Transition-Metal-Assisted Radical/Radical Cross-Coupling: A New Strategy to the Oxidative C(sp^3)−H/N−H Cross-Coupling

Liangliang Zhou,[†,§] Shan Tang,[†,§] Xiaotian Qi,[‡] Caitao Lin,[†] Kun Liu,[†] Chao Liu,[†] Yu Lan,*[,‡] and Aiwen Lei*[,†]

[†]College of Chemistry and Molecular Sciences, Wuhan University, Wuhan, Hubei 430072, P. R. China
[‡]School of Chemistry and Chemical Engineering, Chongqing University, Chongqing 400030, P. R. China

Ⓢ *Supporting Information*

ABSTRACT: A transition-metal-assisted oxidative C(sp^3)-H/N−H cross-coupling reaction of *N*-alkoxyamides with aliphatic hydrocarbons is described. During the reaction, nitrogen radicals were generated from the oxidation of *N*-alkoxyamides. Experiments and DFT calculations revealed that transition-metal catalyst could lower the reactivity of the generated nitrogen radical by the coordination of the transition metal, which allowed the selective radical/radical cross-coupling with the transient sp^3 carbon radical to construct C(sp^3)−-N bonds. Various C(sp^3)−H bonds could be transformed into C(sp^3)−N bonds through this radical amidation strategy.
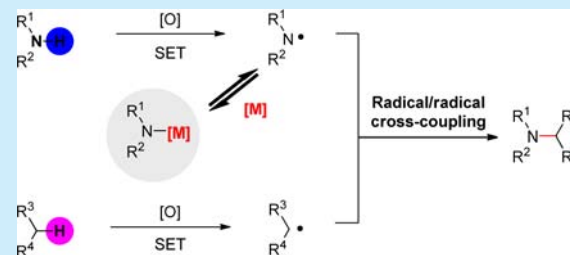
C−N bond formation is of great importance in organic synthesis since nitrogen-containing compounds are found in numerous biological, pharmaceutical, and material molecules.[1] Over the past few years, transition-metal-catalyzed C(sp^2)−N bond formation has been intensively studied.[2] However, C(sp^3)−H bonds, which are naturally more abundant, still face great challenges in C−N bond formation.[3] This may be due to the following two reasons: (1) β-hydride elimination would take place for alkyl metal intermediates,[4] (2) C(sp^3)−N reductive elimination is usually troublesome.[5] Therefore, continuous efforts have been made in this area.[6] Among the processes developed, radical processes have been receiving more and more attention.[6d,f,k,m,t] Zhang et al. developed a significant improvement in this area through metallo-radical-catalyzed radical amidation. In these processes, azides were utilized as the source of nitrogen radical to generate C(sp^3)−N bonds.[6n−s] It is known that the nitrogen radical could also be generated from the oxidation of amides.[7] We wonder whether a radical/radical cross-coupling amidation strategy in C(sp^3)−H/N−H oxidative coupling could be developed to allow the C(sp^3)−N bond formation with more alternatives.

Generally, radicals with a single electron have a strong tendency to form chemical bonds. However, selective bond formation from radical intermediates was less developed compared to ionic intermediates.[8] Since single-electron-transfer processes widely exist in chemical transformations, we believe that direct coupling of two radicals would represent a powerful approach for bond formations. Usually, the selective radical couplings obey the persistent radical effect; only the radical coupling between a persistent radical and a transient radical would lead to a selective bond formation.[9] It is difficult to realize the selective bond formation between two reactive radicals, which limits the application of this protocol in organic synthesis.

If methods could be developed to stabilize one of the reactive radicals, it might provide a solution for the direct cross-coupling between two transient radicals.

It has been demonstrated that transition-metal catalysts might interact with radicals in many different ways, including direct redox bond formation, coordination, and atom transfer, etc.[10] Each of these processes may be reversible or irreversible. Reversible interaction between transition metal and radicals might play an important role in changing the reactivity of the corresponding radicals to allow it to be utilized in many organic transformations such as radical polymerization.[11] The nature of the transition-metal complexes could be considered as radical stabilizer in those cases. Thus, we assume that we could take advantage of this feature of transition metals to stabilize one of the transient radicals to achieve selective radical coupling. Herein, we describe a transition-metal-assisted oxidative radical/radical coupling between nitrogen radical and carbon radical (Scheme 1).

