestingly, these two catalytic steps could be performed in a one-pot process starting with the enal (Table 2). Thus, in the optimized protocol, **5d**, KO^{t}Bu, nitrosobenzene, and the enal were reacted for 1−6 h. After solvent evaporation, the residue was diluted in methanol, $HClO_4$ was added to the mixture, and the reaction was continued to produce the *N*-PMP protected *β*-amino acid esters in good to excellent yields. Traces of *N*-*p*-hydroxyphenyl *β*-amino acid ester and *N*-*o*-methoxyphenyl *β*-amino acid ester were also formed in some cases.

Table 2. NHC-Catalyzed One-Pot Synthesis of *β*-Amino Acid Esters



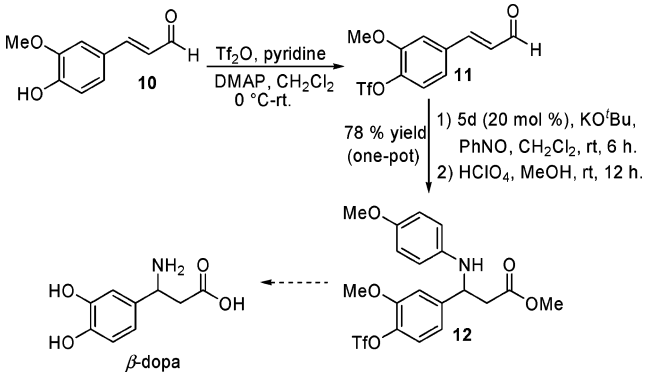
entry	R	yield of **3** (%)[a]	yield of **9** (%)[b]
1	Ph (**a**)	82	75
2	4-NO_2Ph (**b**)	98[c]	85
3	2-NO_2Ph (**c**)	84	70
4	3-Br-4-OTfPh (**d**)	83	79
5	4-COOMePh (**e**)	82	75
6	6-COOMe-2-Np (**f**)	75	68
7	4-CNPh (**g**)	95	40[d]
8	4-CF_3Ph (**h**)	90	80
9	C_6F_5 (**i**)	85	72
10	3,5-F_2Ph (**j**)	88	78
11	EtCOO (**k**)	96	84
12	C_4H_9 (**l**)	40	30

[a] Yields determined by ^{1}H NMR. [b] Overall isolated yields with respect to aldehyde. [c] 10 mol % of catalyst. [d] Lower yield could be due to the hydrolysis of cyano group under acidic conditions.

A variety of aryl (**1a**−**1j**)- and alkyl (**1k**−**1l**)-substituted α,*β*-unsaturated aldehydes were found to form the corresponding *N*-phenylisoxazolidin-5-ones (**3a**−**3l**) and *β*-amino acid esters (**9a**−**9l**) by this method (Table 2). In general, those with an electron-withdrawing group provided higher yields. Substrates with different functional groups, such as ether, ester, nitro, and sulfonate, were readily accommodated in this protocol. The intermediate *N*-phenylisoxazolidin-5-one derivatives were not quite stable for isolation due to potential decarboxylation and further hydrolysis.[21] Hence, their formations were monitored separately by ^{1}H nuclear magnetic resonance (NMR) studies.

Furthermore, we applied this methodology for the synthesis of the natural product *β*-DOPA,[22] starting from the commercially available enal **10** (Scheme 2). Thus, **10** after triflation to **11**, was allowed to react with nitrosobenzene using our one-pot protocol, producing *N*-PMP protected *β*-DOPA ester **12** (see Figure 1) in high yields.

Scheme 2. Application to *β*-DOPA Synthesis



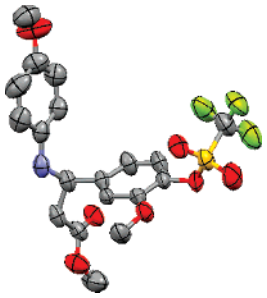


Figure 1. Crystal structure of **12**.

A preliminary study on the enantioselective variant of this methodology by the reaction of the enal **1h** and nitrosobenzene resulted in 44.5% ee and 76% yield of **9h** using the

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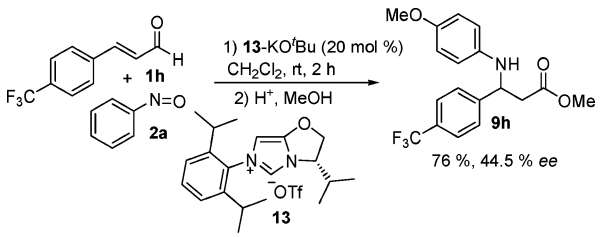
NHC catalyst derived from a chiral imidazolium salt **13**[23] (Scheme 3).

Scheme 3. NHC-Catalyzed Enantioselective Synthesis of β-Amino Acid Esters



In conclusion, we have developed a one-pot protocol for *N*-PMP protected β-amino acid esters by a novel NHC-catalyzed reaction of enals and nitrosobenzene, followed by an acid-catalyzed esterification and Bamberger-like rearrangement of the intermediate *N*-phenylisoxazolidin-5-ones. The reaction of the homoenolate with nitrosobenzene is directed efficiently to either 1,4- or 1,2-addition by manipulating the steric and electronic properties of the NHC catalyst. This new organocatalytic protocol is attractive in terms of both mechanistic and synthetic aspects, in addition to its simplicity and advantages over the current approaches. Further optimization of the enantioselective variant and elaboration of the scope of the reaction are underway.

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Supporting Information Available: Experimental procedures, compound characterization, NMR spectra, HPLC traces, X-ray crystallography data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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