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Copper-Catalyzed Oxidative C(sp^3)−H/N−H Cross-Coupling of Hydrocarbons with P(O)−NH Compounds: the Accelerating Effect Induced by Carboxylic Acid Coproduct

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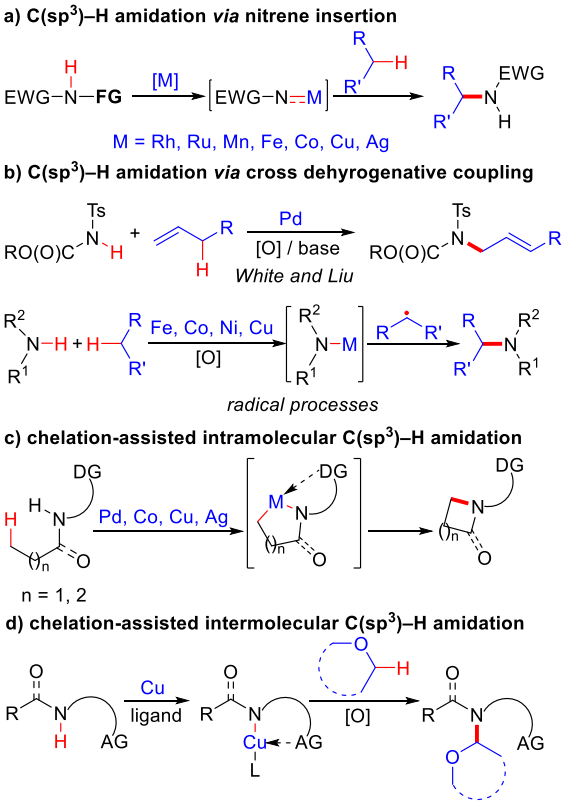
Abstract. An chelation-assisted oxidative C(sp^3)−H/N−H cross coupling of hydrocarbons with P(O)−NH compounds using copper acetate as catalyst is described. The results of kinetic experiments, mechanistic studies and DFT calculations demonstrate the importance of acetic acid coproduct as an additive for promoting the formation of intermediate bis((diphenylphosphoryl)(quinolin-8-yl)amino)copper (**6**), and consequently accelerating the construction of C(sp^3)−N bond. The reaction proceeded efficiently with a wide array of hydrocarbons and P(O)−NH compounds, and the rate acceleration induced by the acetic acid coproduct have been repeatedly proven. Furthermore, the efficiency of small-scale reaction could be retained upon gram-scale synthesis in a continuous manner.

Keywords: copper-catalysis; cross dehydrogenative coupling; hydrocarbons; P(O)−NH compounds; rate acceleration

Progress in the transition metal-catalyzed C−N bonds construction has advanced significantly,[1] and efficient methods for preparing synthetically valuable *N*-functionalized amides starting from ubiquitous C(sp^3)−H bonds are now available.[2] Conventional approaches for C(sp^3)−H amidation proceed through metal-nitrene/imido intermediates.[3–7] Various functionalized compounds such as iminoiodinanes[3], chloramine-T,[4] bromamines-T,[5] *N*-tosyloxycarbamates,[6] and organoazides[7], etc. can be used as nitrogen sources for producing secondary amides with the transfer of nitrene (Scheme 1a). In contrast, the direct amidation of C(sp^3)−H bonds *via* oxidative C−H/N−H dehyrogenative coupling is more attractive in terms of atom economy and tolerance toward both primary and secondary amide reagents as well as a wide range of hydrocarbons (Scheme 1b). For instance, White and Liu illustrated the preparation of linear amides from terminal alkenes and *N*-tosylcarbamates using a Pd-catalyzed protocol.[8] In the past decades, considerable attentions have been paid to the development of amidation methodologies through radical processes



Scheme 1. Transition metal-catalyzed C(sp^3)−H amidation.

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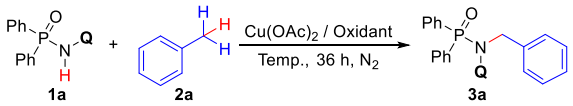
by using catalyst systems based on earth abundant first-row transition metals.[9–11] Among them, the copper ones show perhaps the highest versatility in these transformations.[10–11] In an early study, Katsuki reported the first example .of copper-catalyzed allylic and benzylic amidation based on a Kharasch-Sosnovsky reaction by employing preformed peroxycarbamates as oxidant as well as amine component.[10] Following this pioneering work, a number of copper-catalyzed radical amidation reactions involving C(sp^3)−H/N−H cross-coupling have been exploited using peroxides as mild oxidant.[11]

Recently, the development of chelation-assisted transition-metal catalysis has provided a new complementary route for facile construction of various C−N bonds.[12–13] Reactions of copper-chelation system can be performed even at room temperature.[13h,13j,13k] The intramolecular dehydrogenative amidation protocol have been well established by researchers such as Shi,[13a] Kanai,[13b] Ge,[13c,13e] Shi,[13d] and Bedford[13g] (Scheme 1c). In contrast, intermolecular processes are rarely reported. There are two cases of intermolecular dehydrogenative amidation based on this strategy,[13i–13j] in which only ether derivatives were used as coupling partners and additional ligands were required to promote the transformation (Scheme 1d). Despite the limitations, we expect that this chelation-assisted copper catalytic reaction can be an appealing option for direct C(sp^3)−H amidation.