According to the previous reports, nitrogen radicals can be easily generated from the oxidation of *N*-alkoxyamides by CAN, metal oxides, or peroxides.[12] At the same time, we found that the α-alkoxyl carbon radical could be generated by heating the mixture of THF with organic peroxides through hydrogen atom

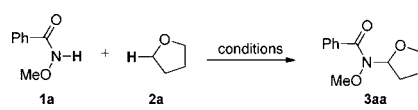**Scheme 1. Transition-Metal-Assisted Radical/Radical Oxidative Cross-Coupling**
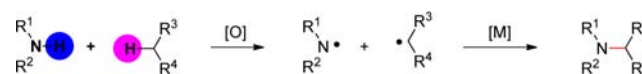
abstraction.[13] At first glance, we wondered whether the direct radical/radical cross-coupling could take place between the nitrogen radical and the transient sp[3] carbon radicals to afford C(sp[3])−N bonds.[9,14] Then the following reactions were carried out to test our initial proposal. *N*-Methoxybenzamide (**1a**) was heated in tetrahydrofuran (THF) at 120 °C in the presence of peroxide compounds, such as dicumyl peroxide (DCP), *tert*-butyl hydroperoxide (TBHP), and di-*tert*-butyl peroxide (DTBP). Reactions did take place but only afforded the C(sp[3])−N bond formation product in low yields (Table 1,

Table 1. Radical/Radical Oxidative Coupling for the C(sp[3])−N Bond Formation[a]

| entry	oxidant	additive[b]	yield[c] (%)
1	DCP		31
2[d]	TBHP		trace
3	DTBP		39
4	DTBP	Cu(acac)$_2$	72
5	DTBP	Ni(acac)$_2$	93

[a]The reaction was carried out in the presence of an oxidant (1.0 mmol) with **1a** (0.50 mmol), **2a** (3.0 mL), 120 °C, 20 h. [b]Additive (0.10 mmol). [c]Yield determined by GC analysis with naphthalin as the internal standard. [d]TBHP (1.0 mmol, 5−6 M in decane).

entries 1−3). DTBP showed a slightly better result with low conversion of the substrate (Table 1, entry 3). These initial results showed that the radical/radical cross-coupling could indeed be realized for C(sp[3])−N bond formations in this transformation, although the selectivity was still unsatisfactory. This might be because both radicals are too reactive to achieve the highly selective cross-coupling. As discussed previously, transition metals could have some effect on the reactivity of radicals. We then screened some transition metal salts as additives to promote selectivity for cross-coupling. Delightfully, transition-metal additives had a significant effect for improving the reaction efficiency. Cu(acac)$_2$ was effective for promoting the selective cross-coupling with an increased yield (72%, Table 1, entry 4), and Ni(acac)$_2$ showed an excellent reactivity for promoting the selectivity in this transformation. The cross-coupling product **3aa** was obtained in a 93% yield (Table 1, entry 5).

To understand the metal effect in this system, the role of Ni(acac)$_2$ was studied. Since Ni catalyst might be involved in the sp[3] C−H activation step, experiments were done to get some insight into the hydrogen abstraction process of THF. An intermolecular competition experiment between THF and THF-d_8 was performed. As a result, the reaction exhibited nearly the same isotopic effects both with and without the nickel catalyst (Scheme 2, k_H/k_D values up to 4.0 and 3.8). This result indicated that the hydrogen abstraction of THF was the key step in which nickel did not play a role.

