Transition Metal-Free Cycloamination of Prenyl Carbamates and Ureas Promoted by Aryldiazonium Salts

Roman Abrams*, Quentin Lefebvre*, and Jonathan Clayden*

Abstract: On treatment with aryldiazonium salts, prenyl carbamates and ureas undergo redox-neutral aza-cycloamination. N-Aryl O-prenyl carbamates in general cyclize in a photocatalytic reaction with visible light and an organic dye. With electron-deficient diazonium salts, electronic matching with an electron-rich N-aryl substituent the reaction to proceed in the ground state, without light or photocatalyst. Cyclic voltammetry suggests that this radical reaction is initiated by hydrogen atom abstraction mediated by an aryl radical, followed by a radical addition cascade and proton-coupled hole propagation. The reaction proceeds at room temperature in short reaction times, and a range of functional groups is tolerated.

Amination of olefins is an attractive approach to aliphatic polyfunctionalized molecules, with allylic alcohols and allylic amines being either feedstock chemicals or easily accessible synthetically. Intramolecular cyclization of carbamates and ureas with an aryl substituent on a pendant olefin is a convenient way of ensuring selectivity. For example, treatment of allyl carbamates and ureas with electrophilic halogen sources leads to regioselective aminohalogenation of the olefin via a halonium intermediate. However, this approach is limited both by the lack of reactivity, and by elimination side-reactions during functional group interconversions of the halide substituents. Some of these issues may be avoided using metal catalysts. Palladium-catalyzed carboamination of allyl carbamates and ureas, using aryl halides as oxidants to form a palladium(II) species, promotes olefin insertion into the amine-metal bond, followed by reductive elimination to the arylated product. Hypervalent iodine oxidants widen the scope of this useful transformation, and enable the formation of two heteroatom-carbon bonds, resulting in aminoaalkoxylation or aminofluorination of the pendant olefin.

Following Nicolaou’s IBX-mediated intramolecular hydroamination of allyl carbamates, advances in amination reactions revealed a new mechanistic approach to the difunctionalization of these substrates. Formation of an N-centred amidyl radical allows 5-exo-trig cyclisation to an intermediate nucleophilic radical whose reaction with fluoride atom donors provides aminofluorinated products. As an extension of this work, copper-mediated amination reactions exhibit interesting mechanistic behavior, at the interface between free-radical chemistry and more standard polar aminometallation. Unfortunately, these reactions generally rely on expensive or synthetically remote electrophilic amination reagents such as NFSI, O-acylhydroxylamines or the Zhdankin reagent, which simultaneously act as two-electron oxidants.

Knowles has shown that proton-coupled electron transfer enables oxidation of amides, carbamates and ureas to electrophilic N-centered radicals. A weakly basic but strongly hydrogen-bonding additive significantly lowers the oxidation potential of the substrate, permitting the use of milder oxidants such as excited-state iridium photocatalysts. However, this approach was only applicable to hydro- or carboamination reactions when the intermediate nucleophilic radical was trapped by hydrogen atom donors or electron-deficient olefins.

In this paper we show that diazonium salts constitute a class of reagents capable of trapping such intermediate radicals to form a new C–N bond (Scheme 1). Diazotization of anilines is straightforward under either aqueous or anhydrous conditions, making diazonium salts far more accessible than any other electrophilic amination reagent. Most diazonium tetrafluoroborate salts are stable crystalline solids, indefinitely stable in the fridge. Although free-radical addition onto diazonium salts has been known for over 30 years, their full potential as electrophilic amination reagents has been revealed only recently. Their reduction requires only mild temperatures, in the presence of nucleophilic bases, visible-light irradiation, or weak reductants such as DABSO, and could initiate radical reactions forming intermediates which would ultimately be trapped by an additional equivalent of diazonium salt, terminating the reaction.
We began our study by submitting 6-phenyl-O-prenyl carbamate 1a to Knowles’ photoredox catalysis conditions, in the presence of a diazonium salt. Neutral organic dyes 4CzIPN (1,3-dicyano-2,4,5,6-tetrakis(4-CzIphenyl)-benzene) and 4DPAIPN (1,3-dicyano-2,4,5,6-tetrakis(N,N-diphenylamino)-benzene) were used as cheaper alternatives to iridium photocatalysts. Upon irradiation with blue LED, 1a and diazonium salt 2a gave the coupling product 3 in 74% and 47% yield in the presence and absence of photocatalyst, respectively (Table 1, entries 1 and 2). There was almost no conversion in the dark and in the absence of photocatalyst (entry 3). This shows that a purely photoinduced reaction between the two substrates, without intervention of 4DPAIPN as redox mediator, is operative to some extent.

