JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
Communication
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Urea Activation of α-Nitrodiazoesters: An Organocatalytic Approach to N−H Insertion Reactions

Sonia S. So and Anita E. Mattson*

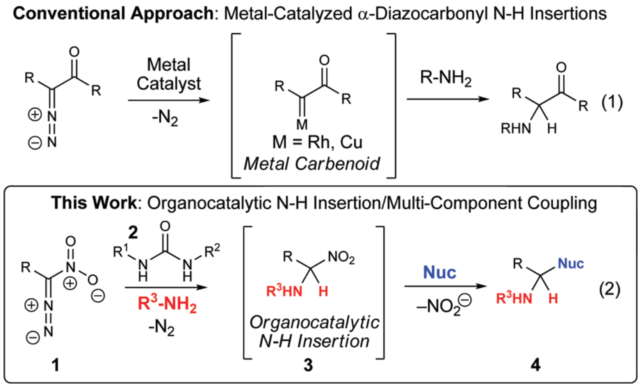
The Ohio State University, Department of Chemistry, 100 West 18th Avenue, Columbus, Ohio 43210, United States

Supporting Information

ABSTRACT: The combination of a urea catalyst and an α-nitro-α-diazo ester gives rise to a reactive species able to undergo insertion into the N−H bonds of anilines. This new strategy to achieve N−H insertion reactivity is in contrast to typical metal-catalyzed conditions for the generation of carbenoids from α-diazocarbonyl compounds. This report includes the extension of the insertion reaction to a three-component coupling for the construction of α-amino-α-aryl esters in high yield.

Metal-catalyzed insertion chemistry of α-diazocarbonyl compounds has evolved into a remarkable synthetic tool enabling the efficient construction of useful building blocks.[1] The insertion into N−H bonds is a particularly attractive subset of metal carbenoid chemistry giving rise to valuable amines with direct applications in bioactive target synthesis (Scheme 1, eq 1).[2] This methodology includes the recently developed benefit of excellent control over the newly formed nitrogen-bearing stereocenter under appropriate conditions.[3] We were inspired by the power of N−H insertion methodology of metal carbenoids and set out to investigate an organocatalytic approach for the insertion of diazo compounds into N−H bonds. In addition to the potential for an organocatalytic method to offer less expensive and more ecological alternatives to metal carbenoid processes, we were also excited to advance N−H insertion chemistry as a new direction in noncovalent organic catalysis. This communication describes our success with the discovery of a multicomponent coupling process resulting from N−H insertion reactions of hydrogen bond donor (HBD)-activated α-nitro diazo compounds (**1**) in the presence of a urea catalyst (**2**).

Scheme 1

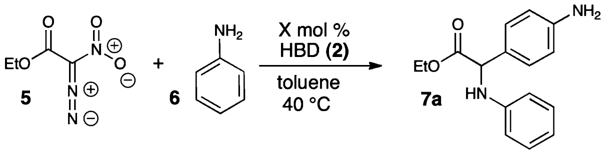


The ability of ureas to recognize nitro groups through hydrogen bonding interactions has led to a successful platform for the development of new HBD-catalyzed processes.[4] Conventionally, urea and thiourea catalysis involving nitro groups is centered on the activation of electrophiles, such as nitroalkenes, for nucleophilic attack.[5] We wished to break away from this traditional reactivity pattern and uncover new opportunities for urea catalysis. We reasoned that we could exploit the urea-nitro group recognition to facilitate the loss of nitrogen gas from **1** to generate a reactive intermediate capable of producing useful products (**3**) as the result of an N−H insertion reaction. The reactivity of HBD-activated diazo compounds in the presence of amines could then be harnessed in the development of new directions in organic catalysis, such as the development of multicomponent coupling reactions to yield valuable synthetic building blocks (**4**). While we were motivated by the promise of HBD-catalyzed N−H insertion methodologies, the project was initiated with a significant amount of uncertainty as to whether a urea could aid in the decomposition of a diazo compound. The assessment of this approach began with studies of the urea-catalyzed insertion of α-diazo-α-nitro ester **5**[6] into the N−H bond of aniline (**6**, Table 1).

