Published in final edited form as:

J Am Chem Soc. 2009 December 23; 131(50): 18028–18029. doi:10.1021/ja9094044.

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

Yasufumi Kawanaka, Eric M. Phillips, and Karl A. Scheidt

Department of Chemistry, Center for Molecular Innovation and Drug Discovery, Chemistry of Life Processes Institute, Silverman Hall, Northwestern University, Evanston, Illinois 60208

Karl A. Scheidt: scheidt@northwestern.edu

Abstract

N-Heterocyclic carbenes (NHCs) catalyze a new Mannich-type reaction to form β -amino acid derivatives in high yield and enantioselectivity. The reaction is initiated by the addition of an NHC to an α -aryloxyaldehyde followed by elimination of a phenoxide anion which generates an enol/enolate. A Mannich addition to a tosylimine proceeds with excellent control over enantioselectivity. In a new carbene catalysis concept, catalyst regeneration is promoted by return, or rebound, and acylation of the phenoxide group which served as the activating component in the first step of the catalytic cycle. The activated ester products formed in situ are manipulated to form a variety of useful compounds including β -amino acids, β -amino amides, and peptides.

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 last decade.² A complementary strategy using secondary amines as catalysts has undergone a resurgence of activity and has become a powerful and general method for enantioselective enolate additions.³ Most recently, N-heterocyclic carbenes (NHCs) have emerged as a different class of small molecules which

Correspondence to: Karl A. Scheidt, scheidt@northwestern.edu.

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

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, thus regenerate the catalyst and create a useful activated ester in the process.^{5e,6} Herein, we report a new enantioselective Mannich reaction using this strategy (eq 1).

(1)

We chose to explore additions to activated imines (Mannich reaction) in order to investigate this new reaction and capture the enolate generated in this process. The products of this approach 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, thereby 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. nucleophilicity, 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 in order 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.

Our investigations began by surveying α -substituted acetaldehydes in combination with azolium salts and bases. The stable and easy to prepare 4-nitrophenoxyacetaldehyde emerged as a competent substrate for facile formation of the enolate in the presence of carbenes. Azolium salt **A** in combination with Et_3N and CH_2Cl_2 led to formation of amide **3** in poor yield (37%), but 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 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 active carbene catalyst from the azolium precursor and b) nucleophilic enough to *re-enter* the catalytic cycle and facilitate turnover by adding to the acyl azolium intermediate (**IV**).¹⁰

4-Nitrophenoxyacetaldehyde in combination with several aromatic imines affords products with good yields and excellent levels of 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 currently 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 LiBH₄ to yield 1,3-amino alcohols without loss of the stereochemical integrity (70% yield, 94% 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Support for this work was generously provided by NIGMS (RO1 GM73072), Amgen, GSK, AstraZeneca, and the Alfred P. Sloan Foundation. E.M.P is a recipient of a 2008-2009 ACS Division of Organic Chemistry fellowship. Y.K. thanks Ono Pharmaceuticals for support.

References

1. (a) Jacobsen, EN.; Pfaltz, A.; Yamamoto, H., editors. *Comprehensive Asymmetric Catalysis*. 1-3. Vol. 1-3. Springer; Berlin, Germany: 1999. (b) Arya P, Qin HP. *Tetrahedron* 2000;56:917–947.
2. Mahrwald, R. *Modern Aldol Reactions*. Wiley-VCH; Weinheim: 2004. For selected examples, see: (a) Yoshikawa N, Yamada YMA, Das J, Sasai H, Shibasaki M. *J Am Chem Soc* 1999;121:4168–4178. (b) Trost BM, Ito H. *J Am Chem Soc* 2000;122:12003–12004. (c) Hamashima Y, Hotta D, Sodeoka M. *J Am Chem Soc* 2002;124:11240–11241. [PubMed: 12236717] (d) Evans DA, Downey CW, Hubbs JL. *J Am Chem Soc* 2003;125:8706–8707. [PubMed: 12862448]
3. (a) List B. *Acc Chem Res* 2004;37:548–557. [PubMed: 15311954] (b) Notz W, Tanaka F, Barbas CF. *Acc Chem Res* 2004;37:580–591. [PubMed: 15311957] (c) Chi Y, Gellman SH. *J Am Chem Soc* 2006;128:6804–6805. [PubMed: 16719457] (d) MacMillan DWC. *Nature* 2008;455:304–308. [PubMed: 18800128] (e) Yang J, Chandler C, Stadler M, Kampen D, List B. *Nature* 2008;452:453–455. [PubMed: 18288105]
4. (a) Enders D, Balensiefer T. *Acc Chem Res* 2004;37:534–541. [PubMed: 15311952] (b) Marion N, Diez-Gonzalez S, Nolan IP. *Angew Chem Int Ed* 2007;46:2988–3000.