Very different results were obtained using the electron-deficient diazonium salt 2c. Although best yields of product 4 were obtained on irradiation, with or without the photocatalyst (entries 4-6), significant background reaction occurred even in the dark. To further investigate this peculiar behavior, we used electron-rich carbamate 1b in combination with an electron-neutral diazonium salt 2b and obtained the expected product 5 in 57% spectroscopic yield under photocatalytic conditions (entry 7). Switching the solvent to DMSO and performing the reaction in the dark in the absence of photocatalyst gave 5 in an improved 75% spectroscopic yield (entry 8). This led to the conclusion that diazonium salts which are more electron-deficient than the substrate promote direct oxidation or hydrogen atom abstraction of 1a or 1b even in the ground state. We then evaluated both sets of conditions using the related prenyl-substituted urea 6c. Photocatalytic conditions in CH₂Cl₂ resulted in low conversion without formation of the expected product 7b (entry 9). In stark contrast, a 75% yield was obtained in DMSO in the dark (entry 10). This unprecedented reactivity, apparently arising from the interaction of the prenyl urea and the diazonium salt in their electronic ground states, is remarkable, so we turned to exploiting its generality.

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Upon treatment of 6c with 2a, 1H NMR gave evidence that the triamine derivative 7a was formed (Table 2, entry 1), but only in low yield even after 17 h. More electron-deficient partners 2b and 2c coupled more successfully (entries 2 and 3). Screening a series of bases (entries 4-8) established that the more soluble sodium dibutylphosphate was optimal, and allowed the reaction to be run at greater concentration. Full conversion of 2c to 7c was achieved in only 15 min (83% isolated yield, entry 9). Reducing the amounts of diazonium salt and base below 2 equiv. led to lower, but still synthetically useful, yields (entry 10). Commercially available lithium phosphate is a more readily available and scalable alternative (entry 7).

Having identified the optimal conditions for this redox-neutral azocycloamination reaction, we explored its scope (Table 3). Variation of the N-substituent of the N-aryl urea...
showed that a range of para- and meta-, but not ortho-substituents, were well tolerated (7c-n).\textsuperscript{12} Halo-substituted substrates gave the products 7f-h in good yields, as did nitriles, esters and acetamides (7k, l, n), and the medicinally important trifluoromethoxy group of 7.

Table 3. Substrate scope of the diamination of ureas.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Starting material, R</th>
<th>Product, yield / %\textsuperscript{[a]}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6c, p-CH\textsubscript{3}OC\textsubscript{6}H\textsubscript{4}</td>
<td>7c, 83%</td>
</tr>
<tr>
<td>2</td>
<td>6d, C\textsubscript{6}H\textsubscript{5}</td>
<td>7d, 76%</td>
</tr>
<tr>
<td>3</td>
<td>6e, m-CH\textsubscript{2}OC\textsubscript{6}H\textsubscript{4}</td>
<td>7e, 87%</td>
</tr>
<tr>
<td>4</td>
<td>6f, p-F\textsubscript{3}C\textsubscript{6}H\textsubscript{4}</td>
<td>7f, 57%</td>
</tr>
<tr>
<td>5</td>
<td>6g, p-ClC\textsubscript{6}H\textsubscript{4}</td>
<td>7g, 80%</td>
</tr>
<tr>
<td>6</td>
<td>6h, p-BrC\textsubscript{6}H\textsubscript{4}</td>
<td>7h, 76%</td>
</tr>
<tr>
<td>7</td>
<td>6i, p-CH\textsubscript{2}SC\textsubscript{6}H\textsubscript{4}</td>
<td>7i, 65%</td>
</tr>
<tr>
<td>8</td>
<td>6j, p-CF\textsubscript{3}C\textsubscript{6}H\textsubscript{4}</td>
<td>7j, 62%</td>
</tr>
<tr>
<td>9</td>
<td>6k, m-\text{Bu}OC\textsubscript{6}H\textsubscript{4}</td>
<td>7k, 59%</td>
</tr>
<tr>
<td>10</td>
<td>6l, p-NCC\textsubscript{6}H\textsubscript{4}</td>
<td>7l, 78%</td>
</tr>
<tr>
<td>11</td>
<td>6m, m,m'-diCH\textsubscript{2}OC\textsubscript{6}H\textsubscript{4}</td>
<td>7m, 67%</td>
</tr>
<tr>
<td>12</td>
<td>6n, p-Ac\textsubscript{6}NC\textsubscript{6}H\textsubscript{4}</td>
<td>7n, 72%</td>
</tr>
<tr>
<td>13</td>
<td>6o, benzyl</td>
<td>7o, 61%</td>
</tr>
<tr>
<td>14</td>
<td>6p, n-butyl</td>
<td>7p, 62%</td>
</tr>
<tr>
<td>15</td>
<td>6q, cyclopropyl</td>
<td>7q, 56%</td>
</tr>
</tbody>
</table>

Isolated yield from reaction of 6 (1 equiv., 0.2 mmol), p-trifluoromethylphenyl diazonium tetrafluoroborate 2c (2 equiv., 0.4 mmol, 104 mg) and base (2 equiv., 0.4 mmol, 93 mg) under nitrogen in dry, degassed DMSO (0.2 M, 1 mL). PMP = p-methoxyphenyl.