In order to get some evidence for the generation of the nitrogen free radical, we conducted a reaction with DCE as the only solvent. When **1a** was applied, we got methyl benzoate (**5a**) with DTBP as the oxidant (Scheme 3). According to the former studies,[12b] the ester came from the decomposition of the corresponding *N*′-benzoyl-*N,N*′-dimethoxybenzohydrazide (**4a**) obtained from the homocoupling of nitrogen free radical (**1a-R**). Similar result on the formation of nitrogen free radical with

Scheme 2. Intermolecular Competition Experiment between THF and THF-d_8
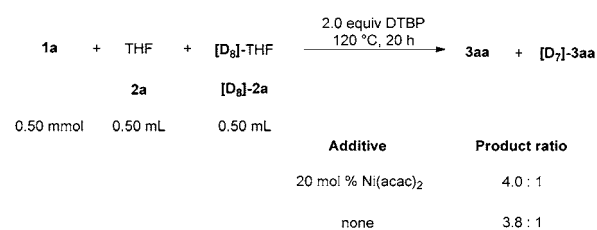

Scheme 3. Decomposition of *N*-Alkoxyamides
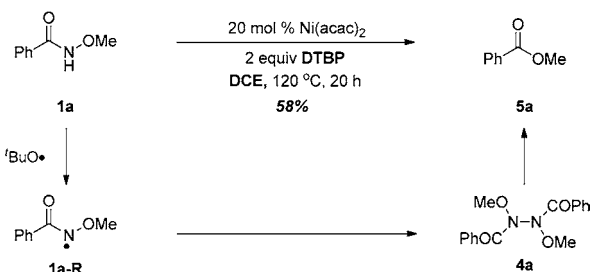
TBHP as the oxidant was observed by Zhao and co-workers recently.[15] Therefore, from this point of view, we can say that the nitrogen free radical did exist in this oxidative condition.[16]

To clarify the exact role of nickel in this reaction system, density functional theory (DFT) calculations were carried out. [B3LYP/6-31+G(d) method][17] The homocoupling energy of nitrogen radical **1a-R** is −13.6 kcal/mol (Scheme 4, eq 1).

Scheme 4. Gibbs Free Energies for the Direct Radical Coupling
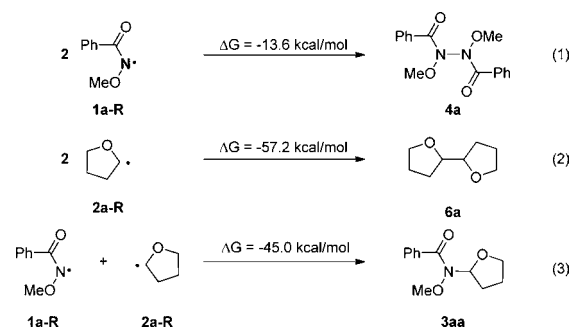
Homocoupling of α-alkoxyl carbon-centered radical **2a-R** is more favorable since the transformation energy is −57.2 kcal/mol (Scheme 4, eq 2). It means that both the nitrogen radical and the carbon radical are reactive radicals, while the nitrogen radical is relatively more stable than the carbon radical. These results might explain why a certain amount of the radical/radical cross-coupling product could be obtained according to the persistent radical effect.[9] DFT calculations agree with our assumption, which shows a favorable energy of −45.0 kcal/mol (Scheme 4, eq 3).

The interaction of nickel catalyst with the substrates and the radicals was then studied (see Scheme S4 in Supporting Information for details). Only the interaction between the nitrogen radical and Ni(acac)$_2$ is exothermic (−1.4 kcal/mol) and exhibits a slightly favorable process for this interaction (Scheme 5). The small energy change means that the coordination of the nitrogen radical to nickel exists as a quick

Scheme 5. Favorable Coordination between Ni(acac)$_2$ and Nitrogen Radical 1a-R
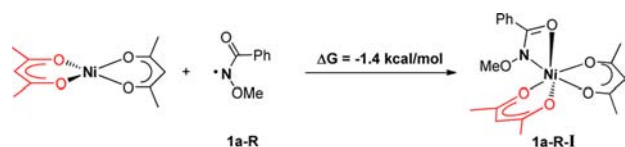
equilibrium with a tendency toward the complexation side (**1a-R-I**). Therefore, the generated complex could be considered as a nitrogen radical pool. This interaction increases the lifetime of the nitrogen radical, which makes it more closer to a persistent radical. Thus, the radical coupling between nitrogen and sp^3 carbon-centered radical can take place in a higher selectivity and efficiency.