5. (a) Chan A, Scheidt KA. *Org Lett* 2005;7:905–908. [PubMed: 15727471] (b) Maki BE, Chan A, Phillips EM, Scheidt KA. *Org Lett* 2007;9:371–374. [PubMed: 17217307] (c) Phillips EM, Wadamoto M, Chan A, Scheidt KA. *Angew Chem Int Ed* 2007;46:3107–3110. (d) Wadamoto M, Phillips EM, Reynolds TE, Scheidt KA. *J Am Chem Soc* 2007;129:10098–10099. [PubMed: 17663558] (e) Phillips EM, Wadamoto M, Roth HS, Ott AW, Scheidt KA. *Org Lett* 2009;11:105–108. [PubMed: 19049403]
6. For approaches not employing rebound catalysis with unstable α -chloroaldehydes, see: (a) Reynolds NT, Rovis T. *J Am Chem Soc* 2005;127:16406–16407. [PubMed: 16305222] (b) He M, Uc GJ, Bode JW. *J Am Chem Soc* 2006;128:15088–15089. [PubMed: 17117850] For a related carbene-catalyzed acyl transfer reaction, see: Thomson JE, Campbell CD, Concellon C, Duguet N, Rix K, Slawin AMZ, Smith AD. *J Org Chem* 2008;73:2784–2791. [PubMed: 18321127]
7. (a) Abdel-Magid AF, Cohen JH, Maryanoff CA. *Curr Med Chem* 1999;6:955–70. [PubMed: 10519907] (b) Juaristi E, Lopez-Ruiz H. *Curr Med Chem* 1999;6:983–1004. [PubMed: 10519909] (c) Liu M, Sibi MP. *Tetrahedron* 2002;58:7991–8035. For carbene-catalyzed additions of ketenes to imines, see (d) Zhang YR, He L, Wu X, Shao PL, Ye S. *Org Lett* 2008;10:277–280. [PubMed: 18085789] (e) Duguet N, Campbell CD, Slawin AMZ, Smith AD. *Org Biomol Chem* 2008;6:1108–11. 1113. [PubMed: 18327339]
8. (a) Breslow R, Schmuck C. *Tetrahedron Lett* 1996;37:8241–8242. (b) Reynolds TE, Stern CA, Scheidt KA. *Org Lett* 2007;9:2581–2584. [PubMed: 17539656]
9. The control experiment combining α -chloroacetaldehyde and imine **1a** under conditions from entry 7, Table 1 resulted in no observable product formation. See Supporting Information for details.
10. Lactams have not been observed in these reactions, even prior to addition of external nucleophile. Three equiv of **1** is required for complete conversion of the imine. Further studies to understand this process are underway.
11. For removal of the tosyl group of **13** with no impact on optical purity, see: Sivakumar AV, Babu GS, Bhat SV. *Tetrahedron: Asymmetry* 2001;12:1095–1099.
12. (a) Appella DH, Christianson LA, Karle IL, Powell DR, Gellman SH. *J Am Chem Soc* 1996;118:13071–13072. (b) Seebach D, Overhand M, Kuhnle FNM, Martinoni B, Oberer L, Hommel U, Widmer H. *Helv Chim Acta* 1996;79:913–941. (c) Cheng RP, Gellman SH, DeGrado WF. *Chem Rev* 2001;101:3219–3232. [PubMed: 11710070]

Scheme 1.
Proposed catalytic pathway

Table 1

Optimization of conditions^a

entry	azolium salt	base	solvent	yield(%) ^b
1	A	Et ₃ N	THF	6
2	A	Et ₃ N	CH ₂ Cl ₂	30
3	B	Et ₃ N	CH ₂ Cl ₂	37
4	C	Et ₃ N	CH ₂ Cl ₂	31
5 ^d	C	NaH ^e	CH ₂ Cl ₂	24
6 ^{d,f}	C	NaOC ₆ H ₄ NO ₂ ^g	THF/CH ₂ Cl ₂ ^h	59
7 ⁱ	C	NaOC ₆ H ₄ NO ₂ ^g	THF/CH ₂ Cl ₂ ^h	72

^aReactions run with 10 mol % of azolium salt and base and 0.07 M in solvent unless otherwise noted.^bIsolated yields.^cDetermined by HPLC.^d2 equiv of **1**.^e1 equiv of NaH.^f4Å MS used as additive.

*g*₁ equiv of base.

h 1:4 THF:CH₂Cl₂ (0.1 M).

*i*₃ equiv of **1** and 4 Å MS used as an additive.

Table 2

Substrate scope^a

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

^a 3 equiv of **1** in 0.1 M THF:CH₂Cl₂ (1:4).^b Isolated yields.^c Determined by HPLC with a chiral stationary phase.

Table 3

Synthetic transformations

entry	trapping reagent
1	MeOH/aq. NaOH
2	LiBH ₄
3	MeONa
4	

^a Isolated yields.

^b Determined by HPLC with a chiral stationary phase.

^c See Supporting Information for absolute configuration determination.