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Urea-Catalyzed N−H Insertion−Arylation Reactions of Nitrodiazoesters

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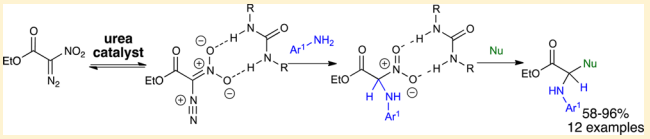
Supporting Information

ABSTRACT: The power of hydrogen-bond donor catalysis has been harnessed to elicit and control carbene-like reactivity from nitrodiazoesters. Specifically, select ureas have been identified as effective catalysts for N−H insertion and multicomponent coupling reactions of nitrodiazoesters, anilines, and aromatic nucleophiles, thereby preparing a variety of α-aryl glycines in high yield. Experimental and computational studies designed to probe the plausible reaction pathways suggest that difluoroboronate ureas are particularly well-suited to catalyze reactions of nitrodiazoesters with a range of anilines through a polar reaction pathway. Urea-facilitated loss of nitrite followed by addition of a nucleophile conceivably generates the observed aryl glycine products.



INTRODUCTION

The discovery of new reactions catalyzed by small organic molecules is essential to advancing the field of organocatalysis. As a means to alleviate concerns of sustainability and environmental impact, the study of organocatalytic alternatives to those reactions typically relying on transition metal catalysis is a particularly attractive direction of research.[1] Ureas and thioureas have emerged as useful organocatalysts operating through hydrogen-bonding interactions and offer promising platforms for development as catalysts for reactions that traditionally require metals.[2]

Etter's groundbreaking co-crystallization data of ureas with various guest molecules contributed to an inspirational starting point for the development of urea catalysis.[3] For example, the urea−nitro group recognition was observed by Etter and coworkers for a urea *N*,*N*-dimethyl-*p*-nitroaniline complex (**1**, Figure 1). Urea−nitro group recognition may play a critical role in a number of recently developed organocatalytic methodologies involving a variety of nitro compounds, including nitroalkanes,[4] nitroalkenes,[5] and nitrocyclopropanes.[6] We have recently discovered that nitrodiazoesters also present compelling opportunities for new organocatalytic method development, plausibly taking advantage of urea−nitro group recognition (**2**).[7] At the onset of our studies, the control of nitrodiazoester reactivity was reliant on catalysis with transition metals, such as rhodium or copper, and limited to cyclopropanation[8] and selected insertion reactions.[9] This paper provides a detailed account of our experimental and computational investigations into the reaction of nitrodiazoesters (**3**) under the influence of various urea derivatives (**6a−e**, Table 1) for N−H insertion/multicomponent coupling[14] reactions for the preparation of aryl glycines[10] (**7**) in high yield (Scheme 1).

RESULTS AND DISCUSSION

Reaction Scope. Urea-catalyzed N−H insertion/multicomponent coupling of nitrodiazoester **3** proved to be a general strategy for the synthesis of aryl glycine derivatives **7** (Scheme 2).[7a] The nucleophilic aryl component **5** was easily extended to a variety of anilines. Both *N*-methylaniline and *N*,*N*-diethylaniline gave rise to high yields of aryl glycines **7a** and **7b** (85% and 87%). Substituted anilines, such as 2,6-dimethylaniline and 2,6-diisopropylaniline, were also readily incorporated into the final products as exemplified by high isolated yields of **7c** and **7d** (91% and 96%). A wide selection of indoles was also accommodated in the multicomponent coupling process. For example, indole and 5-methoxyindole afforded **7e** and **7f** in 72% and 95% yields, respectively. Even electron-poor indoles were tolerated in the reaction. 5-Chloroindole enabled isolation of **7g** in 58% yield, while 5-bromoindole generated **7h** in 68% yield after the urea-catalyzed multicomponent coupling. Interestingly, the scope of the reaction with respect to the aniline for N−H insertion was the most limiting parameter identified thus far. The best N−H insertion partners found in our hands for aryl glycine formation have been aniline (**7i**, 85%), 4-methoxyaniline (**7j**, 78%), 4-fluoroaniline (**7k**, 72%), and 4-methylaniline (**7l**, 70%). At this time, we are able to form the desired product by controlling the stoichiometry of the starting anilines. For example, in the case of **7k**, where both the 4-fluoroaniline and aniline components are capable of undergoing N−H insertion, we selectively insert into the N−H bond of 4-fluoroaniline by adding an excess of this compound.

Plausible Mechanistic Pathways. In light of the discovery of an unexpected, yet general, urea-catalyzed multicomponent

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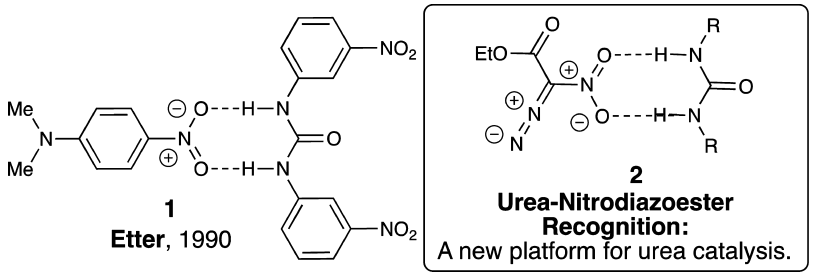
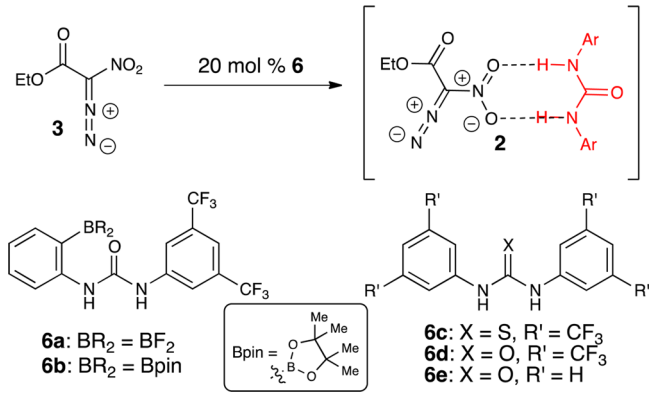


Figure 1. Urea–nitro group recognition as a platform for catalysis.

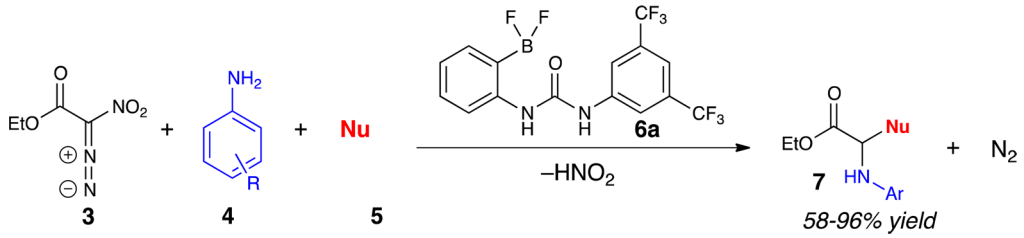
Table 1. Energetics of Complexation between α-Nitrodiazoester 3 and Various Urea Derivatives 6a–e, As Calculated at the B3LYP/6-311++G//B3LYP/6-31G* Level of Theory (in kcal/mol) at 298 K[a]**



entry	urea	C=X	C–N	N–H	H--O	N–O	Δ*E*	Δ*H*	Δ*G*
1	**6a**	1.27	1.37	1.02	2.00	1.23	−9.8	−13.8	−1.5
			1.35	1.02	2.12	1.24			
2	**6b**	1.23	1.39	1.01	2.01	1.23	−7.0	−10.7	−0.2
			1.38	1.01	2.21	1.24			
3	**6c**	1.66	1.38	1.02	2.37	1.22	−3.4	−8.8	+3.3
				1.02	2.15	1.25			
4	**6d**	1.22	1.39	1.01	2.06	1.26	−3.9	−8.2	+2.3
				1.01	2.98	1.22			
5	**6e**	1.23	1.39	1.01	2.18	1.23	−6.4	−8.0	+1.9
				1.01	2.18	1.24			

[a]The various bond distances of the hydrogen bonded complex are given in Å.

