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Syntheses of amides via iodine-catalyzed multiple sp^3 C–H bonds oxidation of methylarenes and sequential coupling with *N,N*-dialkylformamides

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The oxidative coupling of methylarenes and *N,N*-dialkylformamides was developed, and the appropriate reaction conditions were established. By using I_2 as the catalyst, and *tert*-butyl hydroperoxide (TBHP) as the oxidant, the reaction provided *N,N*-dialkylamides or *N*-alkylamides with moderate yields via multiple sp^3 C–H bonds activation of methylarenes in aqueous and metal-free conditions.

oxidative coupling, iodine-catalyzed, methylarenes, amides

1 Introduction

Amide moiety widely exists in biomolecules, since it is essential to sustain life, making up peptide bonds in proteins [1]. It is also one of the most important functional groups in a variety of drug molecules [2] and materials [3]. The most common method for the synthesis of amides is the union of carboxylic acids or their derivatives with amines [4]. In recent years, increasing attention has been devoted to developing efficient methods for amide formation, among which employing metal catalysis in amide syntheses creates the possibility of applying substrates other than carboxylic acids [5]. For example, the oxidative coupling of aldehydes, alcohols and related compounds with nitrogenous compounds by the catalysis of transition-metals such as Rh [6], Ru [7], Cu [8], Fe [9] and Mn [10]. Ru-catalyzed reaction of nitriles with alcohols [11], as well as Ir or Ru-catalyzed rearrangement of oximes [12] were also developed for amide formation. Nevertheless, many of these methods involve toxic solvents, harsh oxidants, expensive reagents, difficulty in preparing transition metal catalysts etc. Thus, to develop synthetic routes, not only atom-economical but also low cost and more environmentally friendly, becomes a big challenge for the chemists.

Recently, a series of metal-free approaches for the formation of amides were developed. For example, the ^{n}Bu$_4$NI-catalyzed oxidative coupling of aldehydes with formamides [13], ^{n}Bu$_4$NI [14] or I_2 [15] -catalyzed oxidative coupling of alcohols with formamides. A ^{n}Bu$_4$NI-catalyzed oxidative coupling of aryl methyl ketones with formamides [16], as well as a I_2-catalyzed oxidative coupling of aryl methyl ketones with secondary amines [17] were also reported for the synthesis of α-ketoamides. We have been continuously interested in the functionalization of inert C–H bond. In our previous work, by using methylarenes as the acylation reagents, the palladium catalyzed chelation-assisted acylation of sp^2 C–H bond was developed [18]. These results promoted us to employ the unprefunctionalized methylarene as the acyl source to form C–N bond. Herein, we present the iodine-catalyzed sequential C–O and

Dedicated to Professor Qian Changtao on the occasion of his 80th birthday.
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C–N bond formation via multiple sp^3 C–H bond activation of easily available and inexpensive methylarenes, providing an efficient approach to arylamides.

2 Experimental

2.1 General information

All reactions were run in a sealed tube with a Teflon lined cap under air atmosphere. All chemical reagents and solvents were purchased from Aldrich, Alfa Aesar and Sinopharm chemical reagent Co. Ltd., and were used without further purification. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a Bruker Avance 400 spectrometers in $CDCl_3$ (using $(CH_3)_4Si$ (for ^{1}H, δ = 0.00; for ^{13}C, δ = 77.00) as internal standard). The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet.

2.2 General experimental procedures and characterizations

Toluene derivatives **1** (1.0 mmol), I_2 (0.2 mmol), TBHP (3.0 mmol), NaOH (0.4 mmol) and H_2O (1 mL) were added in a 25 mL sealed tube with a Teflon lined cap. Then *N*,*N*-dialkylformamides **2** (6.0 mmol) and TBHP (5.0 mmol) were added in batches. The mixture was stirred in an oil bath at 80 °C. After 20 h, the reaction mixture was cooled to room temperature, and diluted with water, then extracted with ethyl acetate (15 mL × 3). The combined organic layer was washed with water and dried with anhydrous Na_2SO_4, the solvent was then removed under vacuum. The residue was purified by flash column chromatography on silica gel using hexane/ethyl acetate as eluent to give the corresponding product.

