Direct Amination of Homoenolates Catalyzed by *N*-Heterocyclic Carbenes

Audrey Chan and **Karl A. Scheidt**[*]
Department of Chemistry, Northwestern University, 2145 Sheridan Road, Evanston, Illinois 60208

The de novo construction of β-amino acids by the direct construction of the C–N bond continues to be an objective because of the continuing utility of these compounds.[1,2] A conventional method to access these molecules is the conjugate addition of a nucleophilic nitrogen source such as azide or an aliphatic amine to an activated ester or ketone (eq 1).[3] Alternatively, formal [3+2] reactions with hydroxylamines provide isoxazolidines in which the N–O bond can be easily cleaved.[4] A polarity reversal strategy to access β-amino acid derivatives would employ unusual reactivity patterns, such as homoenolates, in the context of a formal cycloaddition. In this Communication, we report the catalytic amination of homoenolates by combining α,β-unsaturated aldehydes with diazenes in the presence of *N*-heterocyclic carbenes (NHCs) to generate pyrazolidinones (**3**, eq 2).
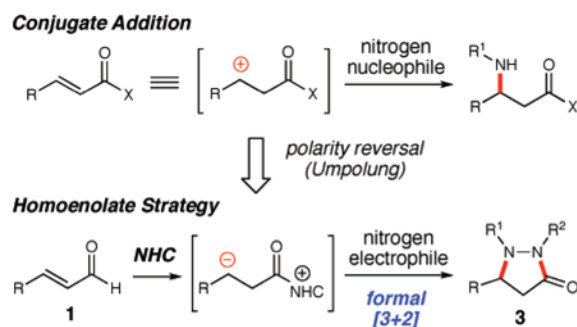
(1) (2)

The direct electrophilic amination of a homoenolate generated under catalytic conditions is an unrealized transformation with significant potential. This approach presents the opportunity to obviate the liabilities of standard azide and hydroxylamine nucleophiles and has potential for stereochemical control over the newly formed asymmetric center. A key caveat to the successful realization of electrophilic amination of carbene-generated homoenolates is identifying reactants and conditions that favor carbene addition to the aldehyde over the nonproductive addition to the electrophilic nitrogen reagent.

Our previous efforts in the area of *N*-heterocyclic carbene catalysis[5] have generated new ways to form C–H and C–C bonds[6] by accessing unique homoenolates from α,β-unsaturated aldehydes.[7] In these processes, the aldehyde is converted into an intermediate that possesses nucleophilic character at the β-carbon which upon addition to an electrophile yields an activated

scheidt@northwestern.edu.

carbonyl species. With this general reactivity pattern, the anticipated catalytic pathway for our amination involves the addition of an NHC to the α,β-unsaturated aldehyde **1** to afford the tetrahedral intermediate **I**. Upon rearrangement, the extended diene homoenolate equivalent **II** is generated, which undergoes addition to the diazene **2** and subsequently generates ketone **III** after tautomerization. This activated carbonyl species facilitates catalyst turnover by intramolecular acylation to produce pyrazolidinone **3**.

The first goal for the direct amination was to identify a suitable nitrogen-containing electrophile. We began by screening cinnamaldehyde (**1a**) with heteroazolium salts **A–D** (Table 1). Diethyl azodicarboxylate provided no desired products (entry 1), but to our delight, diphenyl diazene afforded low yields of pyrazolidinones (entries 2, 3) in the presence of benzimidazolium salts **A,B**. An intensive investigation of different diazo compounds and azolium salts led to the identification of a new triazolium salt **D**, which in combination with acylarydiazenes **2d** afforded the highest yields of the pyrazolidinone product as a single regioisomer.

