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Organocatalysis

Urea-Induced Acid Amplification: A New Approach for Metal-Free Insertion Chemistry

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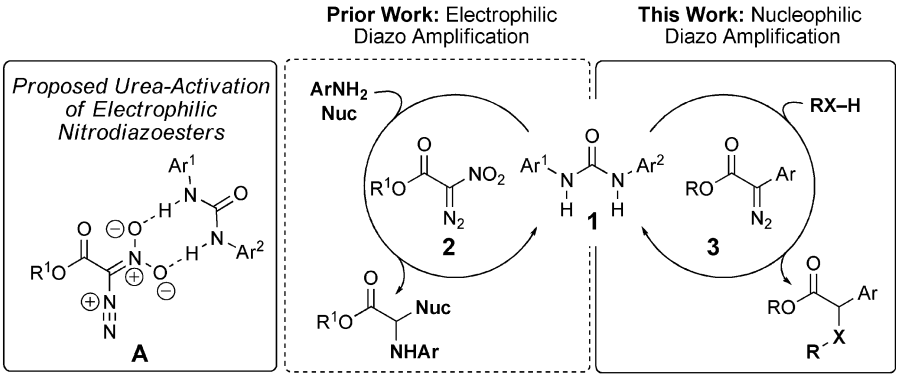
Abstract: The enhanced catalytic activity of difluoroboronate ureas proved to be essential as an acidity amplifier to promote metal-free O–H and S–H insertion reactions of α-aryldiazoacetates in high yield. This methodology was found to be generally applicable to a broad substrate scope and presents a conceptually new approach for organocatalytic diazo insertion reactions. Mechanistic investigations suggest that the reaction pathway involves a urea-induced protonation of the α-aryldiazoester.

Diazo compounds have a rich history in organic synthesis. Their allure can be attributed to the divergent reactivity that arises from their inherent high-energy ground state and easily accessed carbene-like reactivity.[1] Many strategies have been employed to elicit and control the carbene-like reactivity of diazos for heteroatom–hydrogen (X–H) insertion chemistry, the vast majority of which rely on the decomposition to metal–carbenoid intermediates.[2] Recently, our research group discovered that urea catalysis (**1**) is a viable metal-free approach for insertion and multicomponent coupling reactions of nitrodiazoesters (Scheme 1, **2**).[3] In this process, it is reasonably suspected that the urea catalyst amplifies the electrophilicity of the nitrodiazoester through well-established hydrogen-bond recognition of the nitro group (**A**).

Our success in developing reactions of urea-activated electrophilic diazo compounds prompted us to question the ability of urea catalysis to also control reactions of more basic diazo compounds, such as aryldiazoacetates (Scheme 1, **3**).[4] At the onset of our studies, we anticipated that ureas would be unable to affect the outcome of reactions of aryldiazoacetates; it was not obvious to us how a urea could enhance their reactivity. Much to our surprise, urea catalysis proved to be an extraordinary tool for select O–H and S–H insertion reactions of aryldiazoacetates.

Early on, we were delighted to find that just 2.5 mol% of difluoroboronate urea **1a** enabled the formation of α-acyloxy ester **4a** in an excellent 91% yield under mild reaction conditions (Scheme 2).[9] Conventional urea and thioureas (**1b** and **c**) were unable to catalyze the insertion event. Only select ureas benefiting from both internal boron activation[10,11] and appropriate electron-withdrawing substitution patterns were found to be active catalysts (**1a**, **e–f**). The lack of reactivity of control catalyst **5** also suggested that the hydrogen-bonding urea functionality is a necessary component of the catalyst structure, and simple Lewis acid catalysis at boron is unlikely.

Close consideration of our observations, taken along with the recent, inventive investigations of urea/Brønsted acid cocatalyst systems from the groups of both Jacobsen and Seidel,[4] led us to hypothesize that the mechanism may likely not involve urea activation of the diazo compound. Instead, a urea-catalyzed enhancement in the organic acid's acidity (**B**) is proposed to promote the stepwise insertion of aryldiazoacetates via an intermediate ion pair (**C**).[5,6] Although many examples of urea/Brønsted acid cocatalysis in 1,2-additions have been described,[4,7] to the best of our knowledge, this concept has not been applied to catalytic substrate acidification for X–H insertions.[8] Herein, we report our initial success in the area of urea-induced heteroatom acid amplification as an innovative tactic for metal-free O–H and S–H insertion reactions.



Scheme 1. Urea-catalyzed diazo reactivity amplification for X–H insertions.