Scheme 1. Urea-Catalyzed N–H Insertion/Multicomponent Coupling



coupling of diazo compounds, the plausible reaction pathway was considered more closely. Several experimental observations collected during the substrate scope study afforded clues that offered initial direction to our mechanistic studies (Scheme 3). First, direct C–H insertion was ruled out as the first step of the reaction pathway because no reaction was observed between **3** and heterocycles lacking nucleophilic N–H bonds available for insertion, such as diethylaniline or indole, and all starting materials were easily recovered (Observation 1). Not only was **4**, the aniline component, required for the reaction, the success of the reaction hinged on the concentration of the aniline derivative. The best yields were obtained in the presence of at least 10 equiv of 4-fluoroaniline; anything less afforded reduced yields (Observation 2). These experimental observations led us to reason that N–H insertion was the first bond-forming event in the reaction pathway.

With evidence suggesting that N–H insertion is the first step in the reaction pathway, the specifics of this step were more closely considered. Observation 1 of Scheme 4 outlines a control experiment in which two molecules of aniline (one molecule acting as the N–H insertion partner **4** and one molecule acting as nucleophilic component **5**) reacted with **3**

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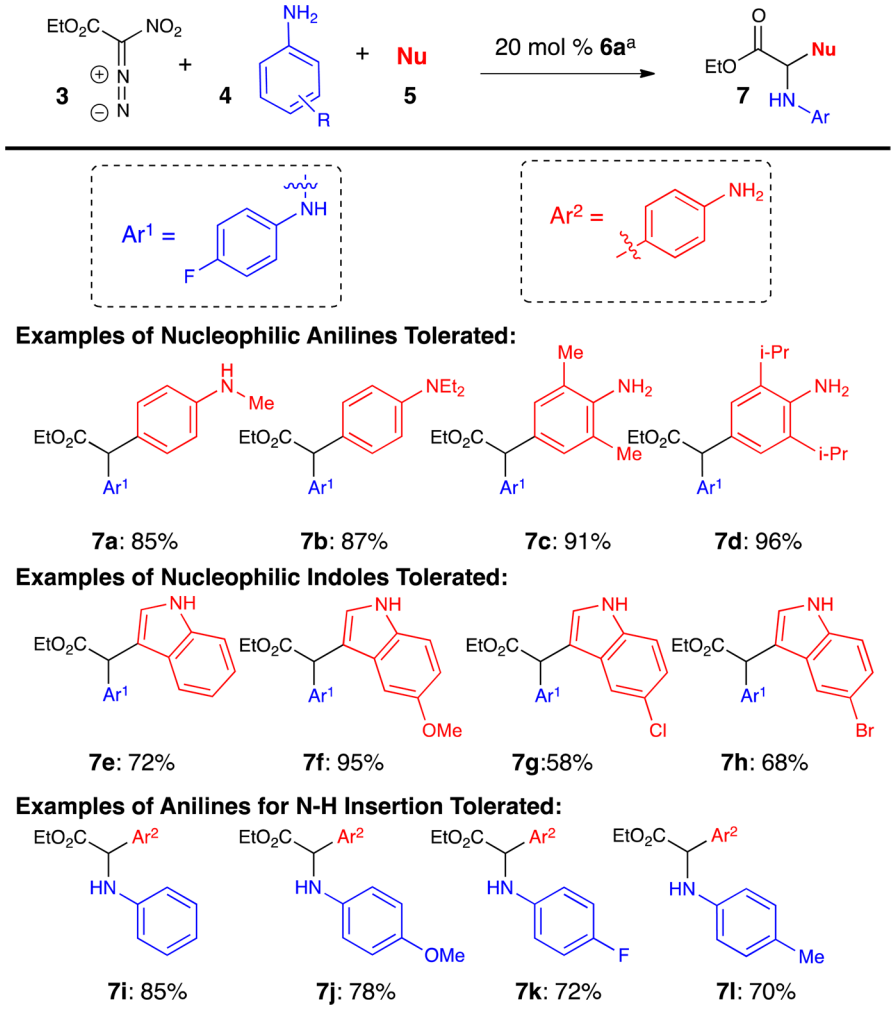
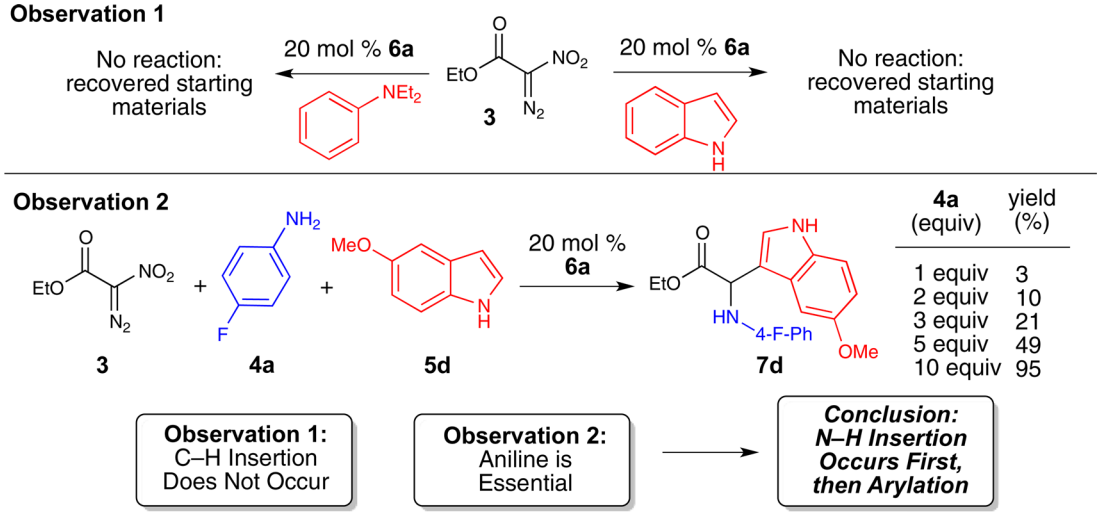
Scheme 2. Urea-Catalyzed N–H Insertion/Multicomponent Substrate Scope[a]



[a]See the Supporting Information for experimental details.