All products are known compounds. The ^{1}H NMR and ^{13}C NMR spectra can be seen in the Supporting Information online. The ^{1}H NMR and ^{13}C NMR data are shown below:

N,*N*-dimethylbenzamide (**3aa**) [15]: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41–7.28 (m, 5H), 3.08 (s, 3H), 2.91 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.6, 136.4, 129.5, 128.3, 127.0, 39.6, 35.3.

4-Fluoro-*N*,*N*-dimethylbenzamide (**3ba**) [15]: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45–7.41 (m, 2H), 7.11–7.06 (m, 2H), 3.10 (s, 3H), 2.99 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 164.5, 162.0, 132.3, 132.2, 129.4, 129.3, 115.5, 115.3, 58.3, 39.6, 35.9.

4-Bromo-*N*,*N*-dimethylbenzamide (**3ca**) [15]: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, J = 8.8 Hz, 2H), 7.29 (d, J = 8.8 Hz, 2H), 3.08 (s, 3H), 2.96 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 135.1, 131. 6, 128.8, 123.8, 39.5, 35.4.

2-Chloro-*N*,*N*-dimethylbenzamide (**3da**) [14]: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39–7.36 (m, 1H), 7.31–7.27 (m, 3H), 3.12 (s, 3H), 2.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.4, 136.4, 130.3, 130.1, 129.5, 127.7, 127.2, 38.0, 34.6.

3-Chloro-*N*,*N*-dimethylbenzamide (**3ea**) [15]: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41–7.29 (m, 4H), 3.11 (s, 3H), 2.98 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 138.0, 134.42, 129.8, 129.6, 127.2, 125.1, 39.5, 35.4.

4-Chloro-*N*,*N*-dimethylbenzamide (**3fa**) [15]: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.35 (m, 4H), 3.10 (s, 3H), 2.97 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 135.6, 134.7, 130.9, 128.6, 39.5, 35.4.

4-Cyano-*N*,*N*-dimethylbenzamide (**3ga**) [15]: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, J = 6.8 Hz, 2H), 7.49 (d, J = 6.8 Hz, 2H), 3.12 (s, 3H), 2.96 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.3, 166.5, 141.3, 131.5, 131.0, 129.4, 37.0, 34.1.

Methyl 4-(dimethylcarbamoyl)benzoate (**3ha**) [13]: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, J = 8.0 Hz, 2H), 7.50 (d, J = 8.0 Hz, 2H), 3.96 (s, 3H) 3.15 (s, 3H), 2.98 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 166.4, 140.7, 131.0, 129.7, 127.0, 52.3, 39.4, 35.3.

3-Methoxy-*N*,*N*-dimethylbenzamide (**3ia**) [14]: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33–7.29(m, 1H), 6.98–6.93 (m, 3H), 3.83 (s, 3H), 3.11 (s, 3H), 2.98 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 159.5, 137.7, 129.4, 119.1, 115.4, 112.4, 55.3, 39.5, 35.3.

3,4-Dichloro-*N*,*N*-dimethylbenzamide (**3ja**) [19]: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (s, 1H), 7.49 (d, J = 8.4 Hz, 1H), 7.26 (d, J = 8.4 Hz, 1H), 3.10 (s, 3H), 2.99 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.1, 136.1, 133.9, 132.8, 130.5, 129.3, 126.4, 39.5, 35.4.

N,*N*,3-trimethylbenzamide (**3ka**) [15]: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26–7.17 (m, 4H), 3.09 (s, 3H), 2.96 (s, 3H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8, 138.2, 136.3, 130.2, 128.1, 127.6, 123.9, 39.6, 35.3, 21.3.

N,*N*,4-trimethylbenzamide (**3la**) [15]: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (d, J = 8.0 Hz, 2H), 7.20 (d, J = 8.0 Hz, 2H), 3.05 (s, 6H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8, 139.6, 133.3, 128.9, 127.2, 39.7, 35.4, 21.4.