With the optimal catalyst **1a** in hand, the scope of the organocatalytic insertion reaction was examined. Methyl 4-

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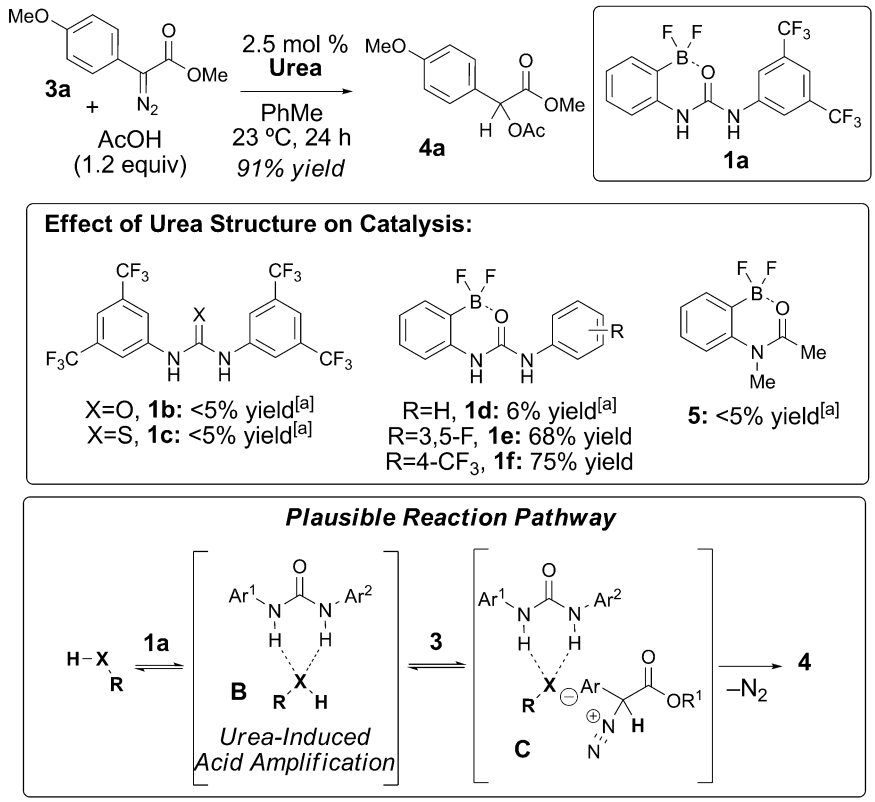
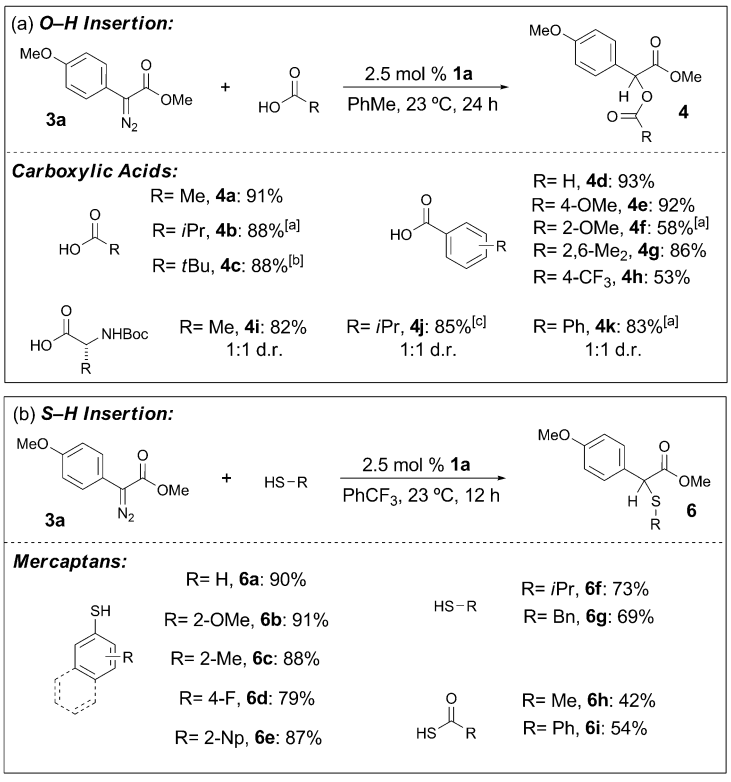


Scheme 2. Urea-catalyzed diazo O–H insertion (see the Supporting Information for experimental details). Yields are of isolated product. [a] Yield was determined by ^{1}H NMR spectroscopy.