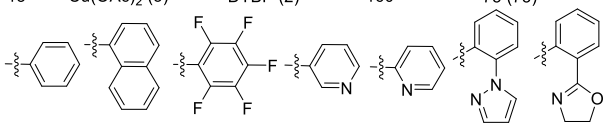
Catalytic C−H functionalization involving metal-chelation systems are catalytic cycles that are potentially complex. For instance, Jutand and coworkers illustrated an autocatalytic process in pyridine-assisted ruthenium-catalyzed arylation of functional arenes through utilizing the carboxylic acid coproduct to promote the formation of ruthenacycle intermediate, and consequently accelerating the C(sp^2)−C(sp^2) construction.[14] Such a process is quite rare in copper catalysis.[15] A notable exception is the recent success on copper-catalyzed azide-alkyne cycloaddition reaction disclosed by Whitesides *et al*.[15c] On the other hand, the improvement by additional acetic acid was observed in a few cases of C−N forming reactions.[9a,13g] The strong development in these fields motivates us to investigate the kinetics of the synthetic processes, and to gain mechanistic insight into the C(sp^3)−H amidation that is based on the chelation-assisted copper-catalysis protocol. Herein, we report a aminoquinoline-assisted oxidative C(sp^3)−H/N−H cross-coupling using simple copper acetate as catalyst. Additional ligand was not required in this transformation. More to the point, a surprising rate acceleration induced by the acetic acid coproduct was found to take part in this reaction.

In view of the prevalence of phosphorus-containing amides in catalytic, synthetic, and biological molecules,[16] and our recent observation that copper powder can facilely promote C−N cross-coupling of phosphinamides and aryl boronic acids

Table 1. Evaluation of reaction parameters.[a]



Entry	$Cu(OAc)_2$ [mol%]	Oxidant [equiv]	Temp. [°C]	Yield of **3a** [%] [b]
1	$Cu(OAc)_2$ (5)	TBHP (2)	100	n.d.[c]
2	$Cu(OAc)_2$ (5)	BPO (2)	100	n.d.
3	$Cu(OAc)_2$ (5)	DCP (2)	100	54
4	$Cu(OAc)_2$ (5)	DTBP (2)	100	93
5	$Cu(OAc)_2$ (5)	DTBP (1)	100	65
6	$Cu(OAc)_2$ (10)	DTBP (2)	100	93
7	$Cu(OAc)_2$ (20)	DTBP (2)	100	93
8	---	DTBP (2)	100	n.d.
9[d]	$Cu(OAc)_2$ (5)	DTBP (2)	100	n.d.
10[e]	$Cu(OAc)_2$ (5)	DTBP (2)	100	n.d.
11	$Cu(OAc)_2$ (5)	DTBP (2)	140	80 (76) [f]
12	$Cu(OAc)_2$ (5)	DTBP (2)	150	78 (74) [f]
13	$Cu(OAc)_2$ (5)	DTBP (2)	160	75 (73) [f]



F1	F2	F3	F4	F5	F6	F7
SM [g] recovered	*SM* recovered	*SM* recovered	*SM* recovered	8%	5%	54%

[a] Reaction conditions: phosphinamide **1a** (0.3 mmol), Cu catalysts, and oxidants dissolved in toluene **2a** (1 mL) under N_2 atmosphere for 36 h.
[b] ^{31}P NMR yield using triphenylphosphine oxide (0.3 mmol) as internal standard.
[c] n.d. = not detected.
[d] Performed under air atmosphere.
[e] Performed under O_2 atmosphere.
[f] Performed for 1h.
[g] SM = starting material.

