RESEARCH ARTICLE

Copper-Catalyzed Carbonylative Cross-Coupling of Alkyl Iodides and Amines

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Abstract: A general copper-catalyzed carbonylative cross-coupling between amines and alkyl iodides is reported. Using a simple combination of catalytic amounts of copper(I) chloride and N,N,N’,N’-pentamethyldiethylenetriamine in the presence of sodium hydroxide under carbon monoxide pressure, a broad range of alkyl iodides and amines can be efficiently coupled to the corresponding amides that are obtained in good to excellent yields. Notable features of this process – the first one relying on a base metal catalyst – include the availability and low cost of the catalytic system, its successful use with primary, secondary, tertiary alkyl iodides and all classes of amines – with no or limited competing nucleophilic substitution without CO incorporation – as well as its efficiency with complex alkyl iodides and amines. Mechanistic studies demonstrated that a radical pathway is operative and the key role of CO.

Introduction

Amides are among the most prevalent building blocks in chemical synthesis and are found in a variety of natural products and bioactive molecules that have a deep impact on human health. The synthesis of amides is thus one of the most widespread processes not only in organic chemistry research laboratories but also from an industrial perspective, finding applications, for example, in the synthesis of bulk chemicals, polymers, agrochemicals or active pharmaceutical ingredients.

They are conveniently prepared from carboxylic acids and amines, a reaction that however requires the preactivation of the acid mediated by a stoichiometric activating agent, generating undesired waste and slowing down atom economy. As a consequence, and due to the importance of amide synthesis, a range of alternative strategies for amide bond formation have been investigated.[7] Among these, the three-component coupling between organic halides, amines and carbon monoxide is one of the most attractive options. Such carbonylative cross-coupling reactions have been extensively developed for the synthesis of benzamides from aryl halides, following pioneering studies reported by Heck in 1974 using palladium catalysts,[8] and various non-noble metal-based catalysts have been shown over the years to efficiently catalyze such processes (Figure 1a).[9] In sharp contrast, they are still underdeveloped in the alkyl series, notably due to competing direct nucleophilic substitution without CO incorporation, β-hydride elimination or metal migration in alkyl-metal complexes, as well as double insertion of carbon monoxide.[9] CO being moreover a strong π-acidic ligand, it typically hampers the oxidative addition of the metal complexes onto the C(sp^2)-X bond.

While the feasibility of radical carbonylative cross-coupling reactions between amines and alkyl iodides has however been demonstrated, with pioneering studies from the Ryu group,[9] they require either the use of toxic and hazardous radical initiators[2] or a palladium–iridium–based catalyst in the presence of a light source (Figure 1b).[8] Major limitations still remain in terms of applicability and cost-efficiency. Despite a gain in interest in recent years due to the higher natural abundance and generally lower toxicity of first row transition metal complexes,[7] there is a strong need for alternative processes based on base metal catalysts associated with simple ligands,[9] which remain untapped for this application. Meeting this challenge would be of high significance in the many areas in which amides are commonly utilized. Based on our long-standing interest in copper-catalyzed cross-coupling[9] and radical[10] reactions, and inspired by the seminal work of the Mankad[11] group on the copper-catalyzed aminocarbonylation of alkyl iodides with nitroarenes and related alkoxy carbonylation reactions,[12] we envisioned that the proper combination of a copper(I) source and a ligand – which has to form a complex stable enough to avoid its displacement with excess carbon monoxide – facilitating the single electron activation of the starting alkyl iodide could promote the carbonylative cross-coupling between amines and alkyl iodides (Figure 1c).[13,14] We report in this manuscript the development of such a process and its broad applicability, notably with complex substrates.[15]

Figure 1. Carbonylative cross-coupling of organic halides and amines: state-of-the-art and current work.
Results and Discussion