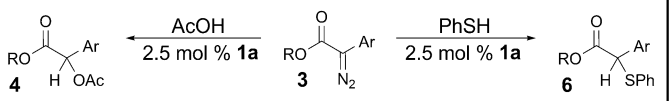
methoxyphenyldiazoacetate (**3a**) inserted readily into a variety of acidic O–H and S–H bonds (Scheme 3). Aliphatic carboxylic acids efficiently underwent insertion to afford α-acyloxy esters **4a**–**c** in the presence of 2.5 mol% **1a** at 23 °C in toluene (Scheme 3a). The steric hindrance of the acid had little effect on the insertions efficiency; even the sterically hindered pivalic acid was a viable O–H insertion partner. Electron-rich, electron-poor, and sterically encumbered benzoic acids underwent insertion giving rise to **4d**–**h** in 53–93% yield. Diazo compound **3a** also inserted into the O–H bonds of α-amino acids, although we observed no diastereoselectivity in the products (**4i**–**k**) under the examined reaction conditions. Importantly, the *N*-terminus of the amino acid required protection as the *tert*-butyl carbamate in order for the insertion to proceed. Mercaptans operated well in catalytic S–H insertion reaction under slightly different conditions (Scheme 3b); utilizing 2.5 mol% of **1a**, good yields of the products **6** could be isolated after 12 h in α,α,α-trifluorotoluene ($PhCF_3$).[12] Thiophenols were efficient substrates for S–H bond insertion, irrespective of the electronic nature of their substituents, providing the insertion products **6a**–**e**. Even alkyl thiols were accommodated under the reaction conditions affording S–H insertion products **6f** and **g** in good yield. Thioacids, which are problematic in S–H insertions catalyzed by BF_3·OEt_2,[13] were tolerated, providing only the *S*-bound insertion adducts **6h** and **i**.

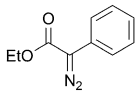
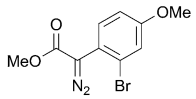
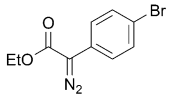
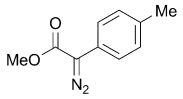
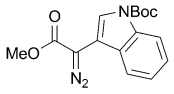
A variety of α-aryldiazoacetates easily inserted into boronate urea-activated O–H and S–H bonds. The efficiency of the insertions was heavily dependent on the diazo compounds' aryl substituents. As a general trend, electron-donating groups sped up the reaction, whereas electron-withdrawing substituents rendered the insertions more sluggish. Ethyl phenyldiazoacetate (**3b**) rapidly inserted into acetic acid in the presence of **1a** (Table 1, entry 1), whereas longer reaction times and 50 °C reaction temperatures were required to insert into thiophenol's S–H bond (entry 6). The introduction of halogens onto the aryldiazo compounds was tolerated. For example, diazoester **3c** inserted into acetic acid providing **4m** in



Scheme 3. Substrate scope of the organocatalytic O–H and S–H insertions. All reactions were performed at 0.5 M with respect to **3a**. [a] Reaction time 36 h. [b] Reaction time 72 h. [c] Reaction time 48 h.

Table 1. Aryldiazoacetate substrate scope.



Entry	4	Yield [%][a]	Aryldiazoester	3	Entry	6	Yield [%][a]
1	**4l**	66		**3b**	6	**6j**	65[b,c]
2	**4m**	89		**3c**	7	**6k**	81
3	**4n**	57[d]		**3d**	8	**6l**	72[c]
4	**4o**	76		**3e**	9	**6m**	75[b]
5	**4p**	50		**3f**	10	**6n**	91

[a] Yields are of isolated product [b] Reaction time 72 h. [c] Reaction temperature 50 °C. [d] Reaction time 48 h. Reactions were performed at 0.5 M with respect to **3** (see the Supporting Information for elaborative experimental details). The X–H insertion conditions are identical to those shown in Scheme 4 unless otherwise noted.

89% yield (entry 2). Similarly, **3c** underwent insertion efficiently into thiophenol to afford **6k** (81%, entry 7). Halogens as the sole substituent were also accepted; **3d** underwent both O–H and S–H insertion at room temperature, albeit longer reaction times were required to provide **4n** and **6l** in 57 and 72%, respectively (entries 3 and 8). As was expected, inductively donating groups facilitated the insertion process; both acetic acid and thiophenol underwent insertion by **3e** more efficiently than **3b**, providing 10% higher yields in each of the studied insertion reactions (entries 4 and 9). Unfortunately, the electron poor α-aryldiazoester, methyl 4-(trifluoromethyl)phenyldiazoacetate was inoperable in both insertion reactions, plausibly due to its relatively poor basicity. The heteroaryl α-diazoester **3f** also operated well in the insertion reactions; insertion of **3f** into acetic acid provided the α-acetoxyester **4p** in 50% yield (entry 5), whereas insertion into thiophenol occurred efficiently providing **6n** in 91% (entry 10).