N−H Insertion Development. Early on into our investigations we were surprised to collect a modest yield of α-amino-α-aryl ester **7a** formed from **5** and **6** after 48 h at 80 °C in toluene with 20 mol % of difluoroboronate urea **2a**; no products containing a nitro group, as in **3**, were isolated. We hypothesized that the N−H insertion product **3** was unstable to the reaction conditions and converted into **7a** by loss of NO$_2$ followed by further reaction with a second equivalent of aniline. This unexpected HBD-catalyzed multicomponent coupling excited us, and driven by the synthetic utility of an organocatalytic single-flask process to access α-amino-α-aryl esters, we set out to further develop the process. After optimization of the reaction concentration, a high yield (83%) of **7a** was isolated with 20 mol % of **2a** after 24 h in toluene at 40 °C (entry 1). A brief survey of ureas and thioureas was next carried out to find the best catalyst for this reaction system. Boronate pinacol ester urea **2b** and traditional urea **2d** both afforded modest yields of desired product **7a** (61% and 58% respectively, entries 2 and 4). Conventional thiourea **2c**, one of the most active dual HBD catalysts in the literature, performed

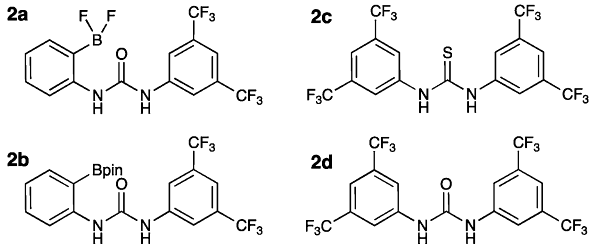
Received: March 30, 2012

Table 1. Urea Catalyzed N−H Insertion Development[a]



entry	2	time (h)	yield (%)[b]	k_{obs} ($\times 10^{-5}$, s^{-1})[c]	
1	20 mol % **2a**	24	83	9.19	catalyst structure study
2	20 mol % **2b**	24	61	0.77	
3	20 mol % **2c**	24	27	1.10	
4	20 mol % **2d**	24	58	1.38	
5	10 mol % **2a**	48	94		catalyst loading study
6	7.5 mol % **2a**	48	77		
7	5 mol % **2a**	72	85		
8	2.5 mol % **2a**	72	73		
9	0 mol % **2a**	24	8		

[a] Reactions performed using 10 equiv of aniline at a concentration of 1 M. See Supporting Information for detailed experimental procedures. [b] Isolated yield. [c] An average of k_{obs}, determined at multiple catalyst loadings; see Supporting Information.



most poorly in this process, likely a result of catalyst decomposition at elevated temperatures (27%, entry 3).[7] Notably, no evidence of the decomposition of difluoroboronate urea **2a** was observed. Excellent yields of product were obtained even at low loadings of optimal catalyst **2a** by simply extending the reaction times. For instance, a 10 mol % loading of **2a** for 48 h gave rise to 94% of **7a** (entry 5). Even reducing the catalyst loading to just 5 mol % afforded an 85% yield of product after 72 h (entry 7). In the absence of an HBD catalyst just an 8% yield of **7a** was isolated (entry 9).

The enhanced activity of **2a** over conventional urea **2d** is proposed to arise from internal coordination of the urea functionality to the strategically placed boron resulting in polarization of the urea carbonyl and enhanced urea acidity.[8−10] Cocrystallization of **2a** with nitrobenzene indicates increased polarization of the urea based upon the carbonyl bond length (1.274 Å for **2a** vs 1.211 Å for ureas lacking internal coordination to boron[9]) and shows urea recognition of the nitro group through hydrogen bonding (Figure 1). The improved activity of difluoroboronate urea **2a** over pinacol ester boronate urea **2b** demonstrates the importance of the tunable nature of internal Lewis acid assisted ureas based on ligand modification. In this case, the more electron-withdrawing fluorine ligands give rise to a more active catalyst. A comparison of the relative rates of these catalysts afforded additional evidence of the superior nature of difluoroboronate urea **2a** in the N−H insertion reaction (Table 1). Urea **2a** offers observed rates nearly 10 times faster than those of **2b**, **2c**, and **2d**. In addition to offering enhanced rates of **7a** formation, it is important to point out that catalysis of the N−H insertion reaction with urea **2a** also prevents undesired side reactions observed with catalysts **2b**−**2d**.

