Organocatalysis

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Arylation of Diazoesters by a Transient N–H Insertion Organocascade**

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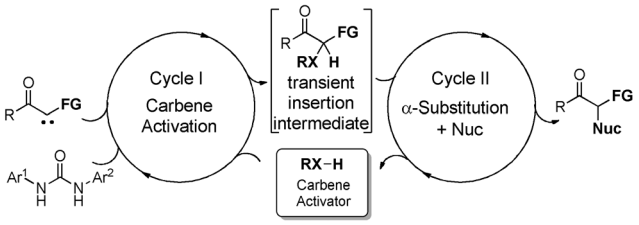
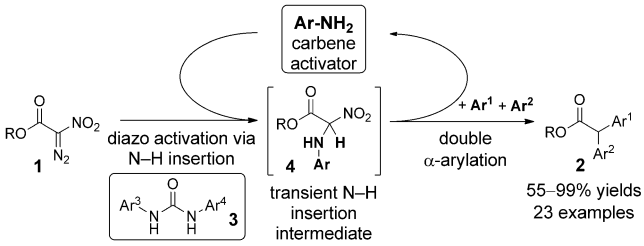
Cascade catalysis is a powerful tool demonstrated both by nature and chemists alike to generate complex products through sequential catalytic processes.[1] These processes benefit from the efficiency of catalyzing multiple steps in a single flask for the rapid construction of molecular complexity without the necessity of intermediate isolation. Autotandem catalytic methods are cascade processes employed to promote two or more distinct reactions with a single catalyst.[2] Inspired by the demonstrated power of autotandem organocascade catalysis,[3] we sought to invoke a fundamentally novel sequence taking advantage of catalytic transient carbene activation. More specifically, we envisioned activating a species having carbene character by a urea-catalyzed[4] insertion reaction with an appropriate carbene activator to generate a transient intermediate which would then enter into a second distinct cycle for further functionalization (Scheme 1). Successful development of this process would



Scheme 1. Transient carbene activation cascade catalysis.

afford a straightforward organocatalytic route to synthetically challenging structural motifs from simple starting materials, and also expose the potential of transient carbene insertion reactions as innovative tools in organocatalytic method development. Herein, we detail our breakthrough discoveries in urea-catalyzed transient N–H insertion reactions for the controlled functionalization of nitrodiazoesters.

The geminal diaryl functionality is frequently found in bioactive target molecules, and several drugs already commercially available to treat a variety of diseases contain this structural motif.[5] Specific examples include the antidepressant Zoloft, and anticancer agents Femara and Etoposide. Aware of the therapeutic significance and synthetic challenges associated with preparing unsymmetrical geminal diaryl frameworks,[6] we focused the development of transient insertion organocascade catalysis on arylation reactions of diazo compounds. The working hypothesis was that an appropriate amine could trigger urea-catalyzed arylation reactions of diazo compounds (**1**)[7] through transient N–H insertion intermediates[8,9] (**4**; Scheme 2). To the best of our



Scheme 2. Double arylation of nitrodiazoesters through transient N–H insertion organocascade catalysis.

knowledge, cascade reactions proceeding through transient carbene insertion intermediates had not been reported at the onset of our investigations. The testing of the feasibility of our hypothesis began with investigating anilines as carbene activators of nitrodiazoesters.[10]

Our studies began with the preparation of **2a** by the double arylation of ethyl nitrodiazoacetate (**1a**) with 5-methoxyindole and 5-bromoindole in the presence of 20 mol% of the boronate urea **3a**[11,12] and an aniline activator (Table 1). Our first attempt afforded a disappointing 12% of the desired adduct **2a** when aniline was employed as the carbene activator (entry 1). Further examination of the reaction led us to identify participation of the aniline activator in the diarylation reaction. Next, we turned to *p*-substituted anilines, activators less likely to be involved in undesired arylation pathways. Indeed, the strategic choice of activators proved fruitful and we were delighted to find that activation of **1a** with *p*-anisidine gave rise to 73% of **2a** (entry 2). Additional tuning of the aniline led us to 4-fluoroaniline as an even better carbene activator (entry 3), potentially because of its better leaving ability. The necessity of an aniline activator able to undergo N–H insertion with the diazoester **1a** is clear: a 0% yield of **2a** was observed when 2,6-dimethylaniline, an aniline too sterically encumbered to undergo N–H insertion,