N,*N*,3,5-tetramethylbenzamide (**3ma**) [20]: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.03 (s, 1H), 7.01 (s, 2H), 3.10 (s, 3H), 2.97 (s, 3H), 2.33 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.0, 137.9, 136.3, 131.0, 124.6, 39.6, 35.2, 21.2.

N,*N*-diethylbenzamide (**3ab**) [15]: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.34 (m, 5H), 3.55 (s, 2H), 3.26 (s, 2H), 1.27–1.24 (m, 3H), 1.21–1.11 (m,3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 137.3, 129.1, 128.4, 126.3, 43.3, 39.2, 14.2, 12.9.

Phenyl(piperidin-1-yl)methanone (**3ac**) [15]: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (m, 5H), 3.72 (s, 2H), 3.34 (s, 2H), 1.68 (s, 4H), 1.53 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 136.5, 129.3, 128.4, 126.8, 48.7, 43.1, 26.4, 25.6, 24.6.

4-Benzoylmorpholine (**3ad**) [15]: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45–7.40 (m, 5H), 3.76–3.66 (m, 6H), 3.53–3.47 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 135.3, 129.9, 128.6, 127.1, 66.9, 48.2, 42.6.

1-(4-Cyanobenzoyl)piperidine (**3gc**) [8b]: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, J = 8.4 Hz, 2H), 7.50 (d, J = 8.4 Hz, 2H), 3.73–3.70 (m, 2H), 3.31–3.28 (m, 2H), 1.72–1.70 (m, 4H), 1.58–1.55 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.6, 164.9, 141.3, 131.7, 130.9, 129.4, 47.1, 42.3, 26.3, 25.5, 24.4.

4-Chloro-*N*-isopropylbenzamide (**3fe**) [21]: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, J = 8.4 Hz, 2H), 7.38 (d, J = 8.4 Hz, 2H), 6.06 (br, 1H), 4.31–4.23 (m, 1H), 1.26 (d, J = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.7, 137.4, 133.3, 128.7, 128.3, 42.0, 22.8, 22.3.

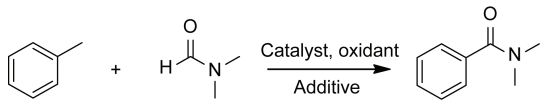
4-Bromo-*N*-isopropylbenzamide (**3ce**) [22]: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, J = 8.8 Hz, 2H), 7.55 (d, J = 8.8 Hz, 2H), 6.02 (br, 1H), 4.32–4.23 (m, 1H), 1.27 (d, J = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.7, 133.8, 131.7, 128.5, 125.9, 42.1, 22.8, 22.3.

3 Results and discussion

We initiated our studies with the oxidative coupling of toluene (**1a**) with *N*,*N*-dimethylfomamide (**2a**) in the presence of an oxidant using iodine or iodide as the catalyst. The results are assembled in Table 1. The oxidant proved to be very important for this reaction. Among three oxidants TBHP, DTBP (di-*tert*-butylperoxide) and $K_2S_2O_8$, TBHP was effective, and in the presence of 8 equiv. TBHP, the reaction gave a yield of 58% in a reaction time of 20 h (Table 1, entry 7), while others were inefficient (entries 9 and 10). Catalyst was also important for the reaction. Without a catalyst, the reaction could not proceed. Iodine and some iodides such as ^{n}Bu$_4$NI, KI, NaI, CuI and PhI(OAc)$_2$ were tested for this reaction (entries 1–7), in which iodine showed the highest catalytic activity. Further studies indicated that 20 mol% of I_2 was optimal for the reaction, as there was no significant increase with the yield when 40 mol% of I_2 was used (entry 16). The presence of base also seemed to be essential. Adding 0.4 equiv. NaOH to the reaction mixture could promote this transformation, while other bases such as KOH, NaOAc and Na_2CO_3 turned out to be inferior (entries 12–14). The assessment of the reaction conditions also indicated that the appropriate reaction temperature was 80 °C. The yield had no significant change when the reaction temperature was elevated to 90 °C, but lowering the temperature to 60 °C resulted in a poor yield of 25%. It should be pointed out that the reaction was conducted in water. Organic solvents, like 1,2-dichloroethane and $CHCl_3$, led to decrease of the yields (entries 17 and 18).