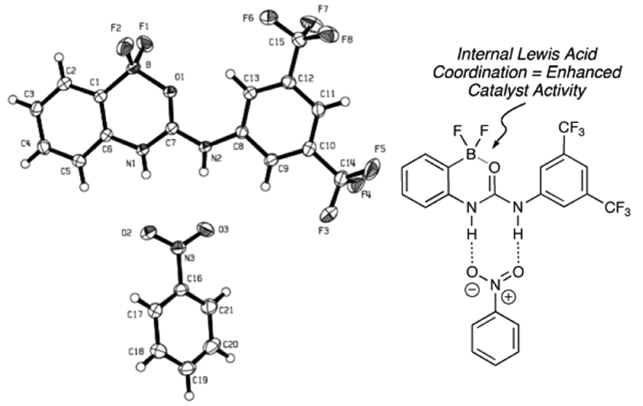
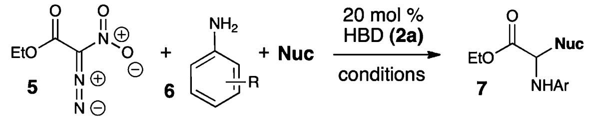


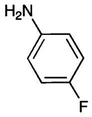
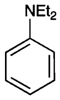
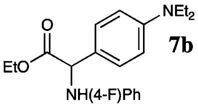
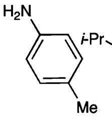
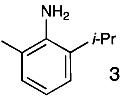
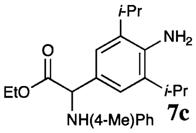
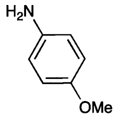
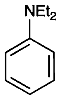
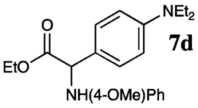
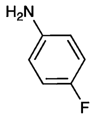
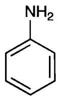
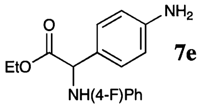
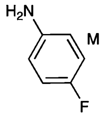
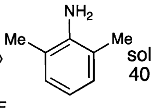
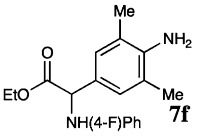
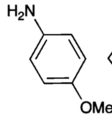
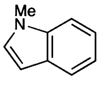
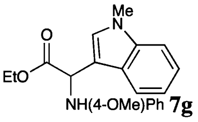
Figure 1. Difluoroboronate urea **2a** cocrystallized with nitrobenzene. The ORTEP plot is drawn with 50% probability ellipsoids for the non-hydrogen atoms. The hydrogen atoms are drawn with an artificial radius.

HBD-Catalyzed Three-Component Coupling. Encouraged by our success with the HBD-catalyzed additions of 2 equiv of aniline to α-nitro-α-diazo ester **5**, we set out to extend the utility of the method by developing it into a three-component coupling reaction (Table 2). More specifically, the reaction of **5**, an amine for N−H insertion (**6**), and a *different* nucleophile would allow access to a wide range of α-amino esters (**7**). The treatment of **5** with 4-fluoroaniline and diethylaniline afforded product **7b** in excellent yield (94%, entry 1). A near-quantitative yield of **7c** was isolated after the multicomponent coupling of **5** with *p*-toluidine in the presence of 2,6-diisopropylaniline (99%, entry 2). *p*-Anisidine was also well tolerated in the process yielding 95% of **7d** after 48 h in toluene (entry 3). The selective insertion into the N−H bond of 4-fluoroaniline in the presence of aniline proceeded well giving rise to 72% of **7e** after 72 h in toluene (entry 4). An improvement in yield for the selective N−H insertion reaction was observed with multicomponent coupling of 4-fluoroaniline and 2,6-dimethylaniline to generate **7f** (91%, entry 5). It is reasoned that the steric bulk of the substituents in the 2 and 6 positions slows N−H insertion into 2,6-dimethylaniline leading to higher yields of insertion into 4-fluoroaniline. In addition to aniline derivatives, indoles were also found to operate well as nucleophiles in the coupling reaction. For example, the urea-catalyzed insertion of **5** into *p*-anisidine followed by reaction with *N*-methylindole provided a high yield of **7g** after 48 h in toluene at room temperature (83%, entry 6). The N−H insertion reaction is limited to anilines at this time; initial attempts to insert into *tert*-butyl carbamate and tosylamide were unsuccessful. Investigations are ongoing to expand the reaction scope with respect to other amines.

