Communication

Synthesis of Hindered #-Amino Carbonyls: Copper-Catalyzed Radical Addition with Nitroso Compounds

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Synthesis of Hindered α-Amino Carbonyls: Copper-Catalyzed Radical Addition with Nitroso Compounds

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Supporting Information Placeholder

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 amination[4] 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 α-substituted alkyl[6] (**1** and **3**) and α-amino carbonyl compounds with N-containing quaternary stereocenters[7] (**2** and **4**). As such, 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 using an arylation of an amine derivative (Figure 1a). Initially, these transformations relied heavily on highly reactive organometallic reagents.[8] However, more recently 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 aryl boronic esters with *O*-benzoyl hydroxylamines[9] and recently Buchwald 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 α-amino carbonyl compounds bearing hindered anilines is electrophilic amination with arylnitroso compounds (Figure 1b). Despite progress, this approach suffers from several drawbacks: (1) the reduced reactivity of arylnitroso compounds requires the use of tin enolates[11] or activated carbonyl compounds;[12] (2) the N- vs. O-regioselectivity is often difficult to control.[13]

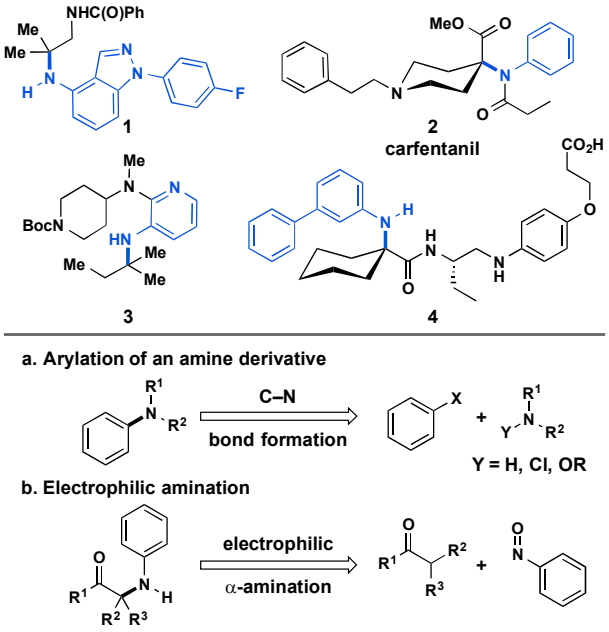


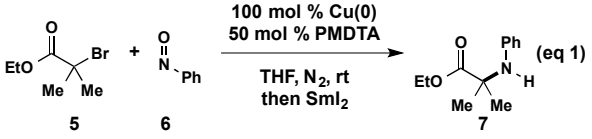
Figure 1. Examples of sterically hindered amines and strategies for their preparation.

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 such as spin trapping agents, surprisingly, their use in synthesis remains rare.[14] However, Baran and coworkers 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 prompts 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. In this communication, we describe our initial efforts in this area using a copper-catalyzed radical addition with aryl nitroso compounds to access sterically hindered α-amino carbonyl compounds. This new process can be conducted at room temperature, uses readily available starting materials, and an abundant copper salt as a catalyst.

Our recent work on photocontrolled atom transfer radical polymerization (ATRP) led us to explore the coupling between alkyl halides and nitrosobenzene.[16] 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.[17] The key step in ATRC is the formation of a persistent nitroxyl radical,[18] 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 the 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 THF (eq 1). Using standard stoichiometric Cu(0) ATRP conditions[19] and introducing Sm-mediated reduction of the N–O adduct, the desired amine **7** was isolated 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 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,[20] ascorbic acid,[21] and zerovalent metals including Cu, Zn, Mg, and Fe,[22] we envisaged that an unexplored, yet practical redox-neutral alternative could be utilized (Figure 2). By replacing the nitrosoarene with an *N*-aryl hydroxylamine, the Cu(I) necessary for the formation of the carbon centered radical (**A**) could be regenerated via a Cu(II)-catalyzed oxidation of *N*-aryl hydroxylamine. This would result in the formation of nitrosobenzene (**B**), the radical trapping species. Radical addition would then form the persistent nitroxyl radical that could subsequently undergo another radical addition to form **10**.

