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Copper-catalyzed Ring-opening C(sp³)–N Coupling of Cycloketone Oxime Esters: Access to 1º, 2º and 3º Alkyl Amines

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A novel copper-catalyzed C(sp³)-N coupling of cycloketone oxime esters with nitrogen nucleophiles has been realized. All of the Naryl/alkylanilines, anilines and benzophenone imine could be employed in this protocol to produce a variety of 1º, 2º and 3º alkyl amines through one or two steps. These resultant cyanocontaining alkyl amines were proven to be versatile synthetic building blocks in a variety of chemical transformations.

The C(sp³)–N formation plays an important role in organic synthesis, as it could offer an efficient access to alkyl amines that are frequently engaged motifs in alkaloids and bioactive molecules.1 The most common method to construct these bonds relies on direct substitution of alkyl electrophiles with nitrogen nucleophiles (Figure 1a).² However, such processes suffer from some limitations including deactivation of nitrogen nucleophiles under the acidic conditions in S_N1 reactions; difficult or even impossible for bulky secondary and tertiary alkyl electrophiles; as well as concomitant elimination or overalkylation. A renaissance was stimulated in exploring effective protocols towards their facile preparations over the past few years, such as reductive amination,³ C(sp³)-H amination⁴ and olefin hydroamination⁵. Recently, transition metal-catalyzed alkylation of nitrogen nucleophiles with alkyl electrophiles has been a promising solution to directly forge the C(sp³)-N bonds.⁶ Despite its success, this method poses two distinct challenges simultaneously: β-hydride elimination from metal alkyl intermediates⁷ and the difficulty in C(sp³)-N reductive elimination⁸. The pioneering work have been successively achieved by Fu & Peters,⁹ Hartwig¹⁰ and Hu¹¹, in which alkyl halides or N-hydroxyphthalimide esters were coupled with carbazoles, amides, aryl/alkyl amines and benzophenone-derived imines. Very recently, MacMillan and co-workers disclosed a decarboxylative C(sp³)-N coupling via dual copper and photoredox catalysis by using iodomesitylene dicarboxylates that generated in situ from the corresponding

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alkyl acids.12 These reactions are featured with a singleelectron transfer (SET) process of alkyl electrophiles to produce the alkyl radical intermediates,¹³ which would recombine with the metal and undergo further reductive elimination. Considering the importance of alkyl amines in the reportire of organic synthesis, searching for supplementary method to construct the $C(sp^3)$ -N bonds and ultimately obtain different types of alkyl amines is deemed worthy of pursuit.



Figure 1. C(sp³)–N coupling of alkyl electrophiles with nitrogen nucleophiles.

Recent advance has demonstrated that the generation of alkyl carbon radical containing a cyano group from C-C bond cleavage of cycloketone oxime derivatives could be achieved by transition metal catalysts (Cu, Ni and Fe)14 or photoredox catalysis¹⁵ via a SET process. This strategy has implemented the construction of $C(sp^3)$ -C and $C(sp^3)$ -Y (Y = O, S, Se, Te, N₃, or B) bonds (Figure 1b).¹⁶⁻¹⁸ In this context, we envisaged that the cycloketone oxime esters might fulfill the engagement to introduce alkyl radical intermediates for the coupling of nitrogen nucleophiles. This idea ultimately led to the discovery of a copper-catalyzed C(sp³)-N coupling of cycloketone oxime

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esters with different nitrogen nucleophiles, which provides an efficient and general access to a variety of 1°, 2° and 3° alkyl amines, together with the assembly of synthetically useful cyano moieties.¹⁹

Table 1. Reaction conditions screening^a

[Cu], solvent ligand, 80 °C Ρh 2a 3a Entry Solvent Yield (%)b Copper Ligand 1 CuI toluene 62 2 Cu(MeCN)₄PF₆ toluene 50 CuTC 3 toluene trace 4 Cu(OTf)₂ 77 toluene 5 Cu(OAc)₂ 70 toluene 6 CuCl₂ 12 toluene 7 Cu(OTf)₂ THF 30 8 Cu(OTf)₂ dioxane 10 9 Cu(OTf)₂ CH₃CN trace 10 Cu(OTf)₂ DCE 45 11 Cu(OTf)₂ toluene PMDTA 74 12 Cu(OTf)₂ toluene 1,10-Phen 81 13 Cu(OTf)₂ Bphen 50 toluene 14^c Cu(OTf)₂ 1,10-Phen 42 toluene 15 1,10-Phen 0 toluene

^{*a*} The reactions were carried out with **1a** (0.4 mmol), **2a** (0.2 mmol), copper salt (15 mol%) and ligand (15 mol%) in solvent (2.0 mL) at 80 $^{\circ}$ C. ^{*b*} Isolated yields. ^{*c*} With K₂CO₃ (1.0 equiv). PMDTA = *N*,*N*,*N*',*N*'',*N*''-pentamethyldiethylenetriamine, Bphen = 4,7-diphenyl-1,10-phenanthroline.

