Synthesis of Hindered \( \alpha \)-Amino Carbonyls: Copper-Catalyzed Radical Addition with Nitroso Compounds

David J. Fisher, G. Leslie Burnett, Rocío Velasco, and Javier Read de Alaniz*  
Department of Chemistry & Biochemistry, University of California, Santa Barbara, California 93106, United States  
3 Supporting Information

ABSTRACT: The synthesis of sterically hindered anilines has been a significant challenge in organic chemistry. Here we report a Cu-catalyzed radical addition with in situ-generated nitroso compounds to prepare sterically hindered amines directly from readily available materials. The transformation is conducted at room temperature, uses abundant copper salts, and is tolerant of a range of functional groups.

The construction of carbon–nitrogen bonds using alkylation,1 amine–carbonyl reductive amination,2 C–N cross-coupling,3 and electrophilic amination4 has been extensively explored over the past several decades. This synthetic effort has been fueled by the prevalence of nitrogen-based functional groups in natural products and pharmaceutically relevant agents. Of these compounds, sterically hindered anilines are of particular importance in medicinal chemistry because these groups are known to improve the lipophilicity and metabolic stability of drug molecules.5 Despite these advantageous properties, incorporation of sterically hindered anilines in medicinal chemistry remains a noteworthy challenge.

Compounds containing sterically hindered anilines generally fall into two categories (Figure 1): anilines bearing \( \alpha \)-substituted alkyl groups6 (1 and 3) and \( \alpha \)-amino carbonyl compounds with N-containing quaternary stereocenters7 (2 and 4). Thus, different approaches are generally used to access these types of structural motifs. The most common strategy to generate these scaffolds relies on methods that construct the N-aryl bond by arylation of an amine derivative (Figure 1a). Initially, these transformations relied heavily on highly reactive organometallic reagents.8 More recently, however, a number of milder methods for the synthesis of hindered anilines have been reported. For example, Lalic reported an elegant approach using the copper-catalyzed coupling of arylboronic esters with O-benzoyl hydroxylamines,9 and Buchwald recently reported the use of rational ligand design for the arylation of hindered primary amines.10 Although less developed, a powerful method used for the synthesis of \( \alpha \)-amino carbonyl compounds bearing hindered anilines is electrophilic amination with aryl nitroso compounds (Figure 1b). Despite progress, this approach suffers from several drawbacks: (1) the reduced reactivity of aryl nitroso compounds requires the use of tin enolates11 or activated carbonyl compounds,12 and (2) the N- vs O-regioselectivity is often difficult to control.13

In considering a means to develop a general and practical strategy for the synthesis of sterically hindered amines, we were drawn to the potential use of radical transformations with nitroso compounds. Although nitroso compounds have been used for decades in radical reactions, e.g., as spin-trapping agents, surprisingly, their use in synthesis remains rare.14 However, Baran and co-workers recently described a very general approach for the synthesis of amines by merging radical reactions with nitrosoarene compounds.15 This methodology is of particular relevance to our work and has prompted us to disclose our results.

Given the importance of sterically hindered anilines in medicinal chemistry and the difficulties associated with their synthesis, we sought to develop a new method that was mild, practical, and highly functional-group-tolerant. Here we describe our initial efforts in this area using a copper-catalyzed radical addition with aryl nitroso compounds to access sterically hindered \( \alpha \)-amino carbonyl compounds. This new process can be conducted at room temperature, uses readily available starting materials, and employs an abundant copper salt as a catalyst.

Received: July 27, 2015  
Published: August 28, 2015
Our recent work on photocontrolled atom transfer radical polymerization (ATRP) led us to explore the coupling between alkyl halides and nitrosobenzene. We were particularly drawn to the Cu-based catalysts used in the mechanistically related radical-trap-assisted atom transfer radical coupling (ATRC), in which Cu(I) catalysts can propagate radical reactions between two functionalized polymer chain ends and a radical trapping agent such as nitrosobenzene by undergoing single electron transfer with alkyl halides. The key step in ATRC is the formation of a persistent nitroxyl radical, which is stable enough to steer the reaction away from unwanted radical side reactions such as disproportionation and radical–radical coupling. The persistent radical enables efficient coupling between two polymer chain ends.