Scheme 3. Initial Clues into the Reaction Pathway



without a urea catalyst and afforded just 8% of the desired product **7a**: this demonstrated the importance of the urea (entry 1). Additionally, our results outlined in Observation 2 led us to determine that the boronate ureas were likely acting through hydrogen bonding and not Lewis acid interactions. The diminished, yet still moderate, activities of 3-(trifluoromethyl)phenyl difluoroboronate urea **6f** and phenyl difluoroboronate urea **6g** imply that the boron moiety was most

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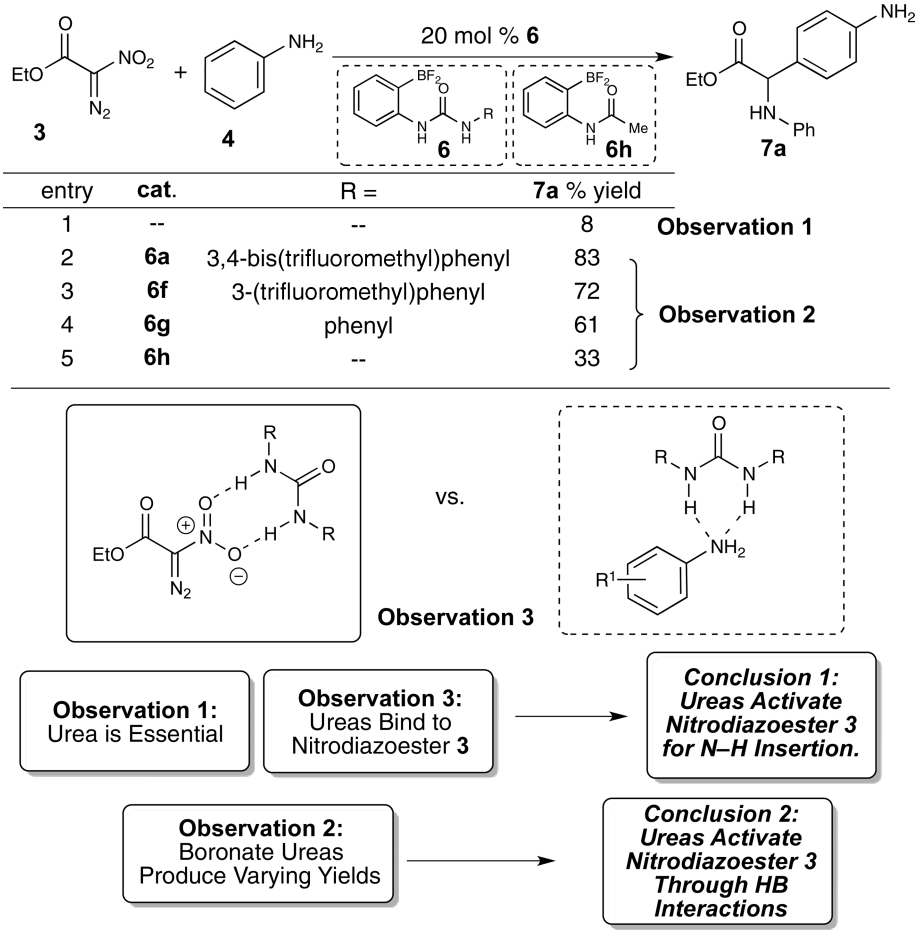
Scheme 4. Evidence Supporting the Role of the Urea Catalyst



likely participating in internal coordination to the urea carbonyl, and not activation of the reaction substrate. We suspect that the electron-withdrawing effects of the trifluoromethyl groups affect the hydrogen bond donating ability of the ureas (72% and 61% yields, entries 3 and 4, respectively), leading to slightly diminished results when compared to 3,5-bis(trifluoromethyl)phenyl difluoroboronate urea **6a** (83%, entry 2). Not surprisingly, acetamide **6h**, a single-hydrogen bond donor catalyst afforded just 33% of the desired product, suggesting that *dual* hydrogen bonding was a necessary component of the boronate urea catalyst for obtaining high yields of the desired product **7a**. ^{1}H and ^{11}B NMR spectroscopic studies probing the structure of boronate urea **6a** in solution, under the reaction conditions, remain inconclusive.

Having established its necessity, two roles that the urea catalyst may play were hypothesized: (1) urea activation of the aniline or (2) urea activation of the nitrodiazoester (Observation 3, Scheme 4). Little experimental evidence suggesting direct activation of the aniline with the urea catalyst by ^{1}H NMR spectroscopic analysis was found. Computationally, we have calculated that protonation of the aniline followed by reaction with the nitrodiazoester is endothermic by 28.22 kcal/mol, rendering this process unfavorable (see the Supporting Information for details). On the other hand, urea–nitrodiazoester binding was readily observed by ^{1}H NMR spectroscopy (Figure 2). Given the literature precedent for urea–nitro group recognition, our own data suggesting urea–nitrodiazoester binding, and the lack of reactivity in the absence of a urea catalyst, we reasoned that coordination of the urea catalyst **6a** to ethyl nitrodiazoacetate **3** forms complex **2** to initiate the catalytic cycle and set out to collect additional computational and experimental data supporting this theory.

Computational Urea–Nitrodiazoester Binding Studies. Foundational discoveries from our laboratory have led us to conclude that select boronate ureas are especially well-suited to activate and catalyze reactions of nitro compounds.[11] In line with our previous observations, difluoroboronate urea **6a** was identified as the highest yielding and most active catalyst for the reaction of nitrodiazoester **3** with aniline **4** and nucleophile **5** (Scheme 1). Two deliberately incorporated design elements contribute to the enhanced activity of catalyst **6a**: (i) the strategically placed difluoroboryl group causing increased polarization of the urea functionality through internal coordination and (ii) the 3,5-bis(trifluoromethyl)phenyl functionality. Since its introduction in 2002 from Schreiner and co-workers,[12] the 3,5-bis(trifluoromethyl)phenyl group has emerged as a privileged structure in hydrogen bond donor catalyst design; it may aid in enhancing the urea acidity and offer added stability to transition states.[12b] To further explore the role of urea catalysis in the activation of nitrodiazoesters, a detailed computational investigation at the B3LYP/6-311++G**//B3LYP/6-31G* level of theory was carried out on the proposed complexes of nitrodiazoester **3** with various urea derivatives **6a–e** to understand the mode and strength of complexation. Out of several possible isomers of the

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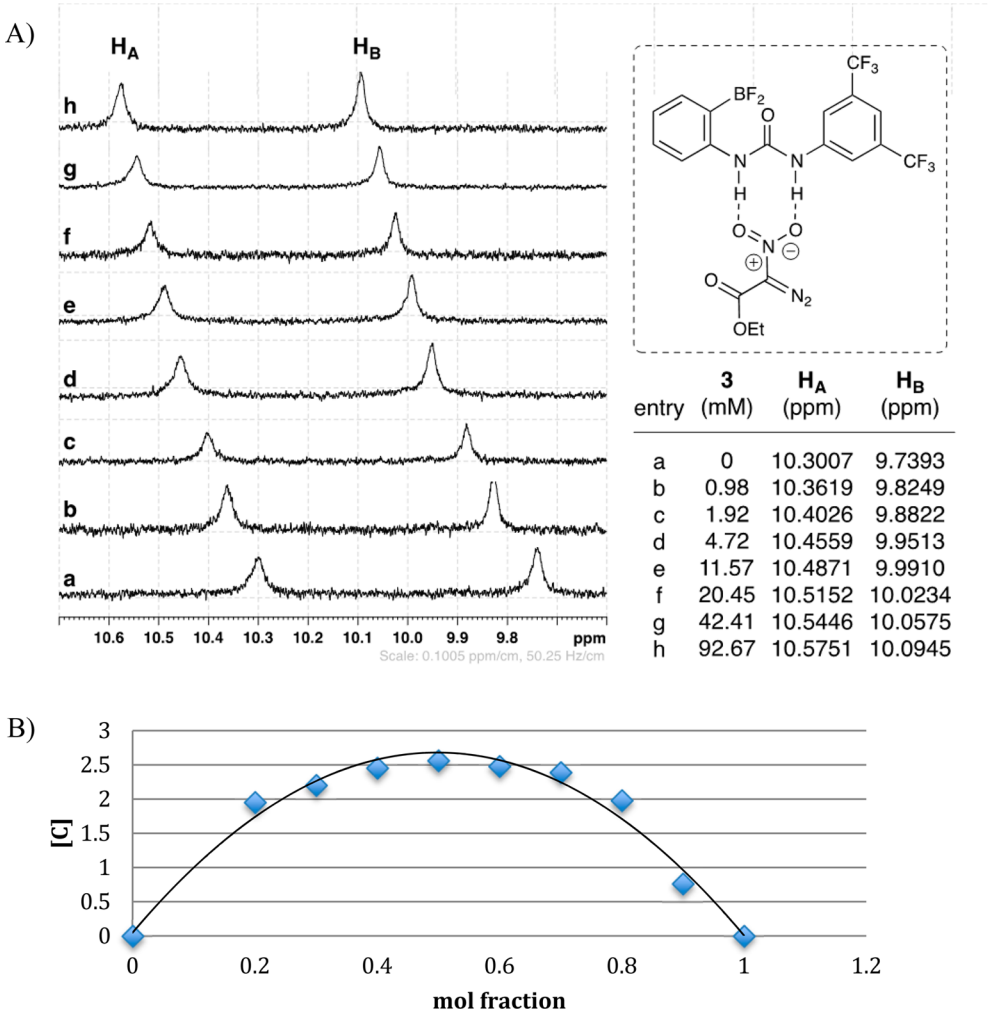