Obviously, the C(sp^3)−N bond formation process could proceed though the direct interaction of **1a-R-I** with α-alkoxyl carbon radical **2a-R** instead of direct radical coupling. As shown in Scheme 6, the possibilities for the formation of Ni(IV) and

Scheme 6. Possible Reaction Pathway for 1a-R-I
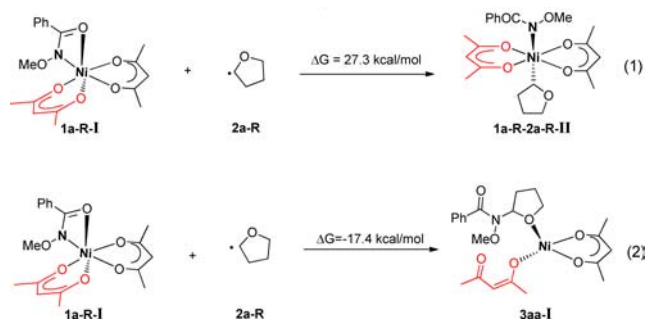
radical homolytic substitution of C−Ni bond were calculated. The formation of Ni(IV) was unfavorable, which shows an energy barrier of 27.3 kcal/mol (Scheme 6, eq 1). Thus, direct reductive elimination from the metal center to form the C(sp^3)−N bond is a disadvantage. Moreover, homolytic substitution by carbon-centered radical **2a-R** with **1a-R-I** complex showed a −17.4 kcal/mol exothermic value (Scheme 6, eq 2), which is still a less effective interaction pathway compared with the energy of direct cross-coupling between radical **1a-R** and **2a-R** (Scheme 4, eq 3).

On the basis of these assumptions and experimental results, a plausible mechanism could be brought forward (Scheme 7). First, homolysis of DTBP takes place under high temperature to generate the *tert*-butoxyl radical.[18] Then *tert*-butoxyl radicals react with both THF and N-alkoxyamides, which afford an α-alkoxyl carbon-centered radical and a nitrogen radical (see

Scheme 7. Transition-Metal-Assisted Radical/Radical Cross-Coupling Mechanism
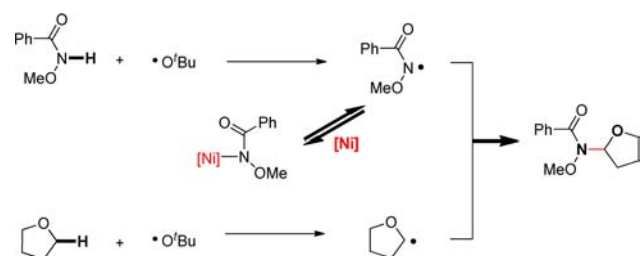
Scheme S3 in the Supporting Information for the dynamics calculations on the generation of both the nitrogen radical and the carbon radical). Transition-metal additives such as nickel coordinates with the generated nitrogen radical in an equilibrium to increase the lifetime of the nitrogen radical. Thus, stabilized nitrogen radical couples with the transient sp^3 carbon radical to result in the cross-coupling product in a highly selective manner according to persistent radical effect.[9,14]

After the study on understanding the reaction mechanism, we turned to explore other kinds of substrates in this C(sp^3)−N bond formation (Scheme 8). A variety of ethers, benzylic