With this in mind, we began by studying the reaction of ethyl α-bromoisobutyrate (5) and nitrosobenzene (6) in tetrahydrofuran (THF) (eq 1). Using standard stoichiometric Cu(0) ATRP conditions and introducing Sm-mediated reduction of the N−O adduct afforded the desired amine 7 in 87% yield. Even though copper is abundant and inexpensive, we sought to render the reaction catalytic; an ongoing challenge in the field of metal catalysis is lowering the catalyst loading and/or removal of residual metals. The significance of this arises in part from the known toxicity of metal salts and the cost of removal from late-stage target compounds. Although the catalyst loading for ATRP can be decreased using reducing agents that regenerate Cu(I) in situ, such as glucose, tin(II) 2-ethylhexanoate, ascorbic acid, and zero-valent metals including Cu, Zn, Mg, and Fe, we envisaged that an unexplored yet practical redox-neutral alternative could be utilized (Figure 2).

By replacement of the nitrosoarene with an N-aryl hydroxylamine, the Cu(I) necessary for the formation of the carbon centered radical A could be regenerated via Cu(II)-catalyzed oxidation of the N-aryl hydroxylamine. This would result in the formation of nitrosoarene B, the radical trapping species. Radical addition would then form the persistent nitroxyl radical, which could subsequently undergo another radical addition to form 10.

To this end, we conducted the reaction using 5 mol % CuCl₂ as the catalyst and phenylhydroxylamine as the nitroso precursor (see Table S1 in the Supporting Information (SI)). Unfortunately, with this redox-neutral protocol only a trace amount of amine 7 was isolated. However, the low yield was due to a competitive condensation reaction between the in situ-generated nitrosobenzene and excess phenylhydroxylamine, a good nucleophile. To our gratification, further optimization revealed that slow addition of phenylhydroxylamine (5 h) and increasing the amount of the ligand, pentamethyldiethylenetriamine (PMDTA), from 0.5 to 1.8 equiv resulted in the formation of 7 in 73% yield.

With a general catalytic protocol in place (5 mol % CuCl₂, 1.8 equiv of PMDTA, room temperature, THF), we next set out to demonstrate the broad applicability of this new approach for a library of α-bromocarbonyl compounds. Various esters and amides were reacted with phenylhydroxylamine under the optimized reaction conditions to generate the α-amino adducts in excellent yields (Table 1). It is worth noting that modifications to the addition rate (5 to 10 h) of the phenylhydroxylamine were necessary to obtain good yields with the amide-derived α-bromocarbonyl compounds because of their decreased reactivity compared with the corresponding

---

Table 1. Scope of the α-Bromocarbonyls

<table>
<thead>
<tr>
<th>α-Bromocarbonyl</th>
<th>Isolated yield (in %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>8 R=CH₂, R’=H, Ar</td>
<td>73%</td>
</tr>
<tr>
<td>12 R=CH₂, R’=H, Ar</td>
<td>87%</td>
</tr>
<tr>
<td>13 R=CH₂, R’=H, Ar</td>
<td>73%</td>
</tr>
<tr>
<td>14 R=CH₂, R’=H, Ar</td>
<td>50%</td>
</tr>
<tr>
<td>15 R=CH₂, R’=H, Ar</td>
<td>70%</td>
</tr>
<tr>
<td>16 R=CH₂, R’=H, Ar</td>
<td>73%</td>
</tr>
<tr>
<td>17 R=CH₂, R’=H, Ar</td>
<td>50%</td>
</tr>
<tr>
<td>18 R=CH₂, R’=H, Ar</td>
<td>63%</td>
</tr>
<tr>
<td>19 R=CH₂, R’=H, Ar</td>
<td>21%</td>
</tr>
<tr>
<td>20 R=CH₂, R’=H, Ar</td>
<td>95%</td>
</tr>
<tr>
<td>21 R=CH₂, R’=H, Ar</td>
<td>51%</td>
</tr>
</tbody>
</table>

---

1Isolated yields based on 8 as the limiting reagent are shown. The reaction conducted with stoichiometric amounts of Cu(0) and nitrosobenzene was used (see the SI). See the SI for details.
meta position with electron-donating or electron-withdrawing groups delivered the desired products 28–33 in excellent yields. Both α-bromo amides and esters are compatible with the different N-aryl hydroxylamines.