As for the scope of this I_2-TBHP catalyzed oxidative coupling reaction, we explored the reaction of various toluene derivatives (**1a–m**) with *N*,*N*-dialkylformamide (**2a–d**) under the established conditions (Table 2). At the beginning of our investigation, DMF was chosen as the amino source for this reaction. For most toluene derivatives, with either

Table 1 Optimization of the reaction conditions [a)]

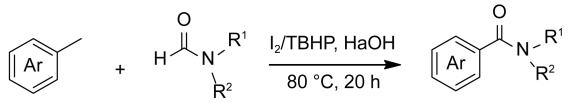


1a **2a** **3aa**

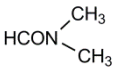
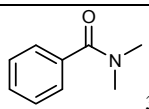
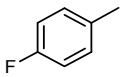
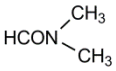
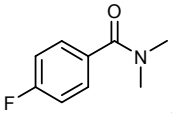
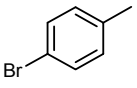
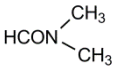
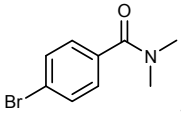
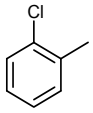
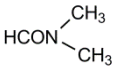
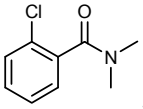
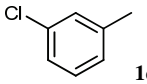
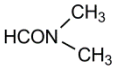
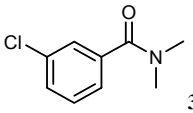
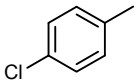
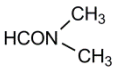
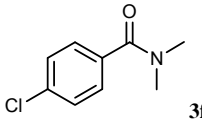
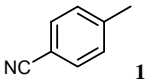
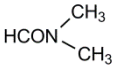
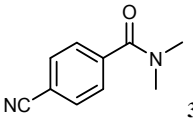
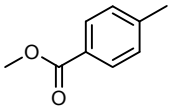
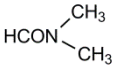
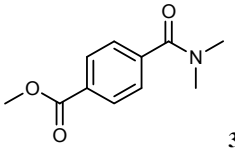
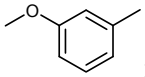
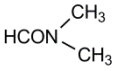
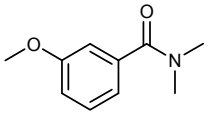
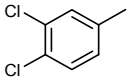
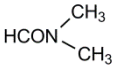
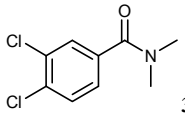
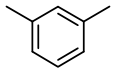
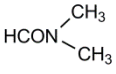
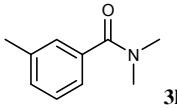
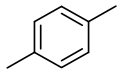
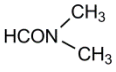
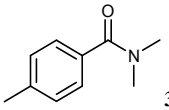
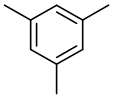
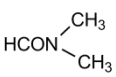
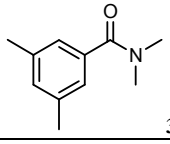
Entry	Catalyst (mol%)	Oxidant (equiv.)	Base (equiv.)	Yield (%)
1	^{n}Bu$_4$NI (20)	TBHP (8)	NaOH (0.4)	38
2	KI (20)	TBHP (8)	NaOH (0.4)	32
3	NaI (20)	TBHP (8)	NaOH (0.4)	35
4	CuI (20)	TBHP (8)	NaOH (0.4)	< 10
5	PhI(OAc)$_2$ (20)	TBHP (8)	NaOH (0.4)	< 10
6	–	TBHP (8)	NaOH (0.4)	trace
7	I_2 (20)	TBHP (8)	NaOH (0.4)	58
8	I_2 (20)	TBHP (6)	NaOH (0.4)	48
9	I_2 (20)	$K_2S_2O_8$ (8)	NaOH (0.4)	trace
10	I_2 (20)	DTBP (8)	NaOH (0.4)	trace
11	I_2 (20)	TBHP (8)	NaOH (0.2)	48
12	I_2 (20)	TBHP (8)	KOH (0.4)	52
13	I_2 (20)	TBHP (8)	NaOAc (0.4)	38
14	I_2 (20)	TBHP (8)	Na_2CO_3 (0.4)	43
15	I_2 (10)	TBHP (8)	NaOH (0.4)	35
16	I_2 (40)	TBHP (8)	NaOH (0.4)	56
17 [b)]	I_2 (20)	TBHP (8)	NaOH (0.4)	42
18 [c)]	I_2 (20)	TBHP (8)	NaOH (0.4)	< 10