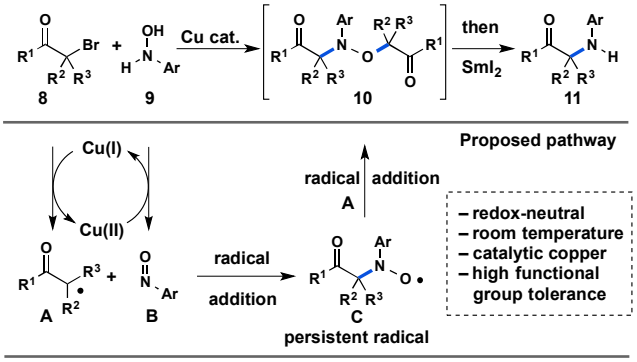


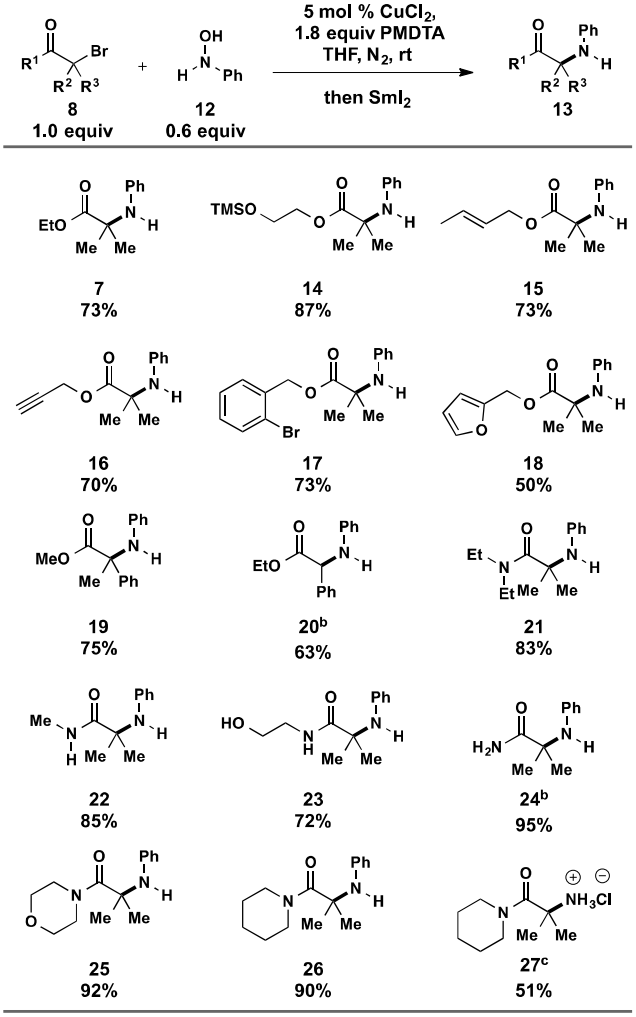
Figure 2. Proposed Cu-catalyzed radical addition with in situ generated nitroso compounds.

To this end, we conducted the reaction using 5 mol % $CuCl_2$ as the catalyst and phenylhydroxylamine as the nitroso precursor (see ESI Table S1). Unfortunately, using 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 equivalents of the ligand pentamethyldiethylenetriamine (PMDTA) from 0.5 to 1.8 resulted in the formation of **7** in 73% yield.

With a general catalytic protocol in place (5 mol % $CuCl_2$, 1.8 equiv of PMDTA, rt, 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 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 due to their decreased reactivity compared to the corresponding esters. The mild reaction conditions and radical nature of this transformation translate to a high degree of functional group compatibility. For example, the acid labile TMS protecting group was well tolerated, affording the desired product (**14**) in 87% yield. Compounds bearing an alkene or terminal alkyne, such as **15** and **16**, were also compatible. The Cu(I)/PMDTA complex selectively reduced the α-bromo-carbon bond in the presence of an aryl bromide (**17**), enabling the synthesis of sterically hindered anilines that could be used in subsequent cross-coupling reactions. The reaction could be used to rapidly access racemic N-containing quaternary stereocenters (**19**) in good yield (75%). Unprotected alcohols and amides are well tolerated (**22**–**24**), eliminating the need to use protecting group chemistry. Of note, Weinreb amides result

in the direct formation of the methyl amide (**22**) because the N–O bond of the Weinreb amides are also reduced by SmI_2. Presumably, other reduction conditions could be used to avoid this reduction if necessary. Alternatively, the morpholine amide could be used as a Weinreb amide surrogate and in this case a 92% yield of the desired product was isolated.[23]

Table 1. Scope of the α-bromocarbonyls.