by taking advantage of the 8-aminoquinoline auxiliary group,[13k] we applied our recently developed Cu^{II}-catalyzed chelation system for oxidative C(sp^3)−H/N−H coupling, employing *P*,*P*-diphenyl-*N*-(quinolin-8-yl)phosphinamide (**1a**) and easily available toluene (**2a**) as model substrates. Our initial investigation focused on C(sp^3)−N formation without the use of unnecessary additives (Table 1). The use of a proper oxidant is critical for the reaction. No reaction took place with *tert*-butyl hydroperoxide (TBHP, entry 1) or benzoyl peroxide (BPO, entry 2). If dicumyl peroxide (DCP) was used instead, **3a** was obtained in 54% yield (Table 1, entry 3). When di-*tert*-butyl peroxide (DTBP) was used as oxidant, the coupling reaction of **1a** with toluene proceeded efficiently to produce the coupling product **3a** in 93% yield, and a decrease in DTBP amount would significantly lower the product yield (Table 1, entries 4 and 5). Increasing the loading of $Cu(OAc)_2$ to 10 mol% and 20 mol% did not further elevate the yields of **3a** (Table 1, entries 6 and 7). If $Cu(OAc)_2$ was omitted, **3a** was not formed (Table 1, entry 8). Further studies showed that the use of alternative copper salts or metal-based oxidants resulted in lower yields of **3a** (see supporting information for details). Of significant relevance is the reaction atmosphere; there was no reaction under air or oxygen (Table 1, entries 9 and 10), indicating that oxygen has a negative effect on reaction efficiency. It was observed that reaction temperature has a direct

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influence on the time for complete reaction (Table 1, entries 11–13). The reaction time could be dramatically reduced from 36 h to 1 h when the reaction took place at 140 °C, 150 °C or 160 °C, albeit the instability of P–N bond in **1a** resulted in lower yields at the elevated temperatures (see supporting information for details). Systematic tuning of *N*-functionalized groups was carried out under the optimal conditions, and yields of the corresponding products are low to negligible (**F1**–**F7**). The results indicate that an appropriate chelation is crucial in this reaction.

To gain insight into this reaction, kinetic experiments were performed. The generation of **3a** with time was monitored by ^{31}P NMR spectroscopy (Figure 1a). The time course of the model reaction under optimal conditions exhibited a parabolic curve in the initial 24 h, which suggests the reaction is accelerated by a product formed in the reaction.[15] After 24 h there is decrease of reaction rate plausibly due to the exhaustion of starting material. Next, we conducted the reaction in the presence of possible

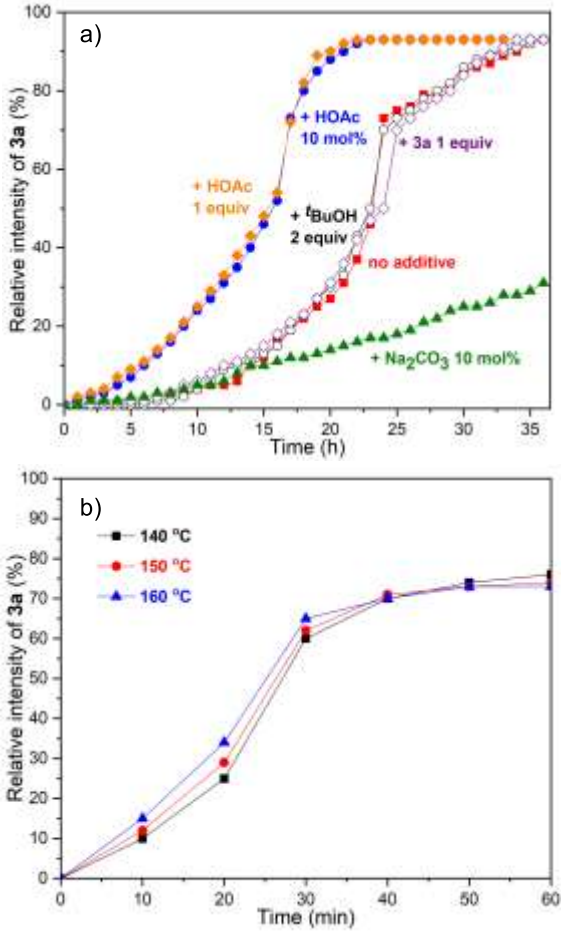
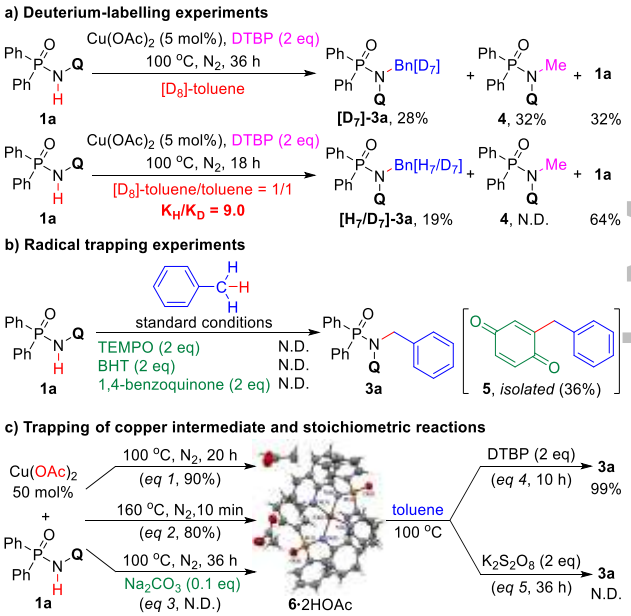