With readily accessible cyclobutanone oxime ester (1a) and diphenylamine (2a) as the model substrates, copper iodide was initially evaluated as the catalyst. As expected, the desired tertiary amine 3a was successfully isolated with 62% yield in toluene at 80 °C (entry 1). A more ionic salt Cu(MeCN)₄PF₆ brought a lower yield (50%, entry 2). However, we observed that copper(I) thiophene-2-carboxylate posed a deleterious effect on the reaction, leading to only trace amount of product (entry 3). Switching the catalyst to copper (II) triflate, pleasingly, afforded the desired product in 77% yield, which outperformed other common copper (II) catalysts (entries 4-6). Concomitantly, solvent effect was shown to be fairly significant in ensuring a satisfactory yield (entries 7-10). Toluene was the best choice. Polar solvents such as acetonitrile completely suppressed the desired reaction, while nonpolar solvent 1,2dichloroethane provided the product in just 45% isolated yield. It merited attention that ligand also proved to be a parameter to affect the developed sequence. The presence of 1,10-phen increased the yield slightly up to 81% (entry 12). In comparison, PMDTA and Bphen had no positive effect on the outcome (entries 11 and 13). When base, such as K₂CO₃ was added into the reaction, the yield was dramatically dropped to 42% (entry 14). In addition, control experiment in the absence of copper catalyst failed to afford any desired product, which showed the importance of copper salt for the transformation

(entry 15). Thus, the standard reaction conditions were submitting the substrates under circumstances consisting of 305 mol% copper (II) triflate and 15 mol% 1,10-phen in toluene at 80 °C.

Table 2. Substrate Scope of Aryl Amines^{a, b}



^o Standard reaction conditions. ^b Isolated yields. ^c Aryl amine **2** (2.0 equiv) and cyclobutanone oxime ester **1a** (1.0 equiv) were used for aniline and its derivatives.

Having established the standard reaction conditions, we explored the substrate scope with a variety of aryl amines 2. As compiled in Table 2, diphenylamine derivatives with electronic diverse substituents (MeO-, Br- and Me-) on the phenyl rings could all react with cyclobutanone oxime ester 1a to give the desired 3º alkyl amines 3b-3d in moderate to good yields, while iminostilbene led to the formation of 3e in 78% yield. This transformation was also compatible with a range of N-alkylanilines, including various N-methylaniline derivatives to produce 3f-3o, and the electronic features on the phenyl ring showed little effect on reactivity. In addition, entities with potentially intractable functional groups, such as bromo, alkene and alkyne moieties (3p-3r) were shown to be well accommodated in this process. Moreover, the cyclic 1,2,3,4tetrahydroquinoline and indoline could also suffer the reaction conditions to give 3º alkyl amines 3s and 3t in 62% and 60% yields, respectively. Similarly, the aniline and its derivatives with electron-deficient phenyl rings were all suitable for the current transformation, and 2º alkyl amines 3u-3x were obtained in good yields. 1-Aminonaphthalene was also tested, which gave product **3y** in an acceptable yield of 33%.

Table 3. Substrate Scope of Cycloketone Oxime Esters^{a, b}

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Cu(OTf)₂ (15 mol%) Bphen (15 mol%) Un Cs₂CO₃ (1.0 equiv) Mn n = 1, 2 toluene, 80 °C 2a 4a, 55% 4b. 50% 4c, 53% R = Me. 4e. 62% X = Cl. 4g. 70%^c 4d, 71% R = ^tBu, 4f, 60%^c X = Br. 4h. 52% Ph R = H, 4j, 51%^d R = 4-Cl, 4k, 53%^d Ph R = 3-OMe, 4I, 55%^d **4i** 83%⁶

 o The reaction were carried out with 1 (0.4 mmol), **2a** (0.2 mmol), Cu(OTf)₂ (15 mol%), Bphen (15 mol%) and Cs₂CO₃ (1.0 equiv) in toluene (2.0 mL) at 80 °C. b Isolated yields. c In the absence of Bphen and Cs₂CO₃. d Standard reaction conditions.

Pressing forward, a range of cycloketone oxime esters were tested to react with diphenylamine (Table 3). The α substituted cyclobutanone oxime esters with diverse functional groups, such as methyl (4a), olefin (4b) and methoxy (4c), could all undergo the desired pathway to deliver corresponding products under modified reaction the conditions. When the cyclobutanone oxime esters with electronic diverse phenyl rings (substituted with alkyl and halides) at para-position were subjected to a simplified procedure with only copper salt, 3º alkyl amines 4d-4h could be obtained. The oxime ester with bis-phenyl installed at paraposition of the cyclic skeleton was shown to be suitable substrate for this transformation, which afforded 4i in 83% isolated yield. It was worth mentioning that this reaction could also be extended to cyclopentanone oxime esters to give 4j-l in moderate yields under standard reaction conditions. However, α -phenyl cyclohexanone oxime ester failed.