entry	3 (mM)	H_A (ppm)	H_B (ppm)
a	0	10.3007	9.7393
b	0.98	10.3619	9.8249
c	1.92	10.4026	9.8822
d	4.72	10.4559	9.9513
e	11.57	10.4871	9.9910
f	20.45	10.5152	10.0234
g	42.41	10.5446	10.0575
h	92.67	10.5751	10.0945

Figure 2. Urea-nitrodiazoester binding titration studied by ^{1}H NMR spectroscopy in acetone-d_6 at 298.0 K. (A) Selected titration spectra with corresponding concentrations and NMR chemical shifts. Titration data (0–262 equiv of guest **3**) were fit to a 1:1 binding model. See the Supporting Information for experimental details. (B) Job plot analysis suggesting 1:1 binding stoichiometry.

complex considered, the most stable complex (**2**, Table 1) has two hydrogen bonds between the nitro group of α-nitrodiazoester **3** and the urea. The calculated energetics of the complexation show that the most stable complex **2** is formed between the α-nitrodiazoester and difluoroboronate urea **6a**, followed by pinacol ester boronate urea **6b** (Table 1). The enhanced acidity of **6a** (pK_a(DMSO) = 7.5) and **6b** (pK_a(DMSO) = 9.5),[11] due to the intramolecular coordination between boron and oxygen, results in stronger hydrogen-bonded complexes with α-nitrodiazoester **3**.[13] The structural parameters of the complex **2** with various urea derivatives are given in Table 1. The shortest hydrogen bond (2.00 and 2.12 Å) is formed between α-nitrodiazoester **3** and urea **6a**, followed by **6b** (2.01 and 2.21 Å). The enhanced hydrogen-bond donating ability of the urea derivative **6a** is also reflected in shorter C–N and longer C=O bonds of the urea complex (C–*N* = 1.37, 1.35 Å and C=*O* = 1.27 Å) when compared to urea **6d** (C–*N* = 1.38 Å and C=*O* = 1.22 Å) and urea **6e** (C–*N* = 1.39 Å and C=*O* = 1.22 Å), respectively, which are incapable of benefiting from internal coordination. X-ray crystallography confirmed that the carbonyl bond length of urea **6a** (1.274 Å) is indeed significantly longer than that of urea **6d** (1.221 Å) when hydrogen bonded to nitrobenzene. Thus, the analysis confirms that urea **6a** is in fact a more enhanced hydrogen bond donor in the formation of complex **2**.

Experimental Urea–Nitrodiazoester Binding Studies. The interaction of nitrodiazoester **3** with difluoroboronate urea **6a** was readily observed with ^{1}H NMR spectroscopy (Figure 2A). An observed shift in the N–H proton signals by ^{1}H NMR allowed for a direct correlation to the binding affinity of urea **6a** to the nitro group of nitrodiazoester **3**. At this time, we are unable to assign protons $\mathbf{H_A}$ and $\mathbf{H_B}$. Extensive 2D NMR experimentation has yielded inconclusive results and analyses are ongoing in our laboratory to definitively designate the urea N–H protons. Following the diagnostic shifts of $\mathbf{H_A}$ and $\mathbf{H_B}$, upon titration of 0 to 262 equiv of nitrodiazoester **3**, enabled the calculation of an apparent experimental binding constant of 245 ± 22 M^{-1} for $\mathbf{H_A}$ and 295 ± 30 M^{-1} for $\mathbf{H_B}$ in acetone-d_6.[13b] A Job plot analysis supported a 1:1 binding stoichiometry of urea **6a** and nitrodiazoester **3** (Figure 2B).[13]

With evidence suggesting that urea activation of diazoesters through hydrogen-bonding interactions initiates the reaction, two plausible reaction steps were considered: (1) an N–H insertion reaction pathway proceeding through a hydrogen-bond stabilized carbene (pathway **A**) and (2) a polar reaction pathway proceeding through a nucleophilic addition of aniline to activated diazoester complex **2** (pathway **B**, Scheme 5).

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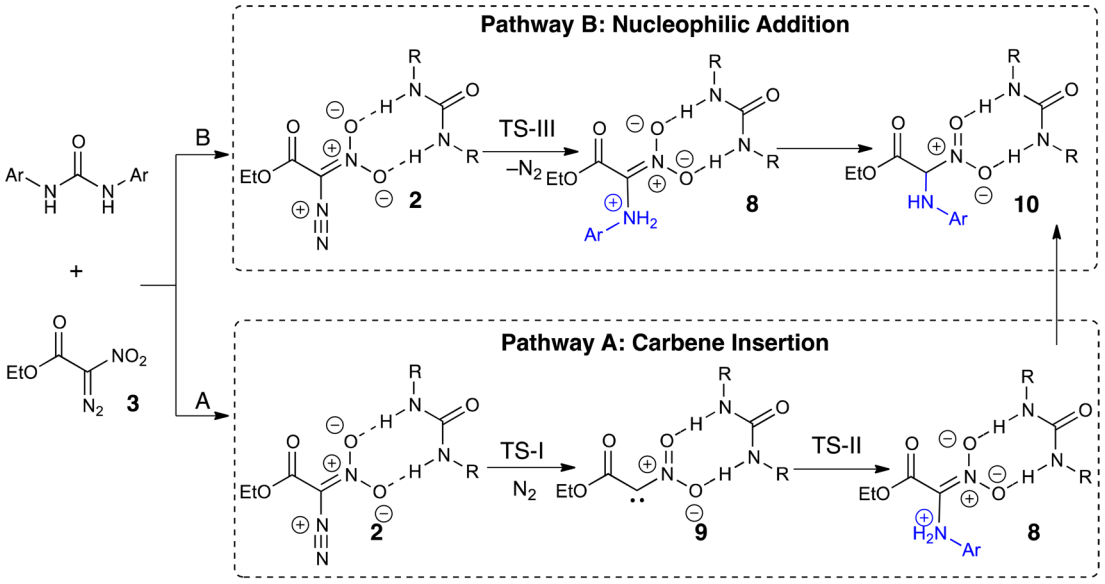
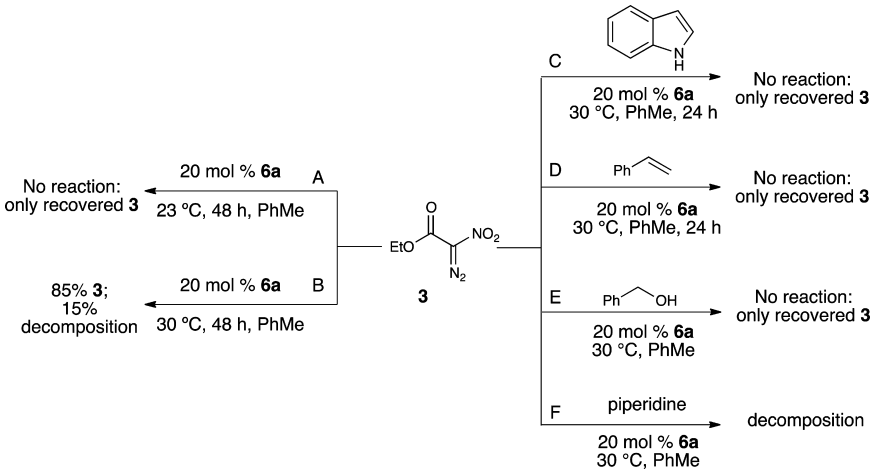
Scheme 5. Plausible Pathways of Urea-Catalyzed N−H Insertion/Multicomponent Coupling of Nitrodiazoesters[a]