Figure 1. a) Time course of the model reaction at 100 °C for 36 h. Relative intensity of desired product **3a** with time: no additive (■), in the presence of 1 equiv of **3a** (◊), 2 equiv of ^{t}BuOH (○), 10 mol% of HOAc (●), 1 equiv of HOAc (♦) or 10 mol% of Na_2CO_3 (▲). b) Time-course of model reaction at 140 °C (■), 150 °C (●) and 160 °C (▲) for 1 h.

products under standard conditions. There was no detectable effect as a result of **3a** or ^{t}BuOH addition. Because acetic acid could be formed in intermolecular deprotonation of acetate ions dissociated from $Cu(OAc)_2$, its effect on the rate of reaction was also evaluated. Delightfully, the reaction time could be significantly reduced from 36 h to 23 h with the addition of HOAc (10 mol%), and there was the disappearance of the initiation period. Further acceleration was not obvious when stoichiometric amount (1 equiv) of acetic acid was added. Strong decelerating effect of a base (Na_2CO_3) was observed as a result of HOAc being neutralized. The reaction kinetics was investigated within an initial period of 60 min, short enough to obtain data for accurate evaluation of **3a** generation rates at elevated temperatures (Figure 1b). The time-course curves obtained at 140 °C, 150 °C and 160 °C have exponential appearance, and the accelerating effect at 160 °C is more obvious than that at 140 °C or 150 °C, demonstrating that a controlled elevation of reaction temperature could be beneficial for excelling the accelerating effect.



Scheme 2. Mechanistic studies.

In the deuterium-labelling experiments of **1a**, the reaction using [D_8]-toluene was slower than that using toluene. Meanwhile, a demethylation reaction of DTBP was found to take place in [D_8]-toluene (not detected in toluene).[11g,11j,17] In the ^{1}H NMR spectrum of products, when the reaction of **1a** was performed in a 1:1 mixture of toluene and [D_8]-toluene, 1.80 H was observed in the benzylic position, evidencing the H-atom abstraction (HAA) of toluene is more favorable than demethylation of DTBP and the C-D scission of [D_8]-toluene (Scheme 2a, k_H/k_D values up to 9.0). The effect of radical scavengers was also examined (Scheme 2b). The addition of TEMPO, BHT or 1,4-benzoquinone resulted in complete

quenching of the reaction. With the successful isolation of 2-benzylcyclohexa-2,5-diene-1,4-dione (**5**), the involvement of benzyl radical in the reaction is confirmed.

The trapping of Cu^{II} species **6** allowed a detailed investigation into the mechanism (Scheme 2c). Treatment of **1a** with $Cu(OAc)_2$ (50 mol%) under nitrogen at 100 °C for 20 h produced an intermediate bis((diphenylphosphoryl)(quinolin-8-yl)amino)copper (**6**) in 90 % isolated yield (eq 1). The structure of Cu^{II} species **6** attached with two HOAc molecules (originated from **1a** deprotonation), was unambiguously characterized by X-ray analysis.[18] The species **6** could be efficiently obtained after 10 min at 160 °C, evidencing that the elevation of temperature is beneficial for **1a** coordination with $Cu(OAc)_2$ (eq 2). The starting materials were recovered with the addition of Na_2CO_3 (10 mol%), revealing the retarding effect of a base (eq 3). The reaction of Cu^{II} species **6**•2HOAc with toluene in the presence of DTBP (2 equiv) afforded **3a** in 99% yield within 10 h (eq 4). The time course of the stoichiometric reaction showing a linear grown of **3a**, indicating the Cu^{II} species **6** is not an off-cycle "spectator" intermediate (Figure 2a).[15b] No reaction took place with $K_2S_2O_8$, which is able to abstract H-atom in hydrocarbons without generating ^{t}BuO• radical (eq 5).[19] In view of the fact that $Cu(O^tBu)_2$ can be employed as a catalyst in this coupling reaction (see supporting information for details), we deduce that there are two potential functions of DTBP in the transformation: (1) generating ^{t}BuO• radicals to engage in HAA of toluene; (2) participating in the formation of copper alkoxide intermediate.