Scheme 8. Substrate Scope of the Radical/Radical Coupling for the Formation of Various C(sp^3)−N Bonds[a]
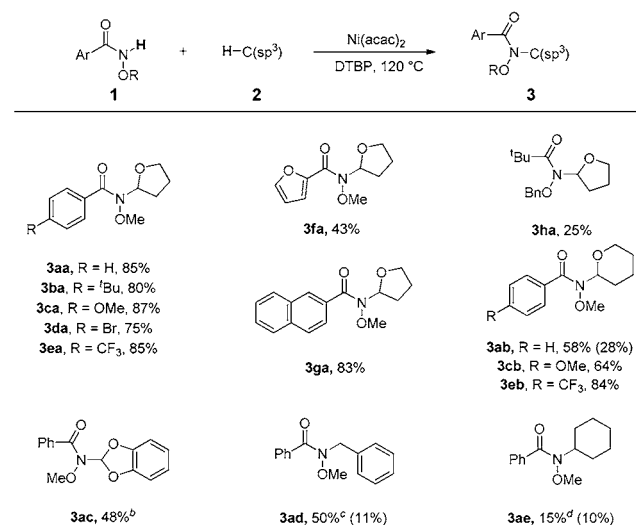
[a]The reactions were carried out with **1** (0.50 mmol), Ni(acac)$_2$ (0.10 mmol) and DTBP (1.0 mmol), **2** (3.0 mL), 120 °C, 20 h. Yields shown in parentheses were obtained in the absence of nickel. [b]1 mL of benzo[d][1,3]dioxole was used with 1 mL of 1,2-dichloroethane. [c]1 equiv of KBr was added. [d]1.5 mmol of DTBP was used.

hydrocarbons, and even simple alkanes were tested in this transformation. Ether derivatives were suitable substrates in this transformation. As for the reaction with THF, electron-donating groups, electron-withdrawing groups, and halide groups at the para position of phenyl ring were all tolerated and afforded the coupling product in good yields (Scheme 8, **3ba−ea**). Substrates with other aromatic groups such as furan and naphthalene were also suitable in this transformation (Scheme 8, **3fa**, **3ga**). Aliphatic acyl alkoxylamine reacted with THF with low yield (Scheme 8, **3ha**). This might be because the substituents on the N-alkoxyamides can affect the reactivity of the nitrogen radical.[7c,d] Besides tetrohydrofuran, tetrahydropyran was tested and afforded the desired products in a good yield (Scheme 8, **3ab**, **3cb**, and **3eb**). When it came to the reaction with benzo[d]-[1,3]dioxole, we obtained the desired product in 48% yield by adding 1.0 mL of DCE to ensure solubility (Scheme 8, **3ac**). Subsequently, we also explored the reaction with other kinds of carbon radicals. To our pleasure, benzylic C(sp^3)−H bonds were also suitable for the direct amidation (Scheme 8, **3ad**). As for cyclohexane, a low yield was obtained, which might due to the mismatch between the nitrogen radical and the more reactive sp^3 carbon radical (Scheme 8, **3ae**).

In conclusion, we have described a transition-metal-assisted oxidative radical/radical cross-coupling reaction. In this trans-

formation, cross-coupling of a nitrogen-centered radical with an sp³ carbon radical was applied in the construction of $C(sp^3)-N$ bonds, which exhibits a brand new concept for C−N bond formation. DFT calculations were applied to support the assistance of transition metal catalyst for achieving high selectivity. Various $C(sp^3)-H$ bonds can be transformed into $C(sp^3)-N$ bonds through the radical/radical cross-coupling process. Most importantly, the idea of introducing transition metal to ensure the radical coupling between two transient radicals is quite important for synthetic organic chemistry.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedure, characterization data, and copies of ^1H, ^{13}C, and ^{19}F NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: lanyu@cqu.edu.cn.
*E-mail: aiwenlei@whu.edu.cn.

Author Contributions

§These authors contributed equally.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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(16) **4a** was synthesized and applied in the reaction system in the presence of nickel catalyst to check whether it was involved for the generation of $C(sp^3)-N$ bond. As a result, only the decomposition product methyl benzoate (**5a**) was observed in a 50% yield, which indicates that formation of **4a** turned to be the termination process for nitrogen radical.
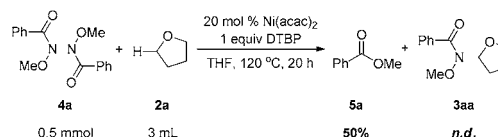
(17) Results shown are of thermodynamics data since radical coupling result from the collision of two radicals without transition states.

(18) It should be noted that temperature has a significant effect on the reaction. When the reaction was conducted at a lower temperature, yields of the product dropped dramatically. This result indicated that nickel does not play a role in promoting the homolysis of DTBP.