A plausible reaction pathway for this urea-catalyzed N−H insertion begins with coordination of boronate urea **2a** to nitrodiazoester **5**, giving rise to complex **I** (Scheme 2). The entropically favorable loss of nitrogen gas generates HBD-stabilized carbene complex **II**, and a subsequent N−H insertion reaction with aniline (**6**) ensues to yield intermediate **III**.[11] The

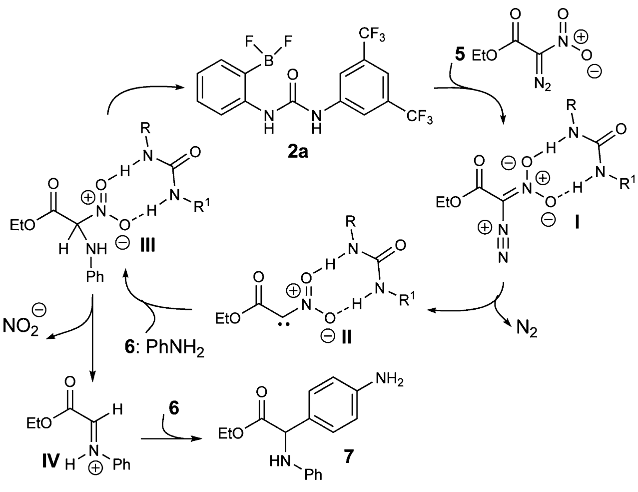
Table 2. HBD-Catalyzed Three-Component Coupling[a]



entry	6	Nuc	conditions	7	yield (%)[b]
1			solvent free 23 °C, 48 h	 7b	94
2			toluene 30 °C, 72 h	 7c	99
3			toluene 30 °C, 48 h	 7d	95
4			toluene 30 °C, 72 h	 7e	72
5			solvent free 40 °C, 48 h	 7f	91
6			toluene 23 °C, 48 h	 7g	83

[a] See Supporting Information for detailed experimental procedures. [b] Isolated yield.

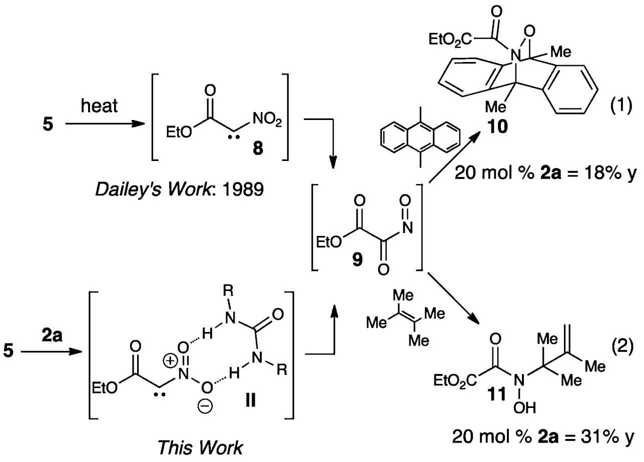
Scheme 2. Plausible Catalytic Cycle



extrusion of NO_2^- from **III** generates iminium ion **IV** and reintroduces the urea catalyst back into the cycle. Iminium ion **IV** goes on to react with a nucelophile, such as a second equivalent of aniline, present in the reaction system affording the observed product **7**. Alternate reaction pathways, such as those involving stepwise N–H insertions, have not been explicitly ruled out at this time.