Based on this working hypothesis, we initiated our studies by a systematic screening of the influence of the different reaction parameters using iodocyclohexane 1a and morpholine 2a as model substrates. First trials gratifyingly led to the formation of the desired amide 3a and revealed the superiority of copper(I) chloride as the copper source, sodium hydroxide as the base, in 1,4-dioxane or THF at 0.1 M, the crude reaction mixture being cleaner in the former, for 15 hours at 70 °C and under a 5 bar pressure of carbon monoxide (see Supporting Information, Tables S1-S4). As a note, the reaction still proceeds with a reduced pressure of carbon monoxide, but with a diminished efficiency (66% NMR yield - see Supporting Information, Table S4), which might be however interesting for some applications. In this perspective, solid sources of carbon monoxide (Mo(CO)₆, W(CO)₆ and Co₂(CO)₉) were also evaluated but the carbonylated product 3a was not observed under these conditions. Notably, the choice of sodium hydroxide was crucial for the reaction to efficiently proceed and an excess of this base is required for the reaction to efficiently proceed, certainly due to its limited solubility in 1,4-dioxane. The influence of the ligand on the carbonylative cross-coupling reaction was next evaluated using a series of representative ligands for copper including NHCs, bipyridine and polyamines, most of these ligands being known to facilitate copper-catalyzed atom transfer radical polymerization (ATRP) and cyclization (ATRC) reactions. Results from this study are shown in Figure 2.

Interestingly, apart from IMes NHC precursor 1,3-bis(2,4,6-trimethylphenyl)imidazolium chloride L₁, all the ligands we tested afforded the carbonylated cross-coupling product 3a in yields higher than 70% (Figure 2). The carbonylative coupling can indeed be promoted by NHCs (L₃, L₅), bipyridine (L₄) as well as bidentate (L₆-L₉), tridentate (L₅, L₇, L₈) and tetradentate (L, L₇, L₉) polyamines. Even if 1,3-bis(sopropyl)imidazolium chloride L₁ led to the best result (96% NMR yield), PMDETA L₁, which displayed similar performances (93% NMR yield) while being significantly cheaper, was selected as the ligand of choice since it offers the best compromise between performance, availability, and cost.

Control experiments revealed that the presence of copper(I) chloride and the base were essential for the reaction to proceed while in the absence of ligand, the carbonylative coupling was still operative, despite a reduced efficiency, the starting amine and/or carbon monoxide acting both as (a) ligand(s) and reactant(s) in this case. Importantly, potential contamination with traces of palladium was ruled out since a similar efficiency was obtained with ultra-high purity reactants and solvents.

In an effort to further optimize the reaction conditions, the catalytic loading could be reduced to 5 mol% of both CuCl and PMDETA without affecting the yield and the excess of cyclohexyl iodide could be reduced to 1.2 equivalents with similar efficiency, amide 3a being obtained in 93% NMR yield and 91% isolated yield (Figure 2).

With these optimized conditions in hands, we then moved to the study of the scope and limitations of this copper-mediated carbonylative cross-coupling reaction, first focusing on the influence of the starting alkyl iodide 1, using morpholine 2a as the model amine. Results from this study, shown in Figure 3, reveal the generality and rather broad scope of this copper-catalyzed aminocarbonylation. Secondary alkyl iodides were indeed readily transformed to the corresponding amides 3a-h in good to excellent yields, except in the case of 4-iodotetrahydro-2H-pyran which failed to undergo the cross-coupling to 3l. The reaction was moreover found to be

![Figure 2. Validation of the working hypothesis and ligand screening. NMR yields determined by ¹H NMR analysis of crude reaction mixtures using 1,1,2,2-tetrachloroethane as internal standard. Py: 2-pyridyl.](image)

![Figure 3. Scope of the copper-catalyzed aminocarbonylation with representative alkyl iodides. * At 0.1 M.](image)
highly diastereoselective when starting from an iodide derived from (-)-menthol, 3d being obtained as a single diastereoisomer, and no products resulting either from direct nucleophilic substitution or double insertion of carbon monoxide could be detected in crude reaction mixtures. To our delight, even challenging tertiary alkyl iodides were found to be suitable reaction partners, although with reduced efficiency, as illustrated with the synthesis of 3j and 3k that could be obtained in 39% and 48% yields, respectively. As for primary alkyl iodides, although they still afforded the corresponding amides 3m-p, their carbonylation cross-coupling was more sluggish and the yields were found to be in the lower range. In the case of highly reactive perfluorooctyl iodide, the competing direct nucleophilic substitution could not be suppressed and amide 3l was thus not obtained. As a note, cyclohexyl bromide was found to be unreactive under the reaction conditions, which is in line with its more challenging activation by both single or two electron processes, and an attempt to perform an in situ retro-Finkelstein reaction with additional sodium iodide failed.

