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Direct Oxidative Amidation between Methylarenes and Amines in Water

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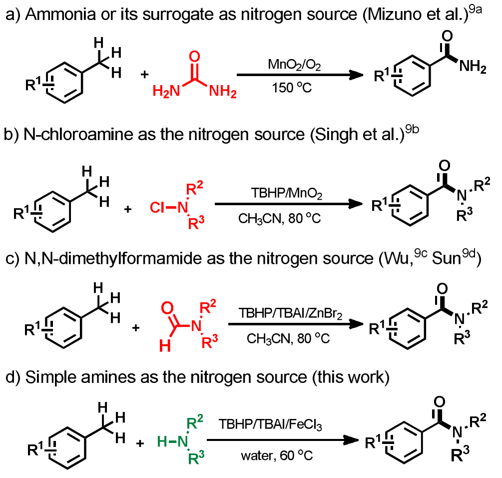
An environmental friendly direct oxidative amidation between methylarenes and free amines was developed. The aromatic amide could be prepared efficiently from raw chemicals by employing TBHP as the "green" oxidant with the co-catalysis of TBAI and $FeCl_3$ in water.

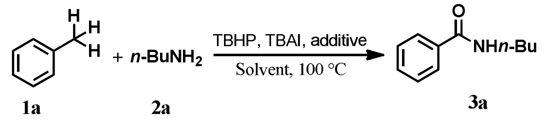
Amide is an important functional group in nature due to its ubiquitous in proteins, pharmaceutical compounds, functional materials and other synthetic chemicals.[1] Chemical reactions for amide formation are among the most executed transformations in organic chemistry.[2] However, traditional chemical synthesis of amide always employs prior activated carboxyl component or coupling reagents and excess of reactants which resulted high cost and large amount of chemical waste.[3] 'Amide formation avoiding poor atom economy reagents' was recognized as one of the top challenge for organic chemistry and green chemistry.[4] Consequently, amide bond formation beyond traditional coupling strategy emerged as attractive alternatives for preparation of amide in recent years.[5] Especially the direct oxidative amidation between aldehydes[6] or alcohols[7] and amine has attracted much attention because of the atom economic and environmental benign issues. Benefited from the studies on benzylic sp^3 C-H activation,[8] toluene and other methylarenes have also been used as acyl donors for oxidative amidations.[9] Mizuno et al. reported an oxidative amidation of methylarenes for the synthesis of aromatic primary amides by using aqueous ammonia or its surrogates as the nitrogen source (Scheme 1 a).[9a] Very recently, this concept had been extended to the synthesis of secondary and tertiary amides by employing activated amine surrogates such as N-chloroamine (Scheme 1 b)[9b] and N,N-dimethylformamide (Scheme 1 c)[9c,9d] as the nitrogen source. Regarding the cheap raw chemicals such as toluene used as starting materials in these pioneer work, they would be more attractive for chemical industry. However, the reaction conditions for oxidative amidation of methyarenes are always rigorous and the substrate scope and functional group tolerance are limited. Moreover, prior activated amine surrogates[10] are necessary to attain satisfied results and thus resulting more synthetic steps and chemical waste. Concerning atom-, step-economical and environmental issues, non-modified amine would be ideal starting material for amide bond formation. We herein reported a highly efficient direct oxidative amidation between methylarenes and free amines which was accomplished in water by employing *tert*-butyl hydroperoxide (TBHP) as the environmental benign oxidant with the co-catalysis of tetrabutyl-ammonium iodide (TBAI) and $FeCl_3$ (Scheme 1 d).



Scheme 1 Oxidative amidation of methylarenes.

We initiated this project by screening oxidants in CH_3CN in the presence of 30 mol% of TBAI at 100 ℃. Unfortunately, no significant amount of amide was detected when 30% H_2O_2 solution, di-*t*-butyl peroxide (DTBP) and *m*-chloroperbenzoic acid (*m*-CPBA) were used as oxidant (See supporting information). Interestingly, amide bond formation was detected albeit with low yield when TBHP (6 equiv)[11] was employed as oxidant (Table 1, entry 1). Among the screened catalysts, TBAI was identified to be the best one (For details, see supporting information). TBHP in water provide higher yield than that of pure TBHP (Table 1, entry 2). This result hinted that water may has some effects on this reaction. To our delight, the yield improved significantly when the reaction was performed in water (Table 1, entry 7). Next, other factors such as additive and temperature were also evaluated. The yield can be further improved with the presence of 15 mol% $FeCl_3{\cdot}6H_2O$ (Table 1, entry 8). The 4 Å molecular sieves is

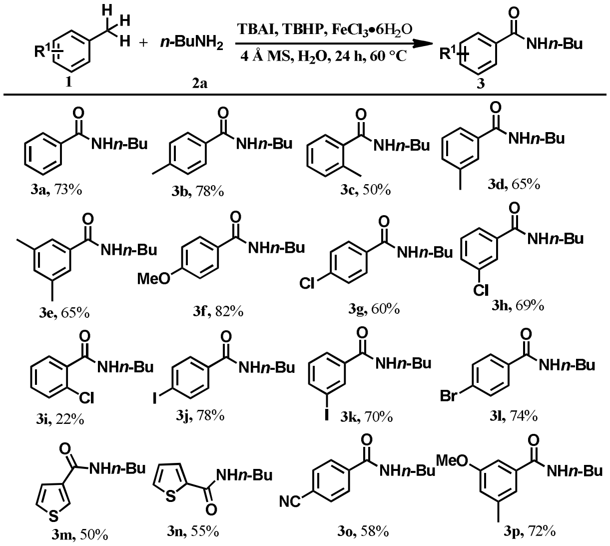
Table 1. Optimization of reaction conditions[a]



entry	solvent	additive	Yield[b]
1[c]	CH_3CN	-	29
2[d]	CH_3CN	-	36
3	DMSO	-	2
4	DMF	-	3
5	DCE	-	27
6	PhMe	-	25
7	H_2O	-	47
8	H_2O	$FeCl_3 \cdot 6H_2O$ (15 mol%)	64
9	H_2O	$FeCl_3 \cdot 6H_2O$ (15 mol%), 4 Å MS	67
10[e]	**H_2O**	**$FeCl_3 \cdot 6H_2O$ (15 mol%), 4 Å MS**	**73**