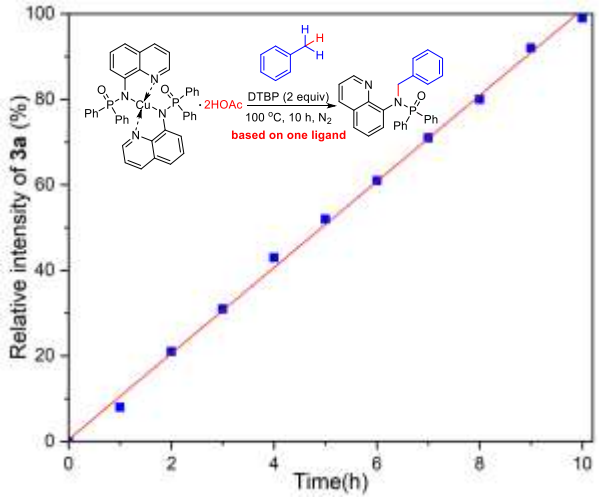


Figure 2. Time course of the stoichiometric reaction of Cu^{II} species **6**·2HOAc with toluene at 100 °C for 10 h. Yields were calculated on the basis of one ligand bound to **6**•2HOAc.

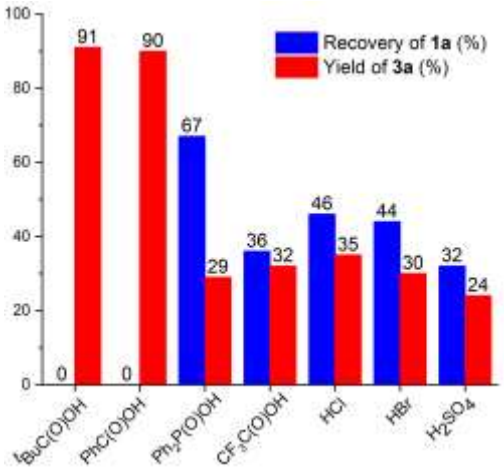


Figure 3. Model reaction in the presence of additional acid (10 mol% of ^{t}BuC(O)OH, PhC(O)OH, $Ph_2P(O)OH$, $CF_3C(O)OH$, HCl, HBr or H_2SO_4) at 100 °C for 23 h.

Because the reaction is induced by acetic acid, the influence of alternative acids was investigated (Figure 3). Similar acceleration effects were obviously observed through the addition of pivalic or benzoic acid (10 mol%), giving the desired product in 91% and 90% yields within 23 h, respectively. With such notation, it is envisioned that the scope of copper carboxylate catalysts can be further enlarged. The addition of diphenylphosphinic acid (10 mol%) seriously limited the reaction efficiency, indicating that phosphoric acid prejudices the current catalysis system. In addition, the instability of P–N bond in substrate **1a** induced by the strong acidity also results in poor reactivity, as in the reactions with the addition of trifluoroacetic acid, hydrochloric acid, hydrobromic acid or sulfuric acid.

On the basis of above results and previous reports,[11d–g,13i–j] a plausible mechanism is proposed as illustrated in Scheme 3. After complexation of substrate **1a** with $Cu(OAc)_2$, Cu^{II} species **A** is formed. Then intermolecular deprotonation of N–H bond in another **1a** by the ligated acetate in species **A** takes place, leading to Cu^{II} species **6**. The acetic acid coproduct promotes the formation of species **6**, consequently accelerates the overall reaction. DFT calculations clarify the role of HOAc as an additive for promoting the complexation of species **A** with **1a**; the energy barrier *via* transition state **TS2** (18.4 kcal/mol) is much lower than that *via* **TS1** (29.4 kcal/mol) (Figure 4). This is in good agreement with the experimental fact that the presence of carboxylic acid is essential to accelerate the reaction. The benzylic radical generated *via* HAA from toluene by ^{t}BuO• radical derived from DTBP decomposition can be rapidly captured by species **6** to afford product **3a**, together with the generation of Cu^{I} species **B**, which could undergo a kind of Kharasch-Sosnovsky

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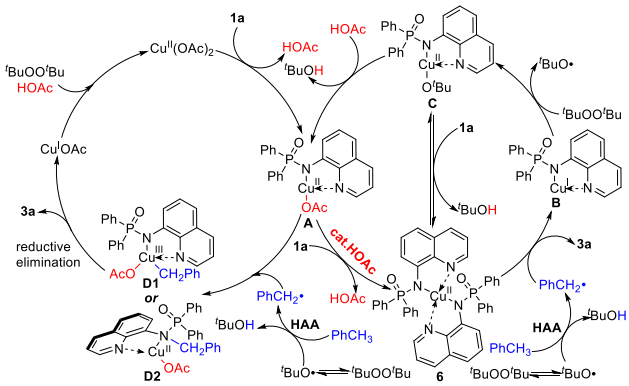


Scheme 3. Proposed mechanism.

reaction with DTBP to afford Cu^{II} alkoxide **C**. Facile acid/base chemistry between **1a** and species **D** regenerates species **6**, and the accumulation of acetic acid further accelerates the reaction. With the exhaustion of **1a**, anion exchange between species **D** and HOAc takes place. Subsequently, the benzylic radical may react directly with the Cu^{II} center or phosphinamide ligand in species **A** to form the intermediate **D1**[11g,13i–j] or **D2**[11d–g]. Reductive elimination of species **D** affords the product **3a** along with Cu^{I} species which would be re-oxidized to Cu^{II} catalyst with DTBP as a terminal oxidant.