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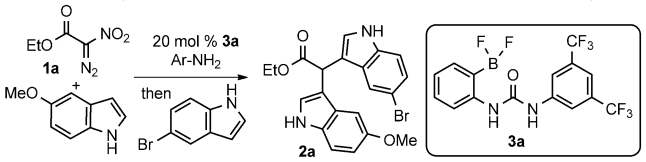
Table 1: Study of aniline activators in transient N–H insertion catalysis.[a]



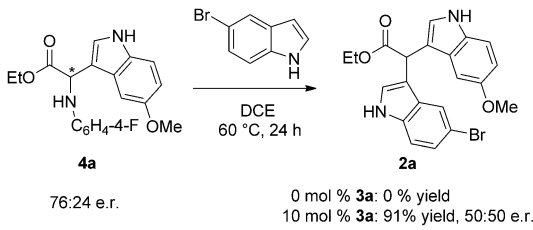
Entry	1	2	3[c]	4	5
Ar-NH_2					none
Yield [%][b]	12	73	78	0	0

[a] Reactions performed at 2 M in DCE. [b] Yield of isolated product. [c] 0% of **2a** was generated in the absence of **3a**.

was tested as the activator (entry 4). From the results of two critical control experiments, we concluded that the urea catalyst and aniline activator working in combination are uniquely able to effect the double arylation of **1a**. Specifically, the first control experiment resulted in no desired **2a** when an N–H insertion activator was excluded from the reaction system (entry 5). Similarly, in the second control, none of **2a** was observed if the boronate urea **3a** was excluded from the optimized reaction conditions (entry 3).

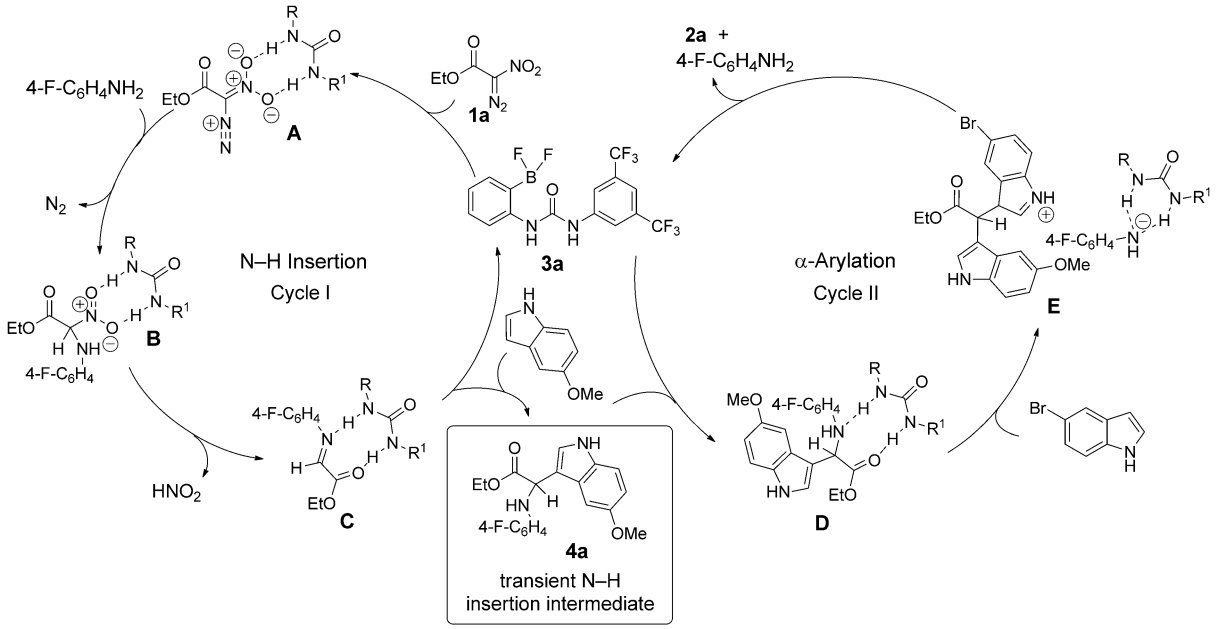
A plausible organocascade for the unsymmetrical diarylation of nitrodiazoesters, depicted in Scheme 3, takes advantage of the urea catalyst (**3a**) in two sequential roles: 1) nitrodiazoester activation for N–H insertion/multicomponent coupling and 2) α-amino ester activation for arylation. In the first cycle, **1a** is activated by **3a** and 4-fluoroaniline, thus affording the N–H insertion adduct **B** through the hydrogen-bonded complex **A**. Upon liberation of nitrous acid, **B** is converted into the iminoglyoxylate **C**. The arylation of the activated iminoglyoxylate then generates the transient N–H insertion intermediate **4a**.[13] In Cycle II, the α-amino ester is activated through dual binding with the urea catalyst, conceivably through the complex **D**. The urea-assisted substitution of the N-bound 4-fluoroaniline with 5-bromoindole then generates the desired double arylated ester product **2a** upon aromatization, thus introducing **3a** and 4-fluoroaniline back into the catalytic cycle.[14,15]