a) Unless otherwise specified, all the reactions were carried out in a sealed tube in the presence of toluene (**1a**, 1 mmol), *N*,*N*-dimethylfomamide (**2a**, 6 mmol), catalyst, oxidant and base in H_2O (1 mL) under air atmosphere at 80 °C for 20 h. The yield is isolated one based on **1a**. b) In 1,2-dichloroethane; c) In $CHCl_3$.

Table 2 I_2-TBHP catalyzed synthesis of amides [a)]

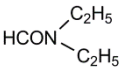
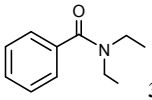
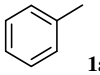
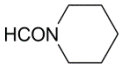
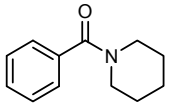
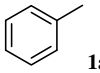
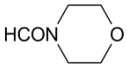
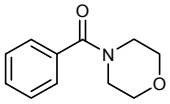
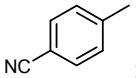
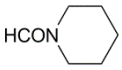
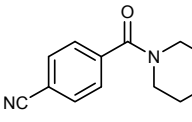


1 **2** **3**

Entry	Substrate **1**	Substrate **2**	Product	Yield (%)
1	 **1a**	 (**2a**)	 **3aa**	58
2	 **1b**	 (**2a**)	 **3ba**	57
3	 **1c**	 (**2a**)	 **3ca**	62
4	 **1d**	 (**2a**)	 **3da**	56
5	 **1e**	 (**2a**)	 **3ea**	60
6	 **1f**	 (**2a**)	 **3fa**	63
7	 **1g**	 (**2a**)	 **3ga**	55
8	 **1h**	 (**2a**)	 **3ha**	43
9	 **1i**	 (**2a**)	 **3ia**	37
10	 **1j**	 (**2a**)	 **3ja**	61
11	 **1k**	 (**2a**)	 **3ka**	55
12	 **1l**	 (**2a**)	 **3la**	52
13	 **1m**	 (**2a**)	 **3ma**	40

(*To be continued on the next page*)

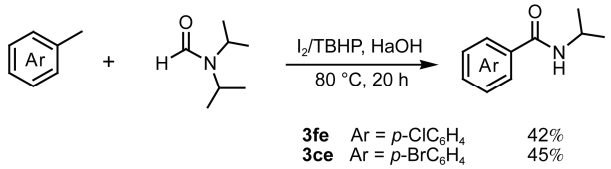
(*Continued*)

Entry	Substrate **1**	Substrate **2**	Product	Yield (%)
14	 **1a**	 (**2b**)	 **3ab**	53
15	 **1a**	 (**2c**)	 **3ac**	60
16	 **1a**	 (**2d**)	 **3ad**	56
17	 **1g**	 (**2c**)	 **3gc**	61

a) All the reactions were carried out in a sealed tube in the presence of toluene derivatives (**1**, 1 mmol), *N*,*N*-dialkylfomamide (**2**, 6 mmol), I_2 (0.2 mmol), TBHP (8 equiv.) and NaOH (0.4 equiv.) in H_2O (1 mL) under air atmosphere at 80 °C for 20 h. The yield is isolated one based on **1**.

electron-withdrawing or electron-donating substitution, the reaction gave the corresponding products in moderate yields within a reaction time of 20 h. The tolerance to the chemically active functional groups was also studied. Halogen (F, Cl, Br), ester and cyano group on benzene ring of toluene were well tolerated for this reaction (entries 2–8, Table 2), and the substituent pattern on the benzene ring had no significant influence on the reaction. Interestingly, toluene derivatives with more than one methyl group such as *m*-xylene, *p*-xylene, and 1,3,5-trimethylbenzene, the reaction took place on one methyl group and the others remained to be untouched (entries 11–13). However, when excessive amounts of TBHP (12 equiv.), and DMF (10 equiv.) were applied, the reaction mixture turned to be quite complicated. Next we employed a series of *N*,*N*-dialkylformamides, including cyclic and acyclic formamides (**2b–d**), as the coupling partner, the results were quite similar to the reaction with DMF (entries 14–17).