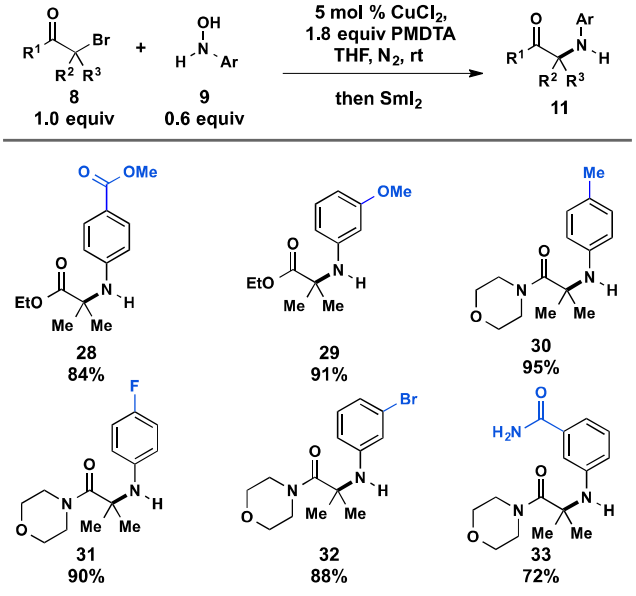


[a] Isolated yields calculated based on **8** as the limiting reagent. [b] Reaction conducted with stoichiometric amounts of Cu(0) and nitrosobenzene was used (see ESI). [c] See ESI for details.

While the catalytic copper conditions proved general, stoichiometric copper conditions were advantageous with α-bromophenylacetate **20** and the primary α-bromo amide **24**. For **20** a 38% yield was obtained using the catalytic conditions and for **24** the stoichiometric conditions were required because the activation of the free amide was prohibitively slow with the catalytic conditions. Finally, this methodology can be used to access the primary amine (**27**) in good yield. In this case commercially available 2-methyl-2-nitrosopropane was used, which can be deprotected using methanesulfonic acid (see ESI for details). This is noteworthy because this scaffold could serve as a valuable building block for non-aniline derived sterically hindered amines.

Having demonstrated the initial scope of the reaction with a variety of α-bromocarbonyl compounds, we focused our efforts next on the incorporation of different *N*-aryl hydroxylamines (Table 2).[24] Phenylhydroxylamines substituted at the *para*- and *meta*-position with electron donating and electron withdrawing groups deliver the desired product in excellent yield **28**–**33**. Both α-bromo amides and esters are compatible with the different *N*-aryl hydroxylamines.

Table 2. Scope of the *N*-aryl hydroxylamines.

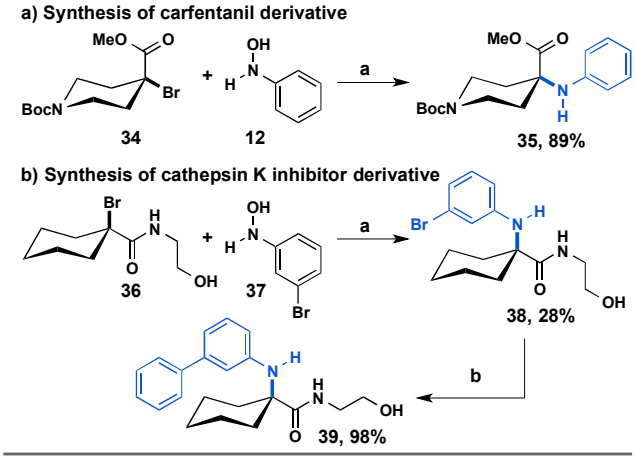


[a] Isolated yields calculated based on **8** as the limiting reagent.

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 to the 4-anilidopiperidine class of opioid analgesics that include 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 analogs (see ESI), 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] Using a radical-based approach with α-bromocarbonyl **34**, available in 1-step from readily available material, 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 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 the 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 arylbromides, where a late-stage cross-coupling reaction could be used to access the biaryl found in **4**.

Scheme 1. Synthetic Application



a) 5 mol % $CuCl_2$, 1.8 equiv PMDTA, THF, rt, then SmI_2. b) 1.6 equiv phenylboronic acid, 6 mol % $Pd(PPh_3)_4$, 2 equiv K_2CO_3, dioxane, H_2O.

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.

ASSOCIATED CONTENT

Supporting Information. Experimental procedures, supporting data and ^1H and ^{13}C NMR. This material is available free of charge via the Internet at http://pubs.acs.org

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The authors declare no competing financial interests.

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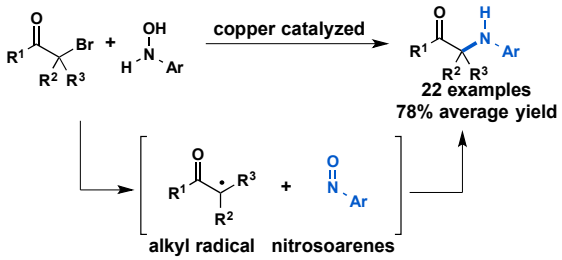
copper catalyzed
22 examples
78% average yield
alkyl radical
nitrosoarenes