In support of the proposed reaction pathway, the enantioenriched transient N–H insertion intermediate **4a** was isolated and subjected to the reaction conditions (Scheme 4).[13] From this experiment we found that **4a** is



Scheme 4. Urea-catalyzed arylation of the enantioenriched **4a**.

converted into a racemic mixture of **2a** in 91% yield under the influence of 10 mol% **3a**. Importantly, the urea is essential for this reaction: no reaction was observed if the urea catalyst was excluded. The loss of enantiomeric excess in the conversion of **4a** into **2a** suggests that an S_N1-like mechanism is operating for the conversion of **D** into **E**. Additional control experiments conducted in our laboratory suggest the stereocenter in the di-α-arylester **2** is stable to the reaction conditions, thus further supporting an S_N1-like reaction pathway as opposed to an S_N2 and subsequent racemization.[16] Stoichiometric amounts of inexpensive 4-fluoroaniline were necessary to prevent the generation of undesired symmetrical α-diarylated esters, which were



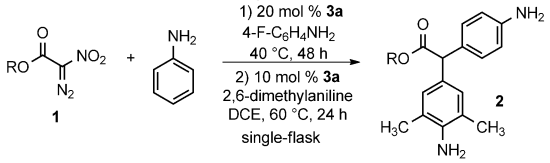
Scheme 3. Plausible reaction pathway for the unsymmetric double arylation of nitrodiazoesters through a transient N–H insertion intermediate.

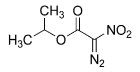
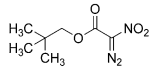
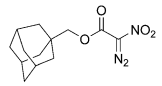
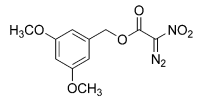
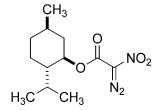
formed when using catalytic quantities of the carbene activator. However, the feasibility of transient insertion cascades requiring only catalytic amounts of the carbene activator is a promising avenue for future studies not featuring double functionalization.

The autotandem catalytic double arylation of **1a** was easily extended to a remarkably wide array of substrates to give rise to the di-α-aryl esters **2** in excellent yields (Scheme 5). Unsymmetrical double indolylation was efficiently achieved in up to 97% yield when indoles were used as both the first and second nucleophiles (**2a–e**). Anilines were also easily incorporated into the diarylation reaction. Examples of indoles working in combination with anilines afforded the products **2f–j** in excellent yields of up to 98% yield. A variety of anilines, as both the first and second nucleophiles, are excellent reactants for this coupling reaction as well. Even sterically encumbered, electron-rich anilines were well tolerated in the diarylation reaction. For instance, 3,5-dimethoxyaniline gave rise to 98% of **2n**. Select halogenated anilines were capable of being integrated into the double arylation sequence, albeit longer reaction times were required for step 2. *o*-Iodoaniline gave rise to 56% of **2o** after 72 hours at 60 °C. Additionally, pyrroles operated moderately well in the cascade sequence (**2q**,**r**).