We next moved to the study of the influence of the amine on the copper-catalyzed aminocarbonylation, using this time iodocyclohexane 1a as the reference alkyl electrophile. As highlighted by results collected in Figure 4, a broad range of primary and secondary amines, including cyclic and acyclic ones, could be efficiently utilized, the corresponding amides 3q-3s being obtained in good to excellent yields in most cases. Sterically hindered amines such as tert-butylamine or adamantlylamine were shown to be suitable reaction partners, the corresponding amides 3ah and 3ai being obtained in 79% and 61% yields, respectively. Even a poorly nucleophilic amine such as 2,2,2-trifluoroethylamine was readily transformed, amide 3u being isolated in 73% yield, and a range of functional groups including aryl groups (3s-t, y, z, a), an alkene (3x), a cyclopropane (3j), a silyl ether (3v), and a ketel (3w) were tolerated, the last one however giving a lower yield most certainly due to partial hydrolysis. Heteroarenes such as a pyridine (3ab), an indole (3ac) or a pyrrole (3ad) were shown to be compatible with our reaction conditions, the former yielding to a much lower yield however, which can be attributed to a competing coordination to the copper-based catalyst, and the presence of heterocyclic systems on the starting amine such as a piperidine (3ae) or a morpholine (3af) was also tolerated. Importantly, an aryl bromide (3e) or chloride (3aa) was not activated, which provides interesting opportunities for post-functionalization and diversification. Primary and secondary amines performed equally well and competing dehydrogenation of the starting amine was never observed.\[18\]

Importantly, the aminocarbonylation could be extended to less nucleophilic anilines, however with a more pronounced impact on the reactivity and a greater substrate-dependence. Indeed, while aniline and electron-rich anilines were aminocarbonylated to the corresponding amides 3as, 3au and 3av in fair yields, the use of an electron-poor aniline such as p-cyano-aniline or N-methyl-aniline resulted in lower yields of 8% (3at) and 22% (3ax), respectively. In addition to chelating amines such as aminoethanol, cysteamine, β-alanine, histamine, isoleucinamide or 4-aminopyridine, which could definitely poison the copper-based catalyst, this represents the main limitation of our copper-catalyzed carbonylation cross-coupling with respect to the amines that can be utilized. Importantly, the reaction is not limited to the small scale used for the scope and limitation studies since the
copper-catalyzed coupling of 1a, 2a and CO could be efficiently performed on a 3 gram scale, amide 3a being isolated in 77% yield, in a virtually pure form, upon simple filtration and concentration under reduced pressure. In an attempt to push further the limits of our copper-catalyzed carbonylative cross-coupling of alkyl iodides and amines and evaluate its efficiency in “real life” situations, the reaction with complex amines or iodides was next envisioned. As highlighted in Scheme 1, L-proline ester 2b could be successfully coupled with cyclohexyl iodide 1a under our standard conditions to afford amide 3ay in 67% yield and with only a slight erosion of the optical purity, even when the reaction time was extended to 3 days. An even higher efficiency was obtained for the carbonylative coupling of N-aryl-piperazine 2c, the corresponding amide 3az being obtained in 87% yield, here again without competing direct nucleophilic substitution or double insertion of carbon monoxide. The reaction is moreover amenable to the carbonylation of natural product or natural-product-derived amines or iodides, as illustrated with the synthesis of abietylamine or estradiol-derived amides 3ba and 3bb, complex amides that could be obtained in 73% and 33% yields, respectively, the lower yield obtained for the latter being certainly due to the limited stability of 1b and the diastereoselectivity arising from preferential aminocarbonylation on the least hindered face.

\[ \text{MeO}_2\text{C} + \text{HN-} + \text{CO} \rightarrow \text{MeO}_2\text{C}-\text{CO}\text{HN} \]

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Scheme 1. Scope of the copper-catalyzed aminocarbonylation with complex substrates. With 5 equivalents of sodium hydroxide.

After carefully studying the scope and limitations of this aminocarbonylation reaction, we then attempted to gain some insights into the reaction mechanism, a radical process being a priori operative. The implication of a radical pathway could indeed be unambiguously demonstrated with both the ring-opening observed starting with cyclopropylmethyl iodide 1c yielding unsaturated amide 3bc and the complete inhibition of the reaction in the presence of TEMPO (Scheme 2).