To illustrate the utility of this catalytic method for the preparation of biologically active hindered amine molecules, we applied it to the synthesis of 35 (Scheme 1), a precursor of the 4-anilidopiperidine class of opioid analgesics that includes carfentanil (2), which is a veterinary sedative for large animals, and remifentanil, a general anesthetic.25 The most common method to prepare carfentanil and its analogues (see the SI) relies on harsh acidic and basic conditions as well as high temperatures that force the use of protecting groups and reduce the efficiency of the overall process.26 With the radical-based approach using α-bromocarbonyl 34, available in one step from readily available materials, and in situ-generated nitroso compounds (Scheme 1a), the reaction can be conducted at room temperature, is high-yielding, and is compatible with acid-labile protecting groups such as tert-butoxycarbonyl (Boc). This useful handle would allow for the synthesis of carfentanil derivatives that often vary at the piperidine nitrogen.27 Moreover, this approach provides entry into the late-stage construction of N-containing quaternary stereocenters, which provides new opportunities for medicinal chemists that were previously difficult. To further explore the utility of the Cu-catalyzed radical addition with arylnitroso compounds, we synthesized 39 (Scheme 1b), a precursor of 4. In this case, we chose to highlight the compatibility with aryl bromides, where a late-stage cross-coupling reaction could be used to access the biaryl found in 4.

In summary, we have developed a general method for the construction of α-amino carbonyl compounds containing sterically hindered anilines. This transformation occurs under mild conditions, uses inexpensive copper salts, and allows the conversion of simple starting materials to complex products containing nitrogen quaternary stereocenters in high yields. The reaction tolerates a range of functional groups such as aryl halides, alkynes, alkenes, amides, esters, and unprotected alcohols, and we anticipate that this methodology will find widespread application in both academia and industry.

Table 2. Scope of the N-Aryl Hydroxylamines6

| R1 | R2 | R3 | R4 | Ar | O     | H | Br | OH | N     | α-Boc | H | α-Boc | N     | R5 | R6 | Br | OH | N     | α-Boc | H | α-Boc | N     | 5 mol % CuCl2; 1.8 equiv PMDTA, THF, rt, then SmI2 | a | b |
|----|----|----|----|----|------|---|----|----|------|------|---|------|------|----|----|----|----|------|------|---|------|------|
| O  | H  | Br | OH | N  | α-Boc | H | α-Boc | N  | R5   | R6   | Br | OH | N  | 8   | 1.0 equiv | 0.6 equiv | then SmI2 | 11   | 5 | 34   | 35 | 12  | 87% | 87% | 9  | 11  | 11  | 9  | 87% | 87% | 9  | 11  | 11  | 9  | 87% | 87% |
| O  | H  | Br | OH | N  | α-Boc | H | α-Boc | N  | R5   | R6   | Br | OH | N  | 28  | 84% | 84% | 29  | 91% | 91% | 30  | 95% | 95% | 31  | 90% | 90% | 32  | 88% | 88% | 33  | 72% | 72% |

Isolated yields based on 8 as the limiting reagent are shown.

Scheme 1. Synthetic Applications6

a) Synthesis of carfentanil derivative

b) Synthesis of cathepsin K inhibitor derivative

Conditions: (a) 5 mol % CuCl2, 1.8 equiv PMDTA, THF, rt, then SmI2 (b) 1.6 equiv of phenylboronic acid, 6 mol % Pd(PPh3)4, 2 equiv of K2CO3, dioxane, H2O.
Supporting Information
The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b07860.

Experimental procedures, supporting data, and 1H and
13C NMR spectra (PDF)

AUTHOR INFORMATION
Corresponding Author
*javier@chem.ucsb.edu

Notes
The authors declare no competing financial interest.

ACKNOWLEDGMENTS
Financial support from UCSB and Amgen is gratefully acknowledged. D.J.F. is thankful for a Mellichamp Sustainability Fellowship, and R.V. thanks Junta de Castilla y León and Fondo Social Europeo for a PIRITU Fellowship. NMR instrumentation was supported by NIH Shared Instrumentation Grant 1S10OD012077-01A1.

REFERENCES