entry	urea	2	TS-I	9	TS-II	8	TS-III	10
1	--	0	32.3	32.8	--	−33.2	31.8	−54.8
2	6a	−9.8	23.9	20.4	25.4	−49.8	21.6	−63.2
3	6b	−7.0	24.1	20.8	25.0	−45.2	22.1	−61.8
4	6c	−3.4	24.9	21.0	22.2	−48.0	23.0	−62.4
5	6d	−3.9	24.6	20.4	22.9	−48.4	22.5	−62.4
6	6e	−6.4	27.2	21.7	25.0	−43.6	25.8	−60.2

[a]The energies listed are total energy differences (ΔE) in kcal/mol calculated at the B3LYP/6-311++G**//B3LYP/6-31G* level of theory.

Scheme 6. Experimental Observations Suggesting Carbene Formation Does Not Occur



Experimentally, several observations suggested that a nucleophilic addition reaction pathway was preferred over a pathway proceeding through a carbene (Scheme 6). Again, it was very interesting to observe the reliance of the reaction on the presence of aniline derivatives. In the absence of anilines, electron-rich aromatic rings, such as indole and *N*,*N*-diethylaniline, were unable to react with **3**, and all starting materials could be recovered (C, Scheme 6). Efforts to cyclopropanate **3** under the influence of urea catalysis were also met with no success, and at 30 °C after 24 h, **3**, styrene ,and the urea catalyst were completely recovered (D). Similarly, all of our attempts at O−H insertion reactions were met with complete recovery of **3** (E). Even any attempt at inserting into the N−H bond of a variety of aliphatic amines produced no reaction and only decomposition of the starting diazoester was observed (F). Further evidence of the preferred reaction pathway surfaced from the lack of reactivity of **3** combined with boronate urea **6a**. At 23 °C, a temperature in which the title N−H insertion/arylation reaction is observed, there are no new products observed and all of **3** is recovered (A). Heating of the same control reaction to 30 °C resulted in only slight decomposition of **1** after 48 h (B). If the reaction was indeed proceeding through a carbene intermediate, then the carbene would form in the absence of the nucleophile; however, we only observed

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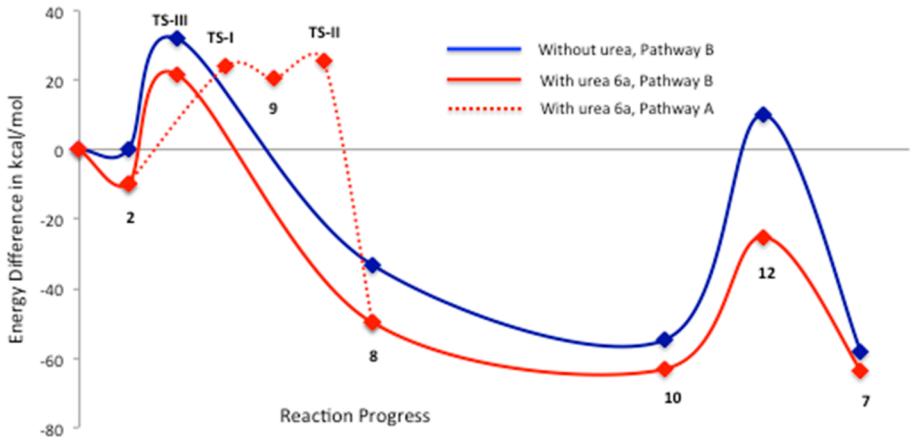
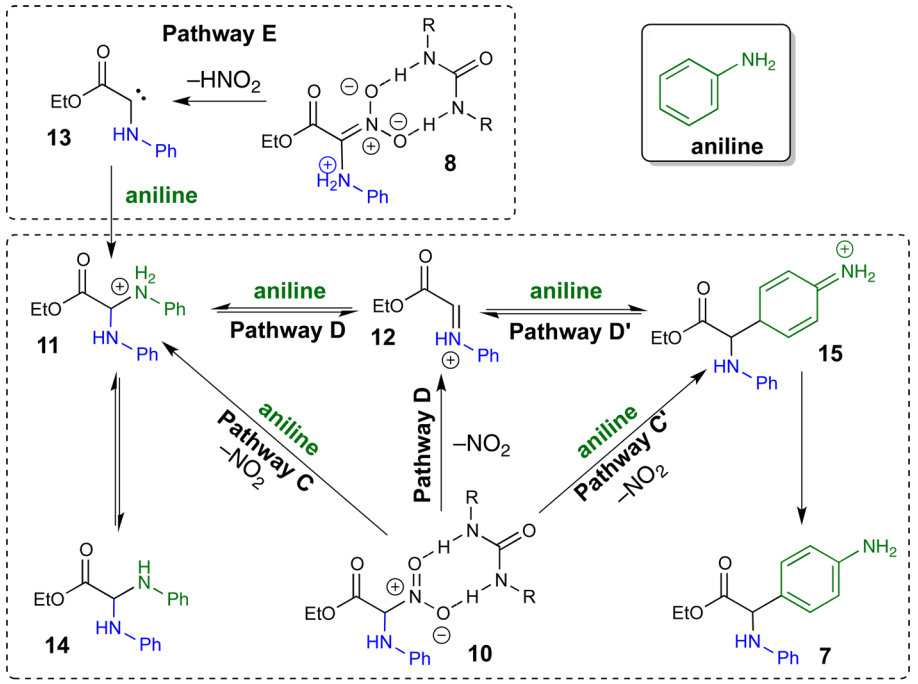


Figure 3. Comparative reaction profile for the insertion reaction of α-nitrodiazoester into the N−H bond of anilines with and without urea catalysts.