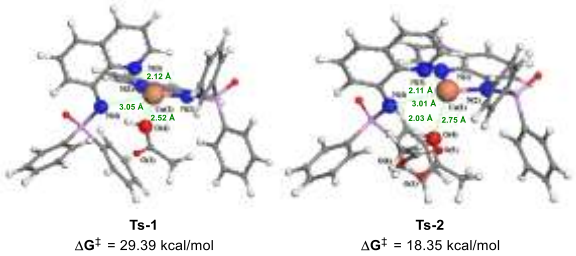
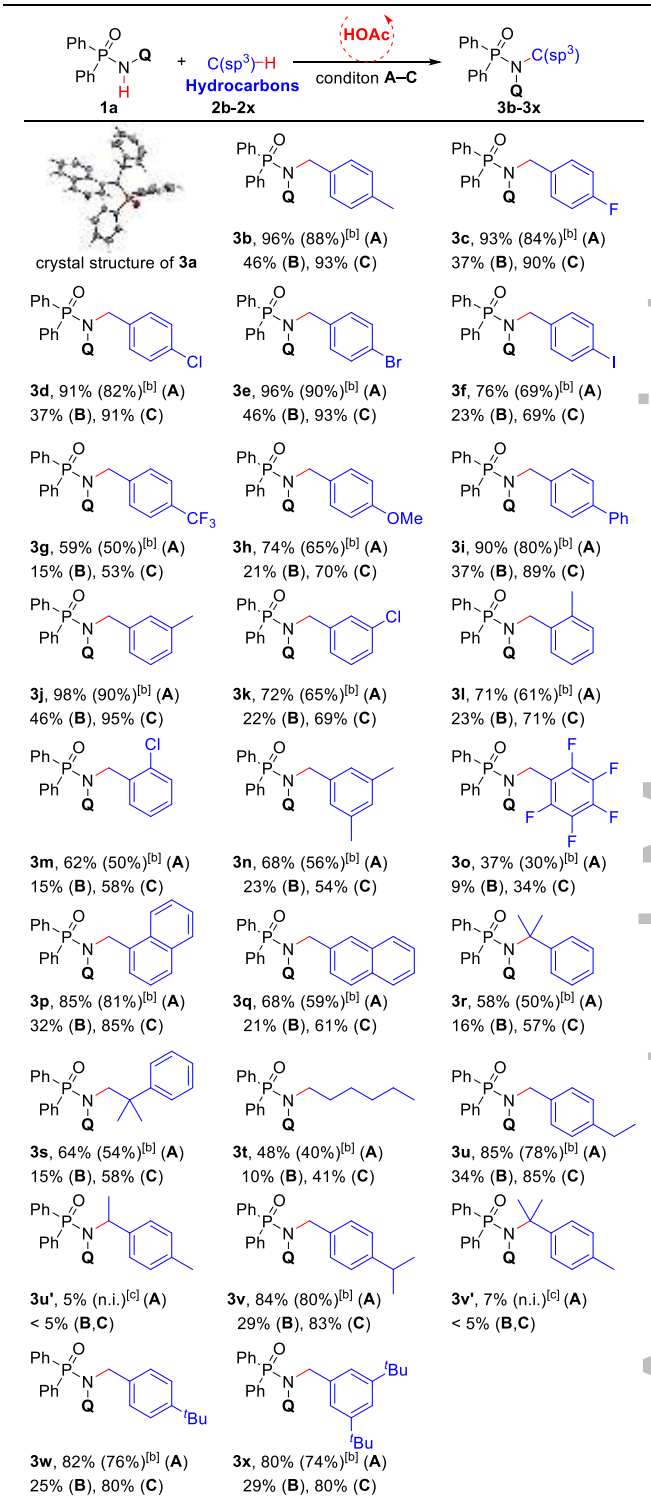


Figure 4. Geometric structures of key transition states.

Having extensively investigated the mechanism, we explored other kinds of substrates in this C(sp^3)–N formation reaction (Tables 2 and 3). A wide variety of functional groups on the toluene derivatives, even bromide and iodide, are tolerated in this catalytic system (**3b**–**3q**). Showing high compatibility for this reaction, the hydrocarbons with 3° benzylic C–H bond give the corresponding product **3r** with good site selectivity. Notably, *tert*-butylbenzene and hexane without benzylic C–H bond can be also activated at the terminal C(sp^3)–H bond to give respectable yields of **3s** and **3t**, respectively. The presence of primary benzylic C–H resulted in almost exclusive products (**3u**–**3x**) in good yields, evidencing the high reactivity of primary benzylic C–H bond. We also examined the reactions using electron-deficient arenes and heteroarenes, e.g. 1-methyl-2-nitrobenzene, 1-methyl-3-nitrobenzene, 1-methyl-4-nitrobenzene, 2-methylpyridine, 2-methylthiophene, and 2-methylquinoline. Unfortunately, no corresponding products could be found.