N-Alkyl ureas were likewise cyclized successfully to the triamine derivatives 7o-q, though yields were slightly lower, and the products were acid-sensitive. Azocycloamination of carbamates allows the use of allylic alcohols as precursors of diamino alcohol derivatives, and a series of N-aryl O-prenyl carbamates 1 were made and treated under the same reaction conditions (Scheme 2). These carbamates also cyclized successfully to products 4, 8, 9 and 10, with the best yields being obtained from substrates with electron-rich N-substituents. Cyclohexane-containing products 11 and 12 could be obtained in moderate yields. Among mono- and disubstituted alkenes, only a,a-disubstituted crotyl carbamates gave a product, as a mixture of isomers. These isomerised to the single hydrazones 13-15 in acid. The carbamate-linkage was not essential: easily accessible 2-alkenyl benzamide 16 gave isoindolinone 17 in good yield.\textsuperscript{13}

Deprotection of the acid-sensitive products required stepwise partial neutral reduction to the hydrazine followed by hydrazine cleavage with acid (Scheme 3). 18, 20 and 21 were isolated after a Boc- or Ts-protection. Basic hydrolysis of 18 gave the diamino-alcohol 19; CAN-mediated deprotection of 21 gave the urea 22.

Scheme 2. Extended substrate scope of the diamination. Yields of isolated products. PMP = p-methoxyphenyl.

Scheme 3. Deprotection of the products, see supporting information for details.  (i) Pd/C, H\textsubscript{2}, MeOH, then HCl\textsubscript{aq} (ii) N\textsubscript{2}, TsCl, DCM; (iii) NaOH, EtOH; (iv) K\textsubscript{2}CO\textsubscript{3}, Boc\textsubscript{2}O, DCM/H\textsubscript{2}O; (v) cerium ammonium nitrate, MeCN/H\textsubscript{2}O. PMP = p-methoxyphenyl.
The mechanism of the reaction was investigated using the reaction between 6c and 2c as a model (see full details in the supplementary information). When the reaction in Table 3 entry 1 was performed in the presence of 2 equiv. 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO), the only product was 6c and its derivatives, with only small amounts of 4-trifluoromethylphenol, within 3 h. This reaction occurred even more rapidly in the presence of a urea lacking an alkene (1,3-bis(4-methoxyphenyl)-1-methylurea: see supporting information). These experiments are consistent with the initiation step of the reaction being base-mediated decomposition of 2c to the corresponding aryl radical, with the diazonium salt and/or the aryl radical interacting with the urea, by electron transfer, hydrogen atom abstraction or charge transfer.

Cyclic voltammetry in DMSO using Bu₄NPF₆ as electrolyte revealed that NaPO₃(OBu)₂ is not redox active within the solvent's electrolysis range, and diazonium salt 2c has a reduction potential of −0.33 V vs Ag⁺/Ag (0.170 V open circuit potential) which does not change upon addition of base. The urea starting material 6c has an oxidation potential of 1.21 V, decreasing to 1.06 V in the presence of 3.8 equivalents of base, in line with Knowles’ previous reports.[6]

Radical addition of an amidyl radical onto an olefin, and radical addition of a tertiary alkyl radical onto a diazonium ion are both precedent, as discussed above. Remarkably, cyclic voltammetry experiments showed that product 7c has a first oxidation potential of 1.26 V, which is higher than that of 6c in the absence or presence of base. Thus, ‘hole catalysis’ appears to be responsible for the propagation of the reaction: a radical cation intermediate resulting from the addition onto 2c oxidizes a molecule of 6c to generate the product and an amidyl radical intermediate ready for cyclization.[17] We therefore propose that the reaction follows the mechanism depicted in Scheme 4.

In conclusion, the use of diazonium salts as both oxidants and radical acceptors leads to a new transition metal-free azocycloamination reaction of prenyl carbamates and ureas by intramolecular radical attack of an amidyl radical on an alkene. The dianimation tolerates a range of functional groups, and generally proceeds in high yields, provided the amidyl radical bears an N-aryl substituted carboxylic acid. The reaction is atom-efficient and easy to perform, and the products are obtained in short reaction times under concentrated conditions. Cyclic voltammetry identified a likely reaction mechanism involving proton-coupled hole catalysis, with a visible light-promoted dianimation reaction providing an alternative method for otherwise unreactive substrates. Further ground state electron-transfer promoted reactions involving ureas are under investigation and will be reported in due course.

Acknowledgements

We thank Gaël Gobaille-Shaw and Prof. David Fermin for assistance with cyclic voltammetry experiments. The work was supported by the Deutsche Forschungsgemeinschaft (research fellowship LE 3853/1-1 to QL), and the EPSRC Centre for Doctoral Training in Catalysis.

Keywords: amination • carbamate • diazonium salt • radical chemistry • urea
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[13] A diastereoselective cyclisation was achieved using a sulfonamide auxiliary; see supporting information.

[14] The formation of a charge-transfer complex was difficult to investigate by UV-Vis spectroscopy due to the formation of highly colored unidentified decomposition products derived from 2e.


Entry for the Table of Contents (Please choose one layout)

Layout 1:

Arenediazonium salts promote the azocycloamination of prenyl carbamates and ureas by acting both as oxidant and radical trap in a mild, metal-free and redox-neutral cascade sequence.

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