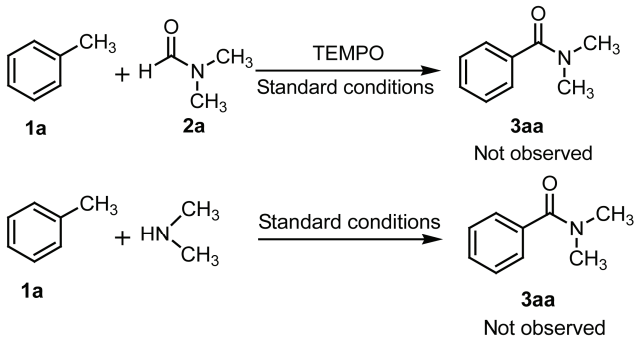
To our surprise, when *N*,*N*-diisopropylformamide was used as the amino source, instead of the general product *N*,*N*-diisopropylarylamide, a *N*-isopropylarylamide was generated (Scheme 1). Though the exact mechanism is unclear, we presume that it may be related to the steric hindrance of isopropyl. Meantime, it also indicated that the cleavage of alkyl C–N bond was possible in this I_2-TBHP catalytic system.



Scheme 1 Formation of *N*-isopropylarylamide.

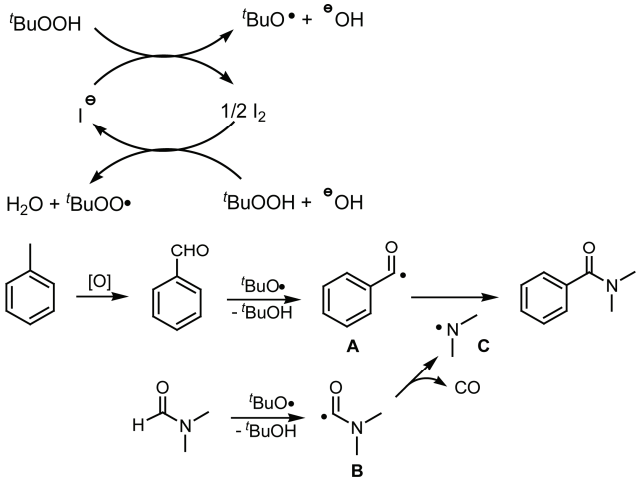
To study the mechanism of this reaction, 1 mmol 2,2,6,6-tetramethyl piperidine-*N*-oxyl (TEMPO, a radical scavenger) was added to the reaction system of **1a** and **2a**, and no desired product was detected. This result revealed that the reaction might go through a radical pathway. In addition, the replacement of DMF with dimethylamine led to no corresponding oxidative coupling product **3aa**, which implied that dimethylamine was not the reaction intermediate (Scheme 2).

In our previous report, the partial oxidation of toluene by TBHP to benzaldehyde was observed [18b]. In addition, the decarbonylation of DMF has been well-documented [23]. A ^{13}C-isotope labeling experiment by Wan further proved that the cleavage of C–N bond of DMF was possible in the TBHP system, giving *N*,*N*-dimethylamino radical [13]. Based on our experimental results and the related reports [13–15, 23], a plausible catalytic mechanism is presented in Scheme 3. Initially, TBHP decomposed to a ^{t}butoxyl radical and a hydroxyl anion catalyzed by I_2. After toluene (**1a**) was partially oxidized to benzaldehyde under the oxidative conditions, ^{t}butoxyl radical abstracted hydrogen from the



Scheme 2 The control experiments.

formyl C–H bond of benzaldehyde to afford benzoyl radical (**A**, Scheme 3). On the other hand, DMF was abstracted hydrogen by ^{t}butoxyl radical to form radical **B**, which could be further converted to dimethylamino radical (**C**) upon the release of CO. The coupling of dimethylamino radical (**C**) and benzoyl radical (**A**) then led to the desired product *N*,*N*-dimethylbenzamide.