Scheme 1. Synthesis of 1º Alkyl Amines



As direct routes to primary amines are highly warranted,²⁰ we tested the possibility to access 1° alkyl amine under current stage. **1a** and benzophenone imine, which commonly used as ammonia surrogate,²¹ were subjected to the standard conditions. To our delight, the proposed alkyl radical coupled with the imine to generate the elongated imine **5**, which could be facilely converted to 1° alkyl amine **6** upon acid hydrolysis (Scheme 1).^{10,11a} In this regard, the collective results illustrated the broadly applicable features of the current approach in performing C(*sp*³)–N coupling to obtain 1°, 2° and 3° alkyl amines.



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Reaction conditions: a) For **7**: PhB(OH)₂ (1.2 equiv), Pd(PPh₃)₄ (5 mol%), K₂CO₃ (10 equiv), toluene/H₂O, refux, overnight; For **8** and **9**: ArB(OH)₂ (1.5 equiv), Pd(PPh₃)₄ (7.5 mol%), K₂CO₃ (3.0 equiv), DMF/H₂O, 90 °C, overnight; b) B₂(pin)₂ (1.5 equiv), CH₃CO₂K (2.0 equiv), Pd(PPh₃)₄ (0.1 equiv), DMSO, 85 °C; c) CH₃I (1.1 equiv), LDA (1.5 equiv), THF, -78 °C to rt; d) LiAlH₄ (3.0 equiv), Et₂O, reflux; e) (Boc)₂O (1.1 equiv), Et₃N (3.0 equiv), DMAP (5 mol%), DCM, rt; f) CH₃MgBr (6.0 equiv), Et₂O, reflux, overnight.

To further demonstrate the synthetic utility of the present coupling method, structural modifications and functional group inter-conversions of the resultant alkyl amines were performed. As delineated in Scheme 2, the 3º alkyl amine 3i, possessing both cyano group and aryl bromide, could be coupled with an array of aryl boric acids via Suzuki-Miyaura coupling to give 7-9 in good to excellent yields. The bromo atom could also be transformed into the corresponding organoboron, and compound 10 was obtained in 95% yield, which maximized the likelihood to do further transformation. For the cyano moiety of **3i**, α -alkylation could be successfully achieved to produce 11 in 65% yield. Reduction of the cyano group followed by the protection of the newly formed primary amine with Boc group would lead to 12 in 45% yield over two steps. What's more, nucleophilic attack of the cyano moiety with methyl magnesium bromide would ultimately generate ketone 13 in 72% yield.

To elucidate the reaction mechanism, we performed preliminary mechanistic studies (Scheme 3). Addition of 3.0 radical equivalent of scavengers 2,2,6,6tetramethylpiperidinooxy (TEMPO) or butylated hydroxytoluene (BHT) into the reaction mixture would totally suppress the desired reaction, and the adducts 14 and 15 were isolated. These experimental results suggested that this reaction involved a radical process. In this context,9-12 we proposed that the nitrogen nucleophiles firstly coordinated to the Cu(I) salt. The formed complexes would undergo SET process with the cycloketone oxime esters to release Cu(II) species and initiate the homolytic ring-opening to generate the alkyl radical intermediates. Then the Cu(II) species could recombine with the alkyl radicals to form Cu(III) intermediates,11,12 which ultimately delivered the desired alkyl amines and regenerate Cu(I) salt through reductive elimination²² (a scheme for the catalytic cycle, see SI).

Scheme 3. Mechanistic Investigations

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In summary, we have developed a copper-catalyzed direct $C(sp^3)$ –N coupling of cycloketone oxime esters and nitrogen nucleophiles. This reaction protocol is featured with wide functional-group compatibility and broad substrate scope. All of the *N*-aryl/alkylanilines, anilines and benzophenone imine could be employed as the nitrogen nucleophiles to react with cyclobutanone or cyclopentanone oxime esters for the efficient assembly of a variety of 1°, 2° and 3° alkyl amines. These resultant cyano-containing alkyl amines were further shown to be versatile building blocks in a variety of chemical transformations. Further applications and mechanistic studies are in progress in our laboratory.

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Conflicts of interest

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The authors declare no competing financial interest.

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Copper-catalyzed Ring-opening C(*sp*³)–N Coupling of Cycloketone Oxime Esters: Access to 1°, 2° and 3° Alkyl Amines

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An access to 1°, 2° and 3° alkyl amines through copper-catalyzed $C(sp^3)$ –N coupling of cycloketone oxime esters was realized.