Table 2. Substrate scope of hydrocarbons.[a]



[a] **Conditions A**: **1a** (0.3 mmol), **2b**–**2x** (1 mL), $Cu(OAc)_2$ (0.015 mmol), DTBP (0.6 mmol), N_2, 100 °C, 36 h. **Conditions B**: **1a** (0.3 mmol), **2b**–**2x** (1 mL), $Cu(OAc)_2$ (0.015 mmol), DTBP (0.6 mmol), N_2, 100 °C, 23 h. **Conditions C**: **1a** (0.3 mmol), **2b**–**2x** (1 mL), $Cu(OAc)_2$ (0.015 mmol), DTBP (0.6 mmol), HOAc (0.03 mmol), N_2, 100 °C, 23 h. The reaction conditions, A–C, used are indicated within parentheses. Yield was determined by ^{31}P

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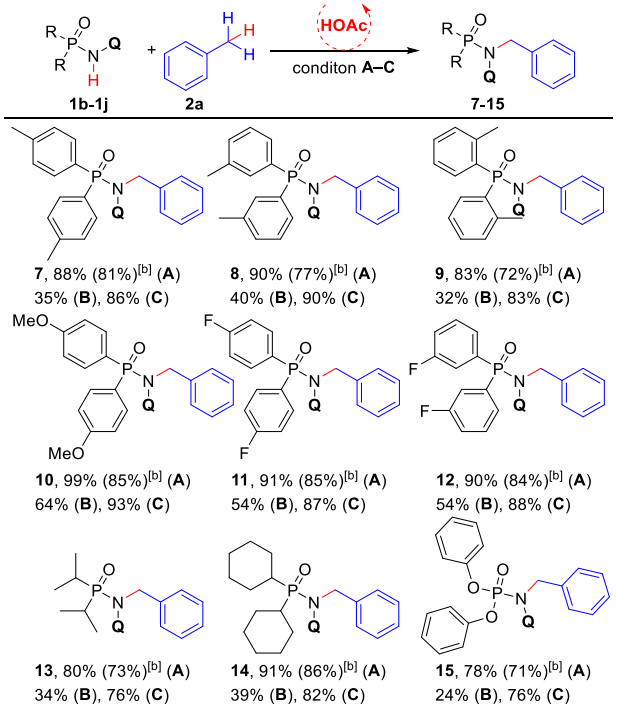
NMR analysis, using triphenylphosphine oxide (0.3 mmol) as internal standard. **Q** = 8-quinolyl group.
[b] Isolated yields.
[c] n.i. = not isolated

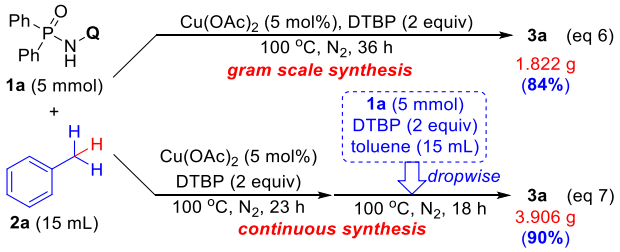
Table 3. Substrate scope of P(O)−NH compounds.[a]



[a] **Conditions A**: **1b**–**1j** (0.3 mmol), **2a** (1 mL), $Cu(OAc)_2$ (0.015 mmol), DTBP (0.6 mmol), N_2, 100 °C, 36 h. **Conditions B**: **1b**–**1j** (0.3 mmol), **2a** (1 mL), $Cu(OAc)_2$ (0.015 mmol), DTBP (0.6 mmol), N_2, 100 °C, 23 h. **Conditions C**: **1b**–**1j** (0.3 mmol), **2a** (1 mL), $Cu(OAc)_2$ (0.015 mmol), DTBP (0.6 mmol), HOAc (0.03 mmol), N_2, 100 °C, 23 h. The reaction conditions, A–C, used are indicated within parentheses. Yield was determined by ^{31}P NMR analysis, using triphenylphosphine oxide (0.3 mmol) as internal standard. **Q** = 8-quinolyl group.
[b] Isolated yields.

The reaction also works well for an array of diarylphosphinamides with either electron rich or electron deficient group (**7**–**12**). Moreover, dialkylphosphinamides and phosphoramide were found compatible in this reaction (**13**, **14** and **15**). The generality of the accelerating effect was further verified by examining the ^{31}P NMR yield of corresponding product obtained within 23 h, and that with the addition of acetic acid (10 mol%), separately (Condition **B**–**C**). The reaction rate could be somewhat accelerated by catalytic amount of acetic acid (**3b**–**15**). The results demonstrate that the electronic and steric properties of hydrocarbons and P(O)−NH compounds can affect both the efficiency of the coupling reaction and the accelerating effect induced by acetic acid. The structure of **3a** was characterized by X-ray crystallography,[18] and those of the other products were assigned by analogy.