Scheme 3 Plausible reaction mechanism.

4 Conclusions

In summary, we developed a convenient method for the synthesis of amides from the low toxic, inexpensive, stable and commercially available substrates toluene and its derivatives. The reaction was conducted in aqueous media and metal-free conditions. To the best of our knowledge, this represents the first example to form C–O and C–N bond sequentially via multiple inert sp^3 C–H bonds activation.

This work was supported by the National Natural Science Foundation of China (21272117, 20972068) and the Priority Academic Program Development of Jiangsu Higher Education Institutions.

1 Crespo L, Sanclimens G, Pons M, Giralt E, Royo M, Albericio F. Peptide and amide bond-containing dendrimers. *Chem Rev*, 2005, 105: 1663–1681
2 Carey JS, Laffan D, Thomson C, Williams MT. Analysis of the reactions used for the preparation of drug candidate molecules. *Org Biomol Chem*, 2006, 4: 2337–2347
3 a) Greenberg A, Breneman CM, Liebman JF. *The Amide Linkage: Structural Significance in Chemistry, Biochemistry and Materials Science*. New York: John Wiley & Sons, 2000; b) Boas U, Brask J, Jensen KJ. Backbone amide linker in solid-phase synthesis. *Chem Rev*, 2009, 109: 2092–2118
4 Valeur E, Bradley M. Amide bond formation: beyond the myth of coupling reagents. *Chem Soc Rev*, 2009, 38: 606–631
5 a) Allen CL, Williams JMJ. Metal-catalysed approaches to amide bond formation. *Chem Soc Rev*, 2011, 40: 3405–3415; b) García-Álvarez R, Crochet P, Cadierno V. Metal-catalyzed amide bond forming reactions in an environmentally friendly aqueous medium: nitrile hydrations and beyond. *Green Chem*, 2013, 15: 46–66
6 a) Zhou B, Du JJ, Yaxi Yang YX, Li YC. Rhodium(III)-catalyzed intermolecular direct amidation of aldehyde C–H bonds with *N*-chloroamines at room temperature. *Org Lett*, 2013, 15: 2934–2937; b) Zhou B, Yang YX, Shi JJ, Feng HJ, Li YC. Rhodium-catalyzed synthesis of amides from aldehydes and azides by chelation-assisted C–H bond activation. *Chem Eur J*, 2013, 19: 10511–10515
7 Fu ZQ, Lee JB, Kang BJ, Hong SH. Dehydrogenative amide synthesis: azide as a nitrogen source. *Org Lett*, 2012, 14: 6028–6031
8 a) Li CJ, Yoo WJ. Highly efficient oxidative amidation of aldehydes with amine hydrochloride salts. *J Am Chem Soc*, 2006, 128: 13064–13065; b) Zhu MW, Fujita KI, Yamaguchi R. Aerobic oxidative amidation of aromatic and cinnamic aldehydes with secondary amines by CuI/2-pyridonate catalytic system. *J Org Chem*, 2012, 77: 9102–9109; c) Zhang C, Zong XL, Zhang LR, Jiao N. Copper- catalyzed aerobic oxidative cross-dehydrogenative coupling of amine and α-carbonyl aldehyde: a practical and efficient approach to α-ketoamides with wide substrate scope. *Org Lett*, 2012, 14: 3280–3283; d) Xie YX, Song RJ, Yang XH, Xiang JN, Li JH. Copper-catalyzed amidation of acids using formamides as the amine source. *Eur J Org Chem*, 2013: 5737–5742
9 a) Ghosh SC, Ngiam JSY, Chai CLL, Seayad AM, Dang TT, Chen AQ. Iron-catalyzed efficient synthesis of amides from aldehydes and amine hydrochloride salts. *Adv Synth Catal*, 2012, 354: 1407–1412; b) Li YM, Jia F, Li ZP. Iron-catalyzed oxidative amidation of tertiary amines with aldehydes. *Chem Eur J*, 2013, 19: 82–86