Scheme 7. Possible Routes for Aryl Glycine Formation[a]



entry	urea	l0	12	11	14	8	13	15	7
1	--	–54.8	9.9	2.5	–49.6	–33.2	–15.3	6.5	–57.9
2	**6a**	–63.2	–25.1	–32.5	–55.1	–49.8	–20.8	–28.6	–63.4
3	**6b**	–61.8	–13.6	–21.0	–53.5	–45.2	–19.2	–17.0	–61.8
4	**6c**	–62.4	–21.3	–28.6	–54.5	–48.0	–20.1	–24.6	–62.8
5	**6d**	–62.4	–21.7	–29.1	–54.5	–48.4	–20.2	–25.1	–62.8
6	**6e**	–60.2	–12.2	–19.6	–53.0	–43.6	–18.7	–15.6	–61.3

[a]The energies listed are total energy differences (ΔE) in kcal/mol calculated at the B3LYP/6-311++G**//B3LYP/6-31G* level of theory.

the starting diazo compound. Although probing the mechanism via the direct observation of a nitrocarbene intermediate would be ideal, the well-documented rearrangement of nitrocarbenes to the *N*-acyl nitroso species prevent study of the reaction mechanism via this method.[15,16] Additionally, it is possible for nitrodiazoester **3** to rearrange to the *N*-acyl nitroso species without formation of a carbene intermediate. Thus, our observation of byproducts resulting from rearrangement to the *N*-acyl nitroso species does not clearly suggest a carbene pathway.[7a] The broad lack of reactivity in the absence of anilines, combined with the recovery of **3** in the presence of **6a** but no aniline, led us to reason the reaction pathway was likely proceeding through a nucleophilic addition reaction pathway and not through the formation of a carbene intermediate.

Density functional theory (DFT) calculations provided further substantiation of a preferred polar reaction pathway as opposed to a pathway proceeding through a carbene. This evidence was achieved through calculating the reaction energies associated with difluoroboronate urea **6a**, pinacol ester boronate urea **6b**, 3,5-bis(trifluoromethyl)phenyl thiourea **6c**,

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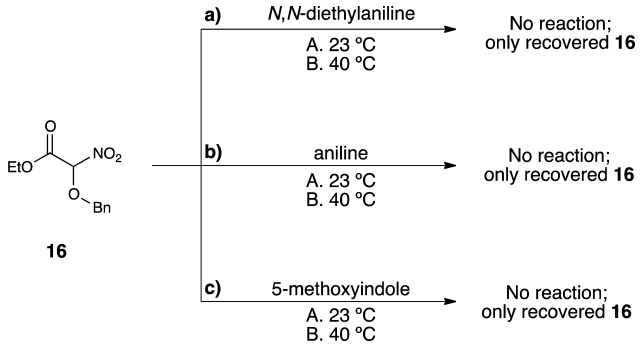
3,5-bis(trifluoromethyl)phenyl urea **6d**, and unsubstituted diphenyl urea **6e** for the N−H insertion/multicomponent coupling of nitrodiazoester **3** with two anilines. As shown in Scheme 5, pathway **A** is proposed to proceed with loss of N_2 through **TS-I** to form urea-stabilized nitrocarbene intermediate **9**. The N−H insertion of carbene **9** into aniline **4** through **TS-II** gives rise to zwitterionic species **8**, which forms α-nitroester **10** after proton transfer. With our most active urea catalyst, boronate urea **6a**, **TS-I** has a calculated ΔE of 23.9 kcal/mol. Insertion of **9** into the N−H bond of aniline occurs with an activation barrier of 5.0 kcal/mol to generate urea complex **8** (−49.9 kcal/mol). The carbene-free mechanism to access α-amino-α-nitroester **10** is outlined in pathway **B**. From complex **2**, nucleophilic attack by aniline, followed by loss of N_2, forms zwitterionic species **8**, providing access to nitroester **10** after a proton transfer. When compared to pathway **A**, **TS-III** has a lower activation barrier than **TS-I** (21.6 vs 23.9, Scheme 5). Although the activation barriers are close, the preference of **TS-III** over **TS-I** is retained, independent of methods of calculation or solvation. Taken collectively, the experimental and computational data support the preference for polar reaction pathway **B**.

Role of Urea on the N−H Insertion Reaction. We have calculated the energies of transition states, intermediates, and products involved in the insertion reaction in the presence of different ureas and compared these values with the insertion reaction in the absence of a urea catalyst. A comparative reaction profile for the insertion reaction in the presence and absence of urea catalysts is shown in Figure 3. The analysis of the insertion of α-nitrodiazoester **3** into the N−H bond of aniline **4a** in the absence of a urea catalyst shows that the transition states and intermediates are less stable when compared to urea-catalyzed reactions. For example, zwitterion **8** without a urea catalyst is less stable by 16.6 kcal/mol (Scheme 5: entry 1, −33.2 kcal/mol vs entry 2, −49.8 kcal/mol). Similarly, formation of nitroester **10** is less favorable by 8.4 kcal/mol than compared with urea **6a** (−54.8 kcal/mol vs −63.2 kcal/mol). However, the energetics of the reaction without a urea catalyst are such that it is feasible for the reaction to proceed, albeit with less efficiency. This is corroborated by the 8% yield of aryl glycine **7i** (Scheme 4) observed when diazoester **3** is reacted with aniline, but without catalyst.

Aryl Glycine Formation. With evidence suggesting a polar N−H insertion reaction pathway, our attention turned toward elucidating the reaction mechanism for the formation of observed aryl glycine products **7**. Three different routes for the conversion of α-amino-α-nitroester **10** to the isolated aryl glycine products **7** were considered (Scheme 7). Through pathway C, direct *N*-addition of nucleophile **5** to nitroester **10** would afford protonated aminal **11** with loss of NO_2^-. Alternatively, through pathway D, loss of NO_2^- facilitated by the formation of iminium **12** allows for addition of the nucleophile to yield **11**, which we propose is in equilibrium with iminium **12**.[18] Lastly, carbene **13** could be formed from loss of HNO_2 from zwitterion **8** (pathway E) followed by insertion into the N−H bond of aniline would lead to **11**. In all cases, it was computed that *N*-attack was preferred over Friedel−Crafts-type addition of the aromatic nucleophile (pathway D′ and pathway C′); however, after proton transfer, aminal **14** is energetically less stable than aryl glycine **7** by 8.3 kcal/mol. Thus, reversible formation of iminium **12** could lead to thermodynamically stable aryl glycine **7** through intermediate **15**. Of the three routes considered, the higher energetic state of **13** (∼40 kcal/mol higher) compared to nitroester **10** makes pathway E unlikely. When comparing the energetics of pathways C and D, it is difficult to assign a clearly preferred pathway. We have not located a transition state for the one-step transformation from nitroester **10** to the structure **11** through pathway C. Both pathways seem plausible, and at this time, all of our efforts to experimentally probe the conversion of nitroesters **10** to aryl glycines **7** have been prevented by the apparent unstable nature of the α-amino nitroester **10**; we have been unable to isolate or independently prepare this species. As a model study, we probed the reactivity of α-alkoxy-α-nitroester **16** as a suitable alternative to α-amino-α-nitroester **10** (Scheme 8). Subjecting **16** with *N*,*N*-diethylaniline and 20 mol % of difluoroboronate urea **6a** at 23 °C yielded no reaction, and only the α-alkoxy-α-nitroester was recovered. Heating the reaction mixture to 40 °C still afforded no desired product, although slight decomposition (<10%) of the starting material was observed. Aniline was also unsuccessful in substituting the NO_2 group. We observed no formation of products of *N*-attack or *C*-attack and only the starting material **16** was recovered. Even the more nucleophilic 5-methoxyindole did not add to the α-alkoxy-α-nitroester **16** at 23 °C nor at 40 °C. These experimental data suggest that S_N2-type substitution of the nitro group by aryl nucleophiles in the reaction system is unlikely. Instead, loss of NO_2^- and formation of an iminium type intermediate is a feasible reaction pathway. We are continuing efforts to directly probe the mechanism of aryl glycine formation.