Finally, to highlight the synthetic utility of the present protocol, **3a** was synthesized in gram scale as well as in a continuous manner (Scheme 4). The efficiency of the small-scale reaction was retained, delivering **3a** in 84% isolated yield (eq 6). In consideration that the rate of reaction could decrease due to the decay of starting material, we explored whether reactivity could be also retained at the efficient state by continuous feeding of starting



Scheme 4. Gram scale and continuous synthesis.

material. To our delight, after 23 h treatment of **1a** with $Cu(OAc)_2$ (5 mol%), the accelerating stage could be retained when the reaction was fed dropwise with a mixture of starting material, oxidant and coupling partner, and **3a** could be obtained in 90% isolated yield under nitrogen at 100 °C for 18 h (eq 7). Note that the continuous feeding was performed without refreshment or new addition of copper catalyst. The results point to a potential industrialization window for producing tertiary unsymmetrical phosphorus-containing amides.

In conclusion, we have developed a copper-catalyzed $C(sp^3)$−N cross-coupling reaction based on aminoquinoline-assisted oxidative $C(sp^3)$−H/N−H cross-coupling of hydrocarbons with P(O)−NH compounds. The results of kinetic experiments, mechanistic studies, DFT calculations and rate acceleration of a wide substrate scope repeatedly demonstrate the accelerating effect induced by the acetic acid coproduct. It is a new strategy for the construction of $C(sp^3)$−N bonds *via* oxidative cross dehydrogenative coupling. The key intermediate in this transformation, bis((diphenylphosphoryl)(quinolin-8-yl)amino)copper, (**6**) was isolated and characterized by X-ray analysis. The accelerating effect is further exemplified by gram-scale synthesis of product **3a** in a continuous manner, with the efficiency of small-scale reaction being retained. Further investigations on the reaction mechanism and bioactive application of the synthesized tertiary unsymmetrical phosphorus-containing amides are currently underway in our laboratory.

Experimental Section

General Procedure for Copper-Catalyzed $C(sp^3)$−H/N−H Cross Coupling of Hydrocarbons with

P(O)−NH Compounds and Determination of Accelerating Effect.

An oven-dried 25 mL Schlenk tube was charged with phosphorus-containing amide (0.3 mmol), $Cu(OAc)_2$ (2.7 mg, 5 mol%), DTBP (114 μL, 2 equiv) and hydrocarbons (1 mL) under nitrogen atmosphere with stirring at 100 °C for 36 h. The mixture was then cooled to room temperature, diluted with CH_2Cl_2 (2 mL), and filtered through a celite pad. The yield of product was determined by ^{31}P NMR spectra of the filtrate, using triphenylphosphine oxide (83.4 mg, 0.3 mmol) as internal standard. After the concentration of the filtrate in vacuo, the residues were purified by silica gel flash chromatography column to give the corresponding product. The generality of accelerating effect by acetic acid coproduct was further verified by examining the ^{31}P NMR yield of the corresponding product obtained within 23 h, and that with the addition of acetic acid (10 mol%), separately.

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[18] CCDC numbers of the crystal structures, **6**·2HOAc: 1574866; **3a**: 1574867. Selected bond distances [Å] and angles [°] of Cu^{II} species **6**·2HOAc: Cu(1)–N(1) 2.002(5), Cu(1)–N(2) 1.938(4), Cu(1)–N(3) 2.015(4), Cu(1)–N(4) 1.929(4), P(1)–N(2) 1.633(4), P(2)–N(4) 1.632(4); N(1)–Cu(1)–N(2) 84.4(2), N(1)–Cu(1)–N(3) 124.0(2), N(1)–Cu(1)–N(4) 102.2(2), N(2)–Cu(1)–N(3) 106.3(2), N(2)–Cu(1)–N(4) 161.4(2), N(3)–Cu(1)–N(4) 84.6(2). Selected bond distances [Å] and angles [°] of **3a**: P(1)–N(2) 1.665(2), P(1)–C(17) 1.809(3), P(1)–C(23) 1.801(3), N(2)–C(8) 1.436(3), N(2)–C(10) 1.491(3), O(1)–P(1)–N(2) 118.2(1), O(1)–P(1)–C(17) 111.8(1), O(1)–P(1)–C(23) 110.2(1), N(2)–P(1)–C(17) 102.7(1), N(2)–P(1)–C(23) 105.4(1), C(17)–P(1)–C(23) 107.8(1).

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