10 a) Zhang C, Xu ZJ, Shen T, Wu GL, Zhang LR, Jiao N. Mn-promoted aerobic oxidative C–C bond cleavage of aldehydes with dioxygen activation: a simple synthetic approach to formamides. *Org Lett*, 2012, 14: 2362–2365; b) Vanjari R, Guntreddi T, Singh KN. MnO_2 promoted sequential C–O and C–N bond formation via C–H activation of methylarenes: a new approach to amides. *Org Lett*, 2013, 15: 4908–4911
11 Kang BJ, Fu ZQ, Hong SH. Ruthenium-catalyzed redox-neutral and single-step amide synthesis from alcohol and nitrile with complete atom economy. *J Am Chem Soc*, 2013, 135: 11704–11707
12 a) Owston NA, Parker AJ, Williams JMJ. Iridium-catalyzed conversion of alcohols into amides via oximes. *Org Lett*, 2007, 9: 73–75; b) Owston NA, Parker AJ, Williams JMJ. Highly efficient ruthenium-catalyzed oxime to amide rearrangement. *Org Lett*, 2007, 9: 3599–3601
13 Liu ZJ, Zhang J, Chen SL, Shi E, Xu Y, Wan XB. Cross coupling of acyl and aminyl radicals: direct synthesis of amides catalyzed by Bu_4NI with TBHP as an oxidant. *Angew Chem Int Ed*, 2012, 51: 3231–3235
14 Li HM, Xie J, Xue QC, Cheng YX, Zhu CJ. Metal-free *n*-Bu_4NI-catalyzed direct synthesis of amides from alcohols and *N*,*N*-disubstituted formamides. *Tetrahedron Lett*, 2012, 53: 6479–6482
15 Xu K, Hu YB, Zhang S, Zha ZG, Wang ZY. Direct amidation of alcohols with *N*-substituted formamides under transition-metal-free conditions. *Chem Eur J*, 2012, 18: 9793–9797
16 Mai WP, Wang HH, Li ZC, Yuan JW, Xiao YM, Yang LR, Mao P, Qu LB. $^{n}Bu_4NI$-catalyzed direct synthesis of a-ketoamides from aryl methyl ketones with dialkylformamides in water using TBHP as oxidant. *Chem Commun*, 2012, 48: 10117–10119
17 Wei W, Shao Y, Hu HY, Zhang F, Zhang C, Xu Y, Wan XB. Coupling of methyl ketones and primary or secondary amines leading to α-ketoamides. *J Org Chem,* 2012, 77: 7157–7165
18 a) Yin ZW, Sun PP. Palladium catalyzed direct *ortho*-acylation through an oxidative coupling of acetanilides with toluene derivatives. *J Org Chem*, 2012, 77: 11339–11344; b) Xu ZP, Xiang B, Sun PP. Palladium catalyzed direct *ortho* C–H acylation of 2-arylpyridines using toluene derivatives as acylation reagents. *RSC Adv*, 2013, 3:

1679–1682
19 Heys JR, Elmore CS. Meta-substituent effects on organoiridium- catalyzed ortho-hydrogen isotope exchange. *J Labelled Compd Rad*, 2009, 52: 189–200
20 Marcus AP, Lee AS, Davis RL, Tantillo DJ, Sarpong R. Pronounced steric effects of substituents in the nazarov cyclization of aryl dienyl ketones. *Angew Chem Int Ed*, 2008, 47: 6379–6383
21 Xia ZH, Zhu Q. A transition-metal-free synthesis of arylcarboxyamides from aryl diazonium salts and isocyanides. *Org Lett*, 2013, 15: 4110–4113
22 Vice S, Bara T, Bauer A, Evans C, Ford J, Josien H, McCombie S, Miller M, Nazareno D, Palani A, Tagat J. Concise formation of 4-benzyl piperidines and related derivatives using a Suzuki protocol. *J Org Chem*, 2001, 66: 2487–2492
23 Muzart J. *N*,*N*-dimethylformamide: much more than a solvent. *Tetrahedron*, 2009, 65: 8313–8323

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