During our optimization studies, we isolated varying amounts of 1-benzoyl-2-phenylhydrazine (**4**) when employing diazene **2d** as the electrophile. On the basis of our carbene-catalyzed hydroacylation studies,[5a] we postulate that tetrahedral intermediate **I** (Scheme 1) can form the desired homoenolate intermediate (path A) or collapse to afford an acyl heteroazolium species with concomitant hydride transfer to the diazene (path B). The undesired reaction reduces **2d** to the observed hydrazine and sacrifices an equivalent of unsaturated aldehyde. Fortunately, by tuning the structure of the carbene catalyst to **D** and lowering the reaction temperature, we can maximize the desired homoenolate amination (Table 1, entry 11).[8]

The reaction scope (Table 2) accommodates a variety of substituted α,β-unsaturated aldehydes, including electron-rich and -poor aromatic systems (entries 2–6), and, importantly, β-alkyl-substituted aldehydes provided excellent yields of **11** and **12** (entries 7, 8). An examination of the acylaryldiazene component of the reaction reveals that variously substituted aryl groups are competent substrates. Electron-withdrawing and electron-donating groups on the aryl ring of the benzoyl portion of the diazene afforded good yields of the pyrazolidinone (entries 9–11). However, only electron-rich substituents on the aryl component of the diazene resulted in product formation (entries 12, 13), while electron poor aryl substituents (i.e., Ar = 4-Br-Ph) gave a low yield (25%).

The use of our chiral triazolium salt **E**[5c] in this new amination reaction provides pyrazolidinone **18** in good yield (61%) and excellent enantioselectivity (90% ee, eq 5). The pyrazolidinone products can be manipulated to afford β-amino amides by initial exposure to 10 mol % Sm(OTf)$_3$ in THF/MeOH[9] to remove the benzoyl functionality (eq 6). A clean reductive cleavage of the N–N bond of pyrazolidinone **19** with Raney nickel produces the β-amino amide **20** in excellent yield (96%).
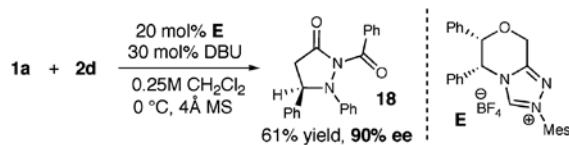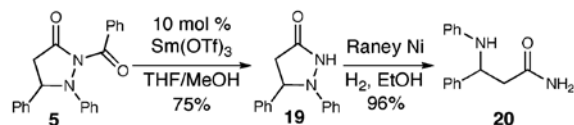
(6)

In summary, we have developed a direct electrophilic amination of homoenolates catalyzed by *N*-heterocyclic carbenes. The addition of a carbene derived from triazolium salt **D** to an α,β-unsaturated aldehyde generates a homoenolate intermediate which undergoes a formal [3 +2] cycloaddition with an 1-acyl-2-aryldiazene to afford pyrazolidinones as a single regioisomer. A chiral triazolium salt can be used to control the newly formed stereocenter of the product, which results in good selectivity. The pyrazolidinone products can be converted into *β*-amino acid derivatives in excellent yields. Carbene catalysis continues to facilitate new strategies for the creation of valuable molecules from simple precursors.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

References

1. (a) Seebach D, Matthews JL. Chem Commun 1997:2015–2022. (b) Cheng RP, Gellman SH, DeGrado WF. Chem Rev 2001;101:3219–3232. [PubMed: 11710070] (c) Liu M, Sibi MP. Tetrahedron 2002;58:7991–8035. (d) Ma JA. Angew Chem, Int Ed 2003;42:4290–4299.(e) Juaristi, E.; Soloshonok, VA., editors. Enantioselective Synthesis of β-Amino Acids. Wiley-VCH; New York: 2005.

2. For the use of β-amino acids in peptides, see: (a) Seebach D, Overhand M, Kuehnle FNM, Martinoni B. Helv Chim Acta 1996;79:913–941. (b) Appella DH, Christianson LA, Karle IL, Powell DR, Gellman SH. J Am Chem Soc 1996;118:13071–13072. (c) Daniels DS, Petersson EJ, Qiu JX, Schepartz A. J Am Chem Soc 2007;129:1532–1533. [PubMed: 17283998]