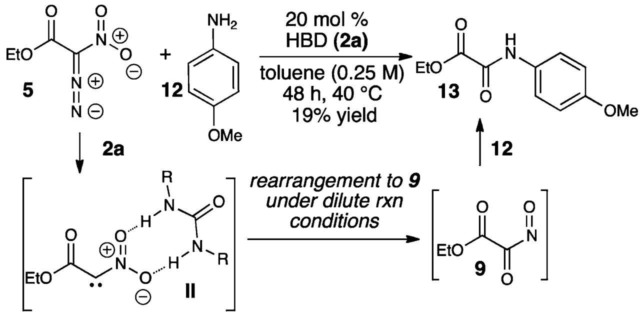
HBD-generated carbenes are a new direction in the field of organic catalysis and we were interested to collect some evidence of potential organocarbene intermediate **II** accessed from *α*-nitro-*α*-diazo ester **5** in the presence of **2a**. In general, it is less common to generate carbenes and carbenoids from *α*-nitro-*α*-diazo carbonyls than *α*-aryl/carbonyl-*α*-diazo carbonyls as there are only a few literature reports in this area.[12] The publication from O'Bannon and Dailey in 1989 exploring the cyclopropanation chemistry of rhodium carbenoids derived from **5** was particularly interesting, as it outlined a proposed decomposition pathway of nitrocarbene **8** (Scheme 3).[12c] This is important because the study of decomposition products is the predominant strategy to probe mechanisms proposed to proceed through nitrocarbenes: the direct observation of a nitrocarbene remains an unsolved challenge.[12a−c] In the absence of a suitable alkene for cyclopropanation, it is proposed that nitrocarbene **8** undergoes rearrangement to acyl nitroso compound **9**, a species that is unstable and cannot be isolated. Due to its instability, evidence for **9** was collected through two different reactions: (1) a Diels–Alder reaction of **9** with 9,10-dimethylanthracene to yield adduct **10** (eq 1) and (2) a reaction of **9** with enophile 2,3-dimethyl-2-butene to yield ene product **11** (eq 2). Based upon these experiments done by O'Bannon and Dailey, we reasoned we could remove aniline from our reaction system and effect either the Diels–Alder reaction or the ene reaction to offer support for a catalytic cycle proceeding through an HBD-generated carbene. Despite the number of decomposition pathways acyl nitroso species can participate in, we were pleased to find when **5** was combined with **2a** in the presence of 9,10-dimethylanthracene an 18% yield of **10** was isolated. The treatment of **5** and **2a** with 2,3-dimethyl-2-butene in toluene at 40 °C gave rise to the expected ene product **11** in 31% yield. These experiments suggest that in the absence of a suitable reaction partner the combination of **5** and **2a** lead to an acyl nitroso intermediate (**9**), conceivably originating from nitrocarbene complex **II**.

Scheme 3. Evidence for HBD-Generated Carbene: Reactions of in Situ Generated Acyl Nitroso Compound 9



More direct evidence for the participation of a carbene-like intermediate in the N–H insertion reaction under development in this report was obtained from the isolation of product **13** in 19% yield when the reaction was conducted in 0.25 M toluene, conditions where it is unlikely the carbene will find an N–H insertion reaction pathway prior to rearrangement (Scheme 4). The product (**13**) is proposed to arise from the addition of *p*-anisidine to the acyl nitroso species **9**.[13] It is reasoned that carbene intermediate **II** undergoes rearrangement to **9** in the

Scheme 4. Evidence for HBD-Generated Carbene: Rearrangement to Acyl Nitroso Species 9 under Dilute Reaction Conditions



absence of an opportunity for rapid participation in an N−H insertion reaction, such as dilute reaction conditions. These results point to the potential involvement of an HBD-generated carbene species (**II**) in the reaction pathway.

In summary, ureas operate as catalysts for the three-component coupling of nitrodiazoesters, amines, and nucleophiles. This report includes evidence for the first organocatalytic activation of diazo compounds for participation in N−H insertion reactions; the reaction pathway may proceed through an HBD-stabilized carbene. Results of ongoing studies in our laboratory exploring the full potential of HBD-activation of diazo compounds, including the development of enantioselective organocatalytic N−H insertion reactions, as new synthetic tools will be reported as soon as possible.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

mattson@chemistry.ohio-state.edu

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Support for this work has been provided by the OSU Department of Chemistry. We acknowledge the Ohio BioProducts Innovations Center (OBIC) for seminal support of the OSU mass spectrometry facility. Dr. Judith Gallucci (OSU) is thanked for expert crystallographic analysis.

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