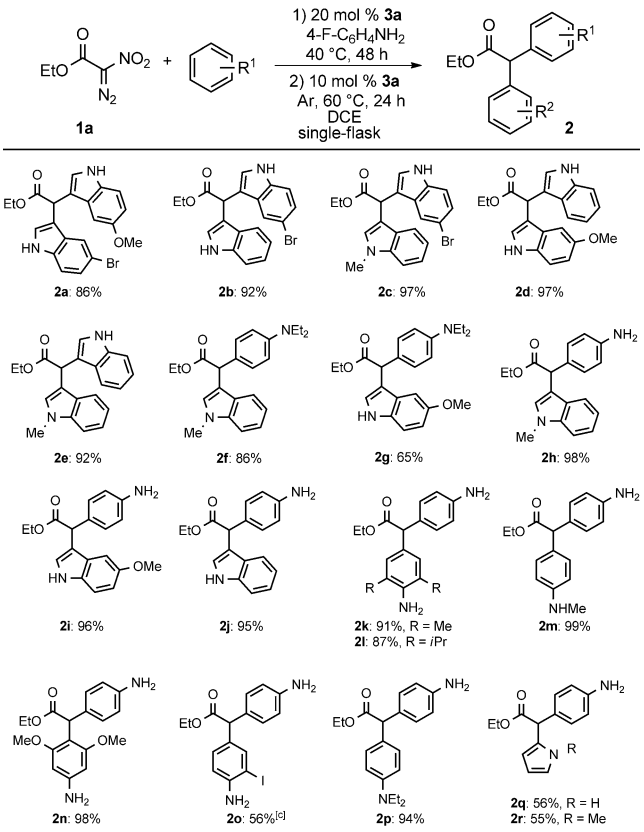
The reaction also proved tolerant of a wide range of nitrodiazoesters (**1**; Table 2). Sterically demanding nitrodiazoacetates (**1b–d**) were well tolerated, thus providing the products **2s–u** in up to 88% yield. Substituted benzyl esters were also easily incorporated into the double arylation sequence. For instance, the product **2v** was prepared in 60% yield from the diazoester **1e** (entry 4). The (−)-menthol-derived nitrodiazoester **1f** gave rise to **2w** in 68% yield as a 1:1 mixture of diastereomers.

Table 2: Diazoester substrate scope.[a]



Entry	Diazoester	1	Product	Yield [%][b]
1		**1b**	**2s**	88
2		**1c**	**2t**	75
3		**1d**	**2u**	63
4		**1e**	**2v**	60
5[c]		**1f**	**2w**	68

[a] Reactions performed at 2 M in DCE in step 2. [b] Yield of isolated product. [c] **2w** isolated as a 1:1 mixture of diastereomers.



Scheme 5. Substrate scope for the double arylation of ethyl nitrodiazoacetate.[a,b] [a] Reactions performed at 2 M in DCE in step 2. See the Supporting Information for details [b] Yield of isolated products. [c] 72 h reaction time in step 2. DCE = 1,2-dichloroethane.

In summary, we have discovered that the intermolecular double arylation of nitrodiazoesters is achieved through a unique urea-catalyzed transient N–H insertion organocascade. The reaction can accommodate a remarkable number of anilines and indoles, thus enabling the efficient preparation of a large family of unsymmetric α-diaryl esters. The proposed reaction pathway invokes the urea catalyst in two distinct, sequential catalytic cycles: N–H insertion and α-arylation. We anticipate transient insertion catalysis may be a fruitful new direction in organocatalysis. Ongoing investigations in our laboratory are focused on exploring the possibility of enantioselective transient N–H insertion catalysis.

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