Scheme 8. Reaction of α-Benzyloxy-α-nitroester with Aryl Nucleophiles



Effects of Urea Derivatives on the Insertion−Arylation Mechanism. We were able to study the effect of the urea catalyst structure on the N−H insertion reaction of nitrodiazoester **3**, aniline **4a**, and another equivalent of aniline **4a** for the formation of aryl glycine **7i** (Table 2). Initial rate studies[7a] demonstrate that urea **6a** is capable of providing rate enhancements up to 8.4 times (k_{obs} = 9.19 × 10^{-5} s^{-1}, Table 2) when compared to the traditional thiourea **6c** (k_{obs} = 1.10 × 10^{-5} s^{-1}) and urea **6d** (k_{obs} = 1.38 × 10^{-5} s^{-1}) in the formation of aryl glycine **7i**. Boronate urea **6b** was found to provide the slowest rate of reaction (k_{obs} = 0.77 × 10^{-5} s^{-1}). These data are supported by our DFT calculations (Scheme 5). The reaction barrier to form the transition state **TS-III** is reduced by 4.2, 3.7, 3.3, and 2.8 kcal/mol in the presence of urea **6a**, **6b**, **6d**, and **6c**, respectively, compared to the reaction with unsubstituted diphenyl urea derivative, **6e**. Among the urea derivatives, nucleophilic addition intermediate **8** is generated most favorably in the presence of urea derivative **6a**, which forms the strongest hydrogen-bonded complex **2** with α-nitrodiazoester **3**. In the multicomponent coupling of two molecules

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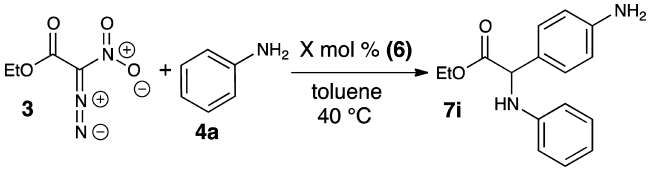
Table 2. Initial Rate Studies of Urea Catalysts[ab]



entry	6	time (h)	yield[c] (%)	k_{obs}[d] ($\times 10^{-5}$, s^{-1})
1	20 mol % **6a**	24	83	9.19
2	20 mol % **6b**	24	61	0.77
3	20 mol % **6c**	24	27	1.10
4	20 mol % **6d**	24	58	1.38
5	--	24	8	--

[a]The concentrations of nitrodiazoester **3** and aniline **4a** were kept high for pseudo-first-order conditions. [b]Reactions performed using 10 equiv of aniline at a concentration of 1 M. See the Supporting Information for detailed experimental procedures. [c]Isolated yield. [d]An average of k_{obs} determined at multiple catalyst loadings; see the Supporting Information.

of aniline **4a** with nitrodiazoester **3**, the formation of aryl glycine **7i** is most stabilized (−63.4 kcal/mol, Scheme 7, entry 2) in the presence of urea **6a**.[19] Boronate urea **6a** provided the highest yield of the N−H insertion product **7i** (83%), followed by boronate urea **6b** (61%), thiourea **6c** (27%), and urea **6d** (58%). Contradictory to the experimentally isolated low yield of aryl glycine product **7i** observed with thiourea **6c**, calculated energetics for the reaction with thiourea **6c** does not show markedly less stable intermediates or transition states compared to other urea derivatives. The decomposition of the catalyst under the reaction conditions could be a possible explanation for the low yield of N−H inserted product in the case of thiourea **6c**.

In summary, boronate ureas have been identified as effective catalysts for the preparation of aryl glycines via the N−H insertion/multicomponent coupling reaction of nitrodiazoesters, anilines, and nucleophiles. The proposed mechanisms of insertion/arylation were deduced from both experimental and computational evidence. Investigations into the reaction pathway suggest urea-facilitated stepwise N−H insertion is more favored than a concerted N−H insertion mechanism proceeding through a urea-stabilized nitrocarbene. Formation of an iminium-type intermediate results in loss of HNO_2, allowing for addition of an aryl nucleophile. In the case of aniline, it is likely that *N*-attack occurs first to reversibly form an aminal moiety. Thermodynamic equilibration leads to isolation of the *C*-bound aryl glycine products. We are working toward reporting results of ongoing investigations currently underway in our laboratory further probing urea-activation of nitrodiazoesters.

COMPUTATIONAL METHODS

The geometries of all of the structures involved in the urea-catalyzed insertion reaction of aniline with α-nitrodiazoester, including local minima and transition states, were optimized using the hybrid DFT method, B3LYP/6-31G*.[20,21] Vibrational frequency calculations were performed for each of the optimized geometries to verify whether the stationary point was a minimum or a transition state on the potential energy surface. Using the B3LYP/6-31G* geometries, single-point energy calculations were performed at the B3LYP/6-311++G** to further evaluate the energetics of the various reactions. Solvent effects were modeled using the polarizable continuum model (PCM), with toluene as the solvent.[22] All calculations are carried out using the Gaussian 09 suite of programs, along with the standard basis sets available in the suite.[23]

EXPERIMENTAL SECTION

General Methods. Methylene chloride was purified by passage through a bed of activated alumina.[24] Purification of reaction products was carried out by flash chromatography using 60 Å (40−63 μm) activated basic aluminum oxide powder that was deactivated to Brockmann Activity II. Analytical thin-layer chromatography was performed on 0.25 μm silica gel 60-F_{254} plates. Visualization was accomplished with UV light and ceric ammonium molybdate stains followed by heating. Melting points (mp) are reported uncorrected. Infrared spectra for liquid products were obtained as a thin film on a NaCl disk and spectra for solid products were collected by preparing a NaBr pellet containing the title compound. Nuclear magnetic resonance spectra were recorded in deuterated solvents on 400 or 500 MHz spectrometers. Proton nuclear magnetic resonances (^{1}H NMR; $CHCl_3$, δ 7.26 and DMSO, δ 2.50) and proton-decoupled carbon (^{13}C NMR; $CDCl_3$, δ 77.16; DMSO, δ 39.5) are reported in parts per million (ppm, δ) using the solvent as internal standard. Proton decoupled fluorine (^{19}F NMR) spectra are reported in ppm using $CF_3C_6H_5$ as an external standard (−63.72). Boron spectra (^{11}B NMR) are reported in ppm using $BF_3{\cdot}OEt_2$ as an external standard (0.00). Electrospray mass spectra (ESI-MS) were obtained using a MicrOTOF. Aniline, *N*,*N*-diethylaniline, 4-fluoroaniline, 2,6-diisopropylaniline, 2,6-dimethylaniline, and *N*-methylindole were freshly distilled before use. Unless otherwise noted, all other commercially available reagents and solvents were used without further purification. **Caution**: While we have not experienced any problems handling ethyl nitrodiazoacetate, appropriate care should be exercised when handling any diazo compound or nitrodiazo compound.

Typical Procedure for N−H Insertion Reactions.[7a] A dry, screw-capped reaction vial containing a magnetic stir bar was charged with ethyl nitrodiazoacetate **3** (30 mg, 0.189 mmol) and catalyst **6a** (15 mg, 0.038 mmol). Toluene (189 μL) was added if necessary. Aniline **4** and nucleophile **5** were added immediately, and the reaction was fitted with cap and septum and put under a positive pressure of Ar. The reaction was allowed to stir at the indicated temperature and duration. The reactions were immediately purified by flash column chromatography with a minimal amount of neutral alumina, basic alumina, or silica gel. All spectra for compounds **7b**,[7a] **7c**,[7a] **7e**,[7c] **7f**,[7b] **7h**,[7c] **7i**,[7a] and **7k**[7a] matched previously reported values.