3. For examples, see: (a) Sibi MP, Shay JJ, Liu M, Jasperse CP. J Am Chem Soc 1998;120:6615–6616. (b) Myers JK, Jacobsen EN. J Am Chem Soc 1999;121:8959–8960. (c) Horstmann TE, Guerin DJ, Miller SJ. Angew Chem, Int Ed 2000;39:3635–3638. (d) Zhuang W, Hazell RG, Jorgensen KA. Chem Commun 2001:1240–1241. (e) Xu LW, Li JW, Xia CG, Zhou SL, Hu XX. Synlett 2003:2425–2427. (f) Doi H, Sakai T, Iguchi M, Yamada K, Tomioka K. J Am Chem Soc 2003;125:2886–2887. [PubMed: 12617650] (g) Xu LW, Xia CG, Li JW, Zhou SL. Synlett 2003:2246–2248. (h) Fadini L, Togni A. Chem Commun 2003:30–31. (i) Palomo C, Oiarbide M, Halder R, Kelso M, Gomez-Bengoa E, Garcia JM. J Am Chem Soc 2004;126:9188–9189. [PubMed: 15281801] (j) Shimizu M, Nishi T. Synlett 2004:889–891. (k) Xu LW, Li L, Xia CG, Zhou SL, Li JW. Tetrahedron Lett 2004;45:1219–1221. (l) Reboule I, Gil R, Collin J. Tetrahedron–Asymmetry 2005;16:3881–3886. (m) Sakai T, Doi H, Tomioka K. Tetrahedron 2006;62:8351–8359. (n) Chen YK, Yoshida M, MacMillan DWC. J Am Chem Soc 2006;128:9328–9329. [PubMed: 16848457]

4. (a) Niu DQ, Zhao K. J Am Chem Soc 1999;121:2456–2459. (b) Lee HS, Park JS, Kim BM, Gellman SH. J Org Chem 2002;68:1575–1578. [PubMed: 12585907] (c) Sibi MP, Prabagaran N, Ghorpade SG, Jasperse CP. J Am Chem Soc 2003;125:11796–11797. [PubMed: 14505383] (d) Ibrahem I, Rios R, Vesely J, Zhao GL, Cordova A. Chem Commun 2007:849–851.

5. (a) Chan A, Scheidt KA. J Am Chem Soc 2006;128:4558–4559. [PubMed: 16594677] (b) Phillips EM, Wadamoto M, Chan A, Scheidt KA. Angew Chem, Int Ed 2007;46:3107–3110. (c) Wadamoto M, Phillips EM, Reynolds TE, Scheidt KA. J Am Chem Soc 2007;129:10098–10099. [PubMed: 17663558]

6. (a) Chan A, Scheidt KA. Org Lett 2005;7:905–908. [PubMed: 15727471] (b) Chan A, Scheidt KA. J Am Chem Soc 2007;129:5334–5335. [PubMed: 17407298]

7. For related studies, see: (a) Burstein C, Glorius F. Angew Chem, Int Ed 2004;43:6205–6208. (b) Sohn SS, Rosen EL, Bode JW. J Am Chem Soc 2004;126:14370–14371. [PubMed: 15521753] (c) He M, Bode JW. Org Lett 2005;7:3131–3134. [PubMed: 15987223] (d) Nair V, Vellalath S, Poonoth M, Mohan R, Suresh E. Org Lett 2006;8:507–509. [PubMed: 16435871] (e) Nair V, Vellalath S, Poonoth M, Suresh E. J Am Chem Soc 2006;128:8736–8737. [PubMed: 16819860]