Our working hypothesis of the catalytic cycle is depicted in Scheme 4a. The process is thought to begin with coordination of the difluoroboronate urea to the acidic heteroatom (X–H), forming complex **B**.[14,15] This complexation enables the amplification of the acidity of the organic acid, which in the presence of a Brønsted basic diazo compound, undergoes a proton transfer through species **D**. The proton transfer, converting **D** to **C**, may be rate determining in this process because it has been shown that α-aryldiazoacetate hydrolysis occurs through a general acid-catalyzed A-S_E2 mechanism, although additional studies are required to provide tangible evidence in this case.[16,17] The catalytic cycle would conclude with the diazonium species in **C** reacting with the urea-stabilized anion (X^-) to generate the observed insertion products (**4** or **6**). The weak interaction of **4** or **6** with difluoroboronate urea **1a** would then free the urea to re-enter the catalytic cycle.

More concrete insight into the proposed reaction pathway was collected through the execution of strategically selected experiments (Scheme 4b–d). We first attempted to trap a potential donor/acceptor carbene intermediate through an intramolecular cyclopropanation of the olefin in the cinnamyl alcohol-derived α-aryldiazoacetate **3g** (Scheme 4b).[18] When **3g** was subjected to the standard O–H insertion reaction conditions, we observed only formation of the α-acetoxyester **4q**. Importantly, when acetic acid was omitted from the reaction, under otherwise identical reaction conditions, we observed no reaction after 48 h at 23 °C. Moreover, when **3g** was subjected to high temperatures in $PhCF_3$, reaction conditions known to generate free carbenes from aryldiazoacetates,[19] 87% of *exo*-(±)-**7** was isolated as a single diastereomer. Collectively, this data contends the formation of a free donor/acceptor carbene intermediate under the optimal reaction conditions.

Further support of the proposed mechanism, depicted in Scheme 4c, can be seen when the X–H bond is not present for HBD activation. For example, when triethylammonium acetate or sodium benzoate were utilized under the optimal reaction conditions, no reaction was observed. Similarly, when sodium thiophenolate was added to the standard S–H insertion conditions, the expected product **6a** was not formed in any appreciable amount, demonstrating that the X–H bond is crucial for the insertion to occur. Confident that the reaction was proceeding through an initial protonation event, we were also curious if the catalyst could be involved in a direct protonation of the α-aryldiazoester. To probe this question, the most active diazo compound surveyed during our studies (**3a**) was subjected to one equivalent of catalyst **1a** in [D_3]acetonitrile for 24 h at 23 °C (Scheme 4d). Under these conditions, we were unable to detect formation of **8**, the product known to form from deprotonation and isomerization of the urea catalyst, to any measureable extent by ^{1}H NMR spectroscopy.[20,21]

In summary, we have discovered that difluoroboronate ureas are unique metal-free catalysts for O–H and S–H insertion reactions of aryldiazoacetates. This innovative approach for diazo insertion chemistry is believed to occur through hydrogen bonding to suitable functionalities giving a urea-induced organic-acid enhancement. The reaction tolerates an assortment of carboxylic acids and thiols, enabling the efficient preparation of a wide array of α-acyloxyesters and α-mercaptoesters under mild reaction conditions. The utility of urea-induced organic acid amplification as a tool for metal-free, enantioselective insertion chemical technologies is of current interest in our laboratory.