*Ethyl 2-((4-Fluorophenyl)amino)-2-(4-(methylamino)phenyl)-acetate (**7a**).* The reaction was allowed to stir neat at 23 °C for 48 h with 4-fluoroaniline (179 μL, 1.89 mmol) and *N*-methylaniline (205 μL, 1.89 mmol). The reaction was immediately purified by flash column chromatography with a minimal amount of silica gel (5:95 ethyl acetate/hexanes to 50:50 ethyl acetate/hexanes), yielding 49 mg (85%) of **7a**: R_f = 0.21 (20:80 ethyl acetate/hexanes); FTIR (film) 3053, 2986, 1732, 1614, 1510, 1421, 1265, 909 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28−7.25 (m, 2H), 6.85−6.80 (m, 2H), 658−6.56 (m, 2H), 6.52−6.48 (m, 2H), 4.88 (d, *J* = 5.6 Hz, 1H), 4.69 (d, *J* = 5.2 Hz, 1H), 4.26−4.24 (m, 1H), 4.24−4.08 (m, 1H), 3.75 (br s, 1H), 2.82 (s, 3H), 1.23 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5, 156.0 (d, *J* = 233.9 Hz), 149.5, 142.8 (d, *J* = 1.5 Hz), 128.3, 125.7, 115.6 (d, *J* = 22.4 Hz), 114.2 (d, *J* = 24.9 Hz), 112.7, 61.7, 61.0, 30.7, 14.2; HRMS (ESI) mass calcd for $C_{17}H_{19}F_1N_2O_2Na$ $[M + Na]^+$ 325.1323, found $[M + Na]^+$ 325.1329.

*Ethyl 2-(4-Amino-3,5-diisopropylphenyl)-2-((4-fluorophenyl)-amino)acetate (**7d**).* The reaction was allowed to stir neat at 40 °C for 48 h with 2,6-diisopropylaniline (1.89 mmol) and 4-fluoroaniline (179 μL, 1.89 mmol). The reaction was immediately purified by flash column chromatography with a minimal amount of basic alumina (20:80 diethyl ether/hexanes to 100% diethyl ether), yielding 68 mg (96%) of **7d**: R_f = 0.78 (100% diethyl ether); FTIR (film) 3401, 2962, 2927, 2870, 1731, 1624, 1510, 1466, 1308, 1280 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09 (s, 2H), 6.87−6.82 (m, 2H), 6.55−6.52 (m, 2H), 4.90 (d, *J* = 6.8 Hz, 1H), 4.55 (d, *J* = 8.8 Hz, 1H), 4.27−4.20 (m, 1H), 4.18−4.10 (m, 1H), 3.76 (br s, 2H), 2.93−2.86 (m, 2H), 1.27−1.21 (m, 15 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 156.1 (d, *J* = 234

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Hz), 143.0, 140.4, 132.7, 126.6, 121.9, 115.6 (d, J = 22.4 Hz), 114.3 (d, J = 7.3 Hz), 61.7, 61.3, 28.1, 22.4, 14.1; HRMS (ESI) mass calcd for $C_{22}H_{29}F_1N_2O_2Na_1$ $[M + Na]^+$ 395.2105, found $[M + Na]^+$ 395.2091.

*Ethyl 2-(5-Chloro-1H-indol-3-yl)-2-((4-fluorophenyl)amino)-acetate (**7g**).* The reaction was allowed to stir at 40 °C for 48 h in toluene (189 μL) with 4-fluoroaniline (179 μL, 1.89 mmol) and 5-chloroindole (48 mg, 0.189 mmol). The reaction was immediately purified by flash column chromatography on silica gel (20:80 ethyl acetate/hexanes to 100% ethyl acetate), yielding 38 mg (58%) of **7g**: R_f = 0.2 (35:65 ethyl acetate:hexanes); FTIR (film) 3409, 3052, 2984, 1734, 1618, 1489 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.19 (br s, 1H), 7.81 (d, J = 2.0 Hz, 1H), 7.30−7.28 (m, 1H), 7.20−7.17 (m, 2H), 6.87−6.83 (m, 2H), 6.57−6.55 (m, 2H), 5.26 (d, J = 4.0 Hz, 1H), 4.68 (d, J = 6.0 Hz, 1H), 4.30−4.22 (m, 1H), 4.17−4.12 (m, 1H), 1.23 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1, 156.2 (d, J = 234 Hz), 142.7, 135.0, 126.8, 125.9, 124.4, 123.0, 119.2, 115.7 (d, J = 22.4 Hz), 114.4 (d, J = 7.3 Hz), 112.5, 112.4, 61.8, 54.9, 14.1; HRMS (ESI) mass calcd for $C_{18}H_{16}Cl_1F_1N_2O_2$ $[M + Na]^+$ 369.0777, found $[M + Na]^+$ 369.0763.

*Ethyl 2-(4-Aminophenyl)-2-((4-methoxyphenyl)amino)acetate (**7j**).* The reaction was allowed to stir at 23 °C for 72 h in toluene (189 μL) with *p*-anisidine (163 mg, 1.32 mmol) and aniline (17.2 μL, 0.189 mmol). The reaction was immediately purified by flash column chromatography with a minimal amount of neutral alumina (5:95 ethyl acetate/hexanes to 50% ethyl acetate), yielding 44.3 mg (78%) of **7j** as an orange solid: R_f = 0.81 (100% diethyl ether); FTIR (film) 3059, 2991, 1739, 1659, 1622, 1519, 1379, cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.26−7.24 (m, 2H), 6.72 (d, J = 8.4 Hz, 2H), 6.64 (d, J = 8.4 Hz, 2H), 6.54 (d, J = 9.2 Hz, 2H), 4.88 (d, J = 5.2 Hz, 1H), 4.53 (d, J = 4.8 Hz, 1H), 4.23−4.17 (m, 1H), 4.16−4.10 (m, 1H), 3.71 (s, 3H), 3.67 (br s, 2H), 1.21 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.7, 152.5, 146.5, 140.6, 128.4, 127.7, 115.4, 115.0, 114.9, 61.6, 61.3, 55.9, 14.2; HRMS (ESI) mass calcd for $C_{17}H_{20}Na_1N_2O_3$ $[M + Na]^+$ 323.1366, found $[M + Na]^+$ 323.1365.

*Ethyl 2-(4-Aminophenyl)-2-(p-tolylamino)acetate (**7l**).* The reaction was allowed to stir at 40 °C for 48 h in toluene (189 μL) with *p*-toluidine (101 mg, 0.945 mmol) and aniline (17.2 μL, 0.189 mmol). The reaction was immediately purified by flash column chromatography with a neutral alumina (5:95 ethyl acetate/hexanes to 50% ethyl acetate), yielding 38 mg (70%) of **7l**: R_f = 0.3 (35:65 ethyl acetate/hexanes); FTIR (film) 3390, 3055, 2986, 1734, 1654, 1515, 1374, 1264, 1046, cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.26−7.24 (m, 2H), 6.93 (d, J = 8.0 Hz, 2H), 6.65−6.63 (m, 2H), 6.50−6.48 (m, 2H), 4.92 (d, J = 6.0 Hz, 1H), 4.67 (d, J = 6.0 Hz, 1H), 4.26−4.18 (m, 1H), 4.17−4.08 (m, 1H), 3.68 (br s, 2H), 3.20 (s, 3H), 1.21 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 146.5, 144.1, 129.8, 128.4, 127.6, 127.2, 115.4, 113.7, 61.6, 60.7, 20.5, 14.2; HRMS (ESI) mass calcd for $C_{17}H_{20}Na_1N_2O_2$ $[M + Na]^+$ 307.1417, found $[M + Na]^+$ 307.1416.

■ ASSOCIATED CONTENT

Supporting Information

Spectral data, titration data, optimized geometries, and energies of important structures. This material is available free of charge via the Internet at http://pubs.acs.org.

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