8. Small amounts (10–15%) of hydrazine byproducts are generated under optimized conditions.

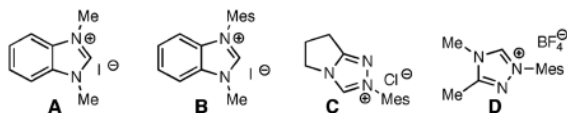9. Evans DA, Scheidt KA, Downey CW. Org Lett 2001;3:3009–3012. [PubMed: 11554830]
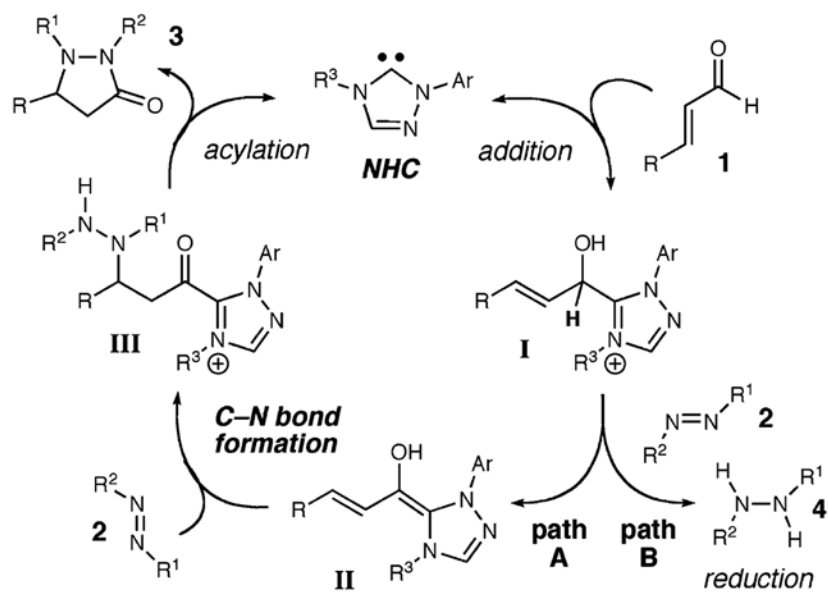
Scheme 1.
Reaction Pathway

Table 1

Optimization of Amination Conditions[a]
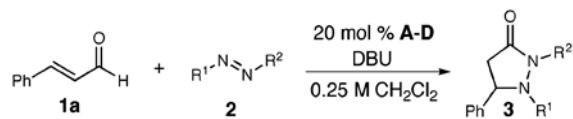
(3)

entry	catalyst	R^1	R^2	yield (%)[b]
1	**A**, **B**, **C**, or **D**	CO$_2$Et	CO$_2$Et (**2a**)	0
2	**A**	Ph	Ph (**2b**)	26
3	**B**	Ph	Ph (**2b**)	29
4	**C**	Ph	Ph (**2b**)	18
5	**D**	Ph	Ph (**2b**)	28
6	**C**	Ph	SO$_2$Ph (**2c**)	16
7	**D**	Ph	SO$_2$Ph (**2c**)	16
8	**A** or **B**	Ph	COPh (**2d**)	0
9	**C**	Ph	COPh (**2d**)	42
10	**D**	Ph	COPh (**2d**)	49
11[c]	**D**	Ph	COPh (**2d**)	63
12[d]	**D**	Ph	COPh (**2d**)	54

[a] 20 mol % DBU and 3 equiv of **2**, 23 °C.

[b] Isolated yields.

[c] 30 mol % DBU, 3 equiv of **2**, and 4 Å molecular sieves, 0 °C.

[d] 30 mol % DBU, 2 equiv of **2**, and 4 Å molecular sieves, 0 °C.

Table 2

Reaction Scope[a]
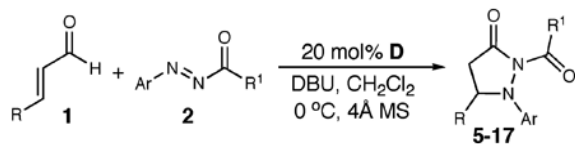
$$(4)$$

entry	R	Ar	R^1	yield (%)[b]
1	Ph	Ph	Ph	63 (**5**)
2	3-OMe-Ph	Ph	Ph	60 (**6**)
3	2-OMe-Ph	Ph	Ph	66 (**7**)
4	2-Naphthyl	Ph	Ph	64 (**8**)
5	4-Cl-Ph	Ph	Ph	61 (**9**)
6	2-OMe-Ph	Ph	3-Me-Ph	64 (**10**)
7	Me	Ph	2-Me-Ph	82 (**11**)
8	CH$_2$CH$_2$CH$_3$	Ph	3-Me-Ph	84 (**12**)
9	Ph	Ph	4-Cl-Ph	68 (**13**)
10	Ph	Ph	4-F-Ph	61 (**14**)
11	Ph	Ph	3-Me-Ph	73 (**15**)
12	Ph	3-Me-Ph	Ph	71 (**16**)
13	Ph	4-Me-Ph	Ph	63 (**17**)

[a]3 equiv of **2**.

[b]Isolated yields after chromatography.