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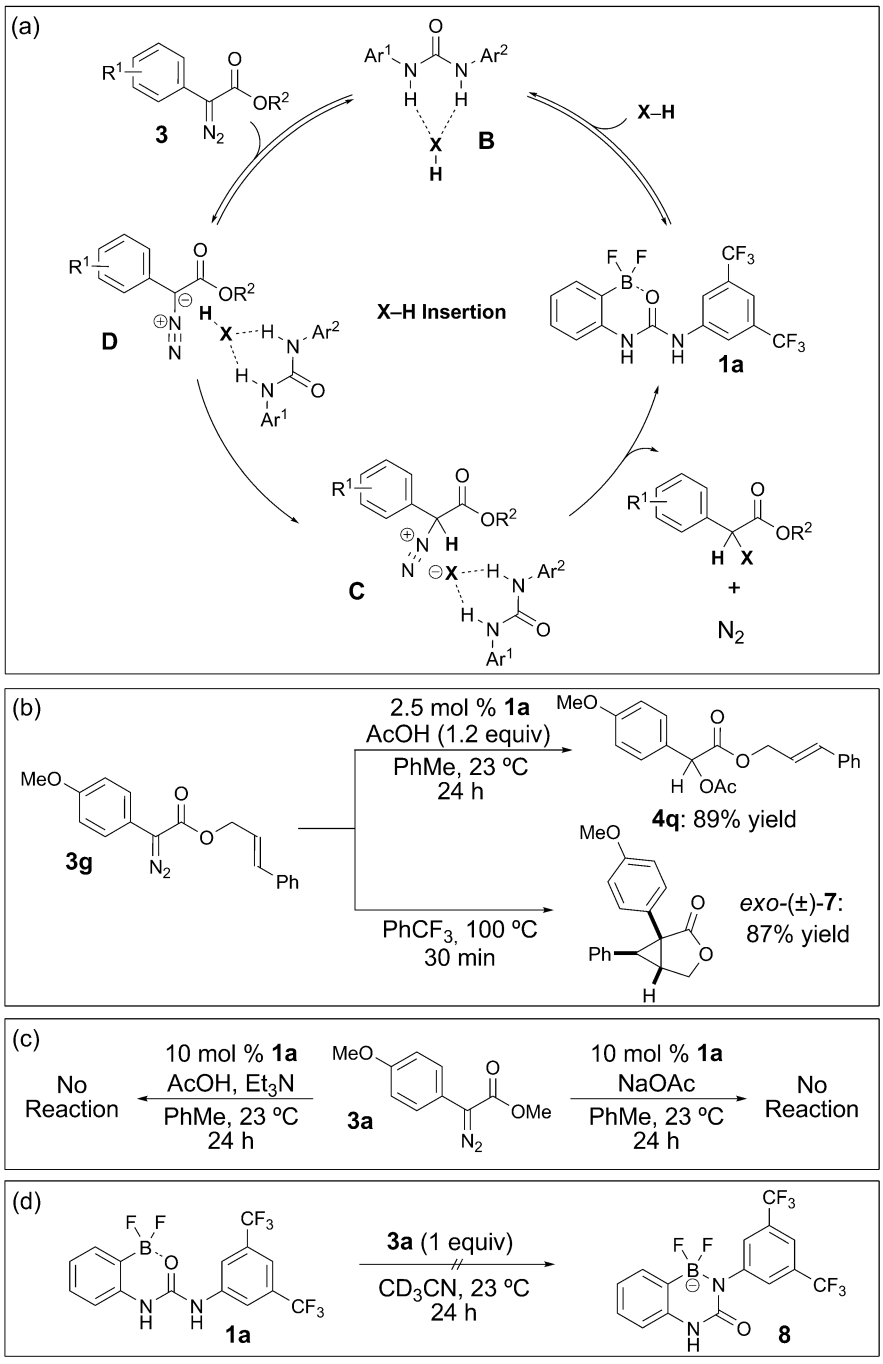

Scheme 4. Proposed reaction mechanism with mechanistic support (see the Supporting Information for full experimental details).

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Keywords: acidity · diazo compounds · insertion · organocatalysis · urea

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[21] Please see the Supporting Information for elaborative experimental and crystallographic details.

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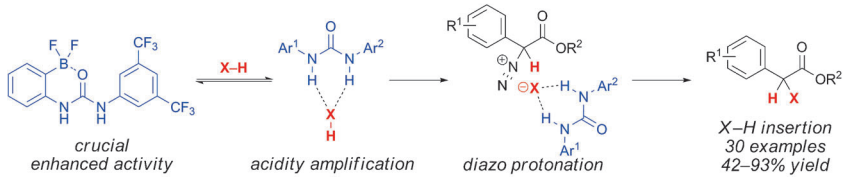

All amped up: Boronate ureas amplify the acidity of protic heteroatoms for metal-free, catalytic O–H and S–H insertions by α-diazocarbonyls. The enhanced activity of difluoroboronate ureas is essential for successful insertion reactions; conventional (thio)ureas do not catalyze the desired transformations. This new strategy for metal-free insertions provides access to a broad array of α-acyloxy esters and α-mercaptoesters in high yield (see scheme).