These experiments are clearly in line with a radical pathway. Combined with the reactivity of primary/secondary alkyl iodides that are in agreement with the relative stabilities of the corresponding radical species, the known difficult oxidative addition into C(sp³)-X bonds, and the limited impact of the steric hindrance of the starting amine, the catalytic cycle shown in Figure 5 is most likely involved. It would be initiated by a single electron transfer from a copper(I) complex to the starting alkyl halide 1 generating the corresponding copper(II) complex and the alkyl radical species. Addition of the latter to carbon monoxide would yield a transient acyl radical intermediate that would be next oxidized by the copper(II) complex, closing the catalytic cycle and yielding an intermediate acyl iodide. Its final reaction with the starting amine 2 in the presence of the base, required to trap the equivalent of hydriodic acid released, would then afford the desired carbonylated product 3, this last step involving a highly reactive acyl iodide providing a rationale for the little difference observed in reactivity with sterically hindered amines. Importantly, the intermediacy of this acyl iodide is supported by the reaction of cyclohexanecarbonyl iodide with morpholine and aniline under our reaction conditions, affording the corresponding amides 3a and 3as in 59% and 48% yield, respectively, without detectable amounts of cyclohexanecarboxylic acid that would result from a competing reaction with sodium hydroxide (see Supporting Information for details). These results, which support our overall mechanism, are in line with the higher nucleophilicity of morpholine and aniline compared to the hydroxide anion (\(\text{N}\)morpholine: 15.6\(^{15}\) and \(\text{N}\)aniline: 12.6-13.0\(^{16,17}\) vs \(\text{N}\)OH: 10.5\(^{18,19}\) in the Mayr reactivity scale). As a note, a radical chain pathway cannot be excluded, and the copper(I) complex would in this case act as a smart initiator. Importantly, while Cu(PMDETA) is a common catalyst for ATRP and ATRC,\(^{16,17}\) it cannot be the actual catalytic species in this transformation due to its redox potentials being in disagreement with its ability to reduce uncatalyzed alkyl halides.\(^{20}\) Carbon monoxide might therefore have a dual role in this copper-catalyzed carbonylative cross-coupling reaction, acting not only as a C1 source but also as a key ligand that would facilitate the overall process, CO being known to have a strong impact on Cu(I)/Cu(II) redox potentials.\(^{21}\)
Conclusion

In conclusion, we have reported an efficient and broadly applicable copper-catalyzed carboxylative cross-coupling of unactivated alkyl iodides and amines. Primary, secondary, and tertiary alkyl iodides and primary, cyclic, and acyclic secondary amines as well as anilines were all shown to be suitable reaction partners, affording the corresponding amides in good to excellent yields. A broad range of functional groups were found to be tolerated and the aminocarbonylation of both complex and highly functionalized alkyl iodides further highlights the efficiency of this three-component cross-coupling. In addition to being the first broadly applicable catalytic system for such an aminocarbonylation relying on a base metal, which should have an impact on amide synthesis, notable features include the availability and low cost of the metal source, the ligand as well as the base. Further studies to expand the scope of such carboxylative cross-coupling reactions are underway, notably to elucidate the key role of CO, and will be reported in due course.

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In the case of a less nucleophilic amine such as 4-cyano-aniline, which did only give the corresponding amide 3at in 8% yield (Figure 4), its reaction with cyclohexanecarbonyl iodide under our optimized reaction conditions did only produce the corresponding amide in 61% yield, without a trace of cyclohexanecarboxylic acid. The lower yield obtained for the carbonylative cross coupling of 4-cyano-aniline might thus be a result of both its reduced nucleophilicity and side reactions involving the addition of radical species to this electron-poor aniline.


A general copper-catalyzed carbonylative cross-coupling between amines and alkyl iodides based on a simple combination of catalytic CuCl and PMDETA in the presence of NaOH is reported. Primary, secondary and tertiary alkyl iodides and primary, cyclic and acyclic secondary amines as well as anilines were all shown to be suitable reaction partners, affording the corresponding amides in good to excellent yields. Mechanistic studies demonstrated that a radical pathway is operative and the key role of carbon monoxide.