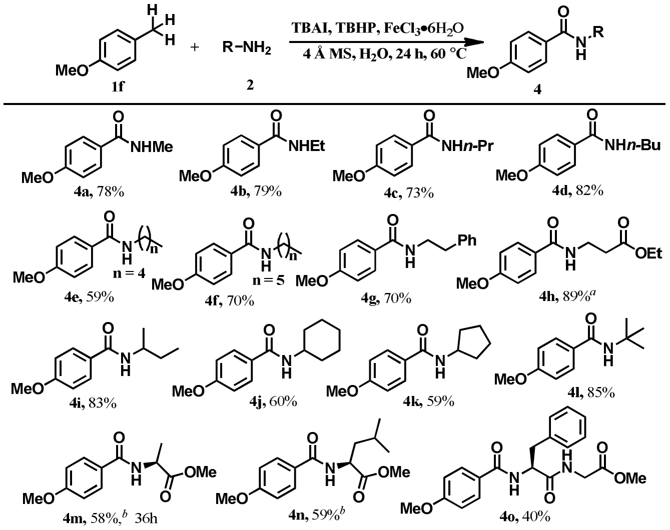
[a] **1a** (5 mmol), **2a** (0.24 mmol), solvent (1.5 mL), 24 h. [b] Isolated yield. [c] Pure TBHP (6 equiv). [d] TBHP 70 wt % in water (6 equiv). [e] This reaction was carried out at 60 ℃. MS = molecular sieves.

also helpful for this reaction (Table 1, entry 9). Interestingly, the yield was furhter increased a little when the reaction was carried out at 60 ℃. Finally, the highest yield up to 73% was obtained when the reaction was carried out at 60 ℃ in water with the presence of 6 equivalent of TBHP, 30 mol% of TBAI, 15 mol% of $FeCl_3 \cdot 6H_2O$ and 4 Å molecular sieves (Table 1, entry 10).



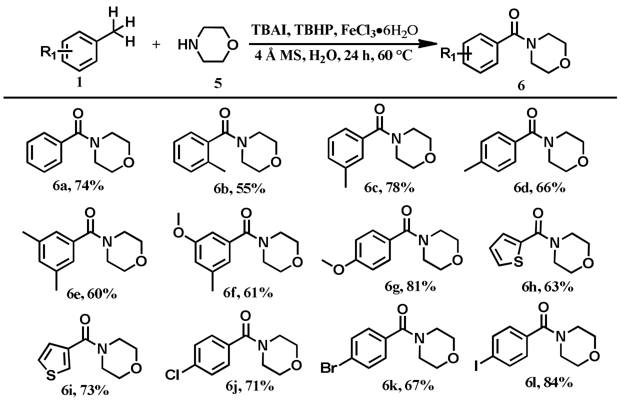
Scheme 2 Scope of the reaction with methylarenes **1**. Reaction conditions: methylarene (5 mmol), **2a** (0.24 mmol), water (1.5 mL), TBHP 70 wt % in water (6 equiv), TBAI (30 mol%), $FeCl_3 \cdot 6H_2O$ (15 mol%), 4 Å MS (100 mg), 60 ℃, 24 h.

With this optimized reaction conditions in hand, we next studied the substrate scope of this reaction. A variety of methylarenes were examined and the result was shown in Scheme 2. Both electron-donating and weak electron-withdrawing groups are compatible for this reaction. Generally, methylarenes containing electron-donating groups offer better yields than those containing electon-withdrawing ones. While slightly decreased yield was observed, the sterically demanding *ortho*-xylene works well for this transformation (**3c**). Excellent chemo-selectivity was obtained and no *bi* or *tri* amide was detected when *ortho*-, *para*-, *meta*-xylene and 1, 3, 5-*tri*-methyl benzene were used as the starting materials (3b-3e). Notably, the reaction of heterocyclic methylarene, such as methyl thiophene also went smoothly to provide the amide in moderate yields (**3m, 3n**).



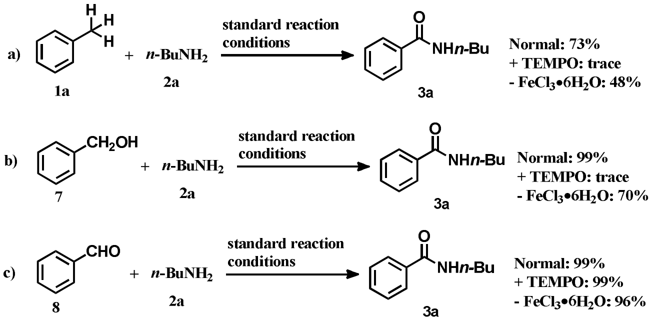
Scheme 3 Scope of the reaction with amines **2**. Reaction conditions: **1f** (5 mmol), amines **2** (0.24 mmol), water (1.5 mL), TBHP 70 wt % in water (6 equiv), TBAI (30 mol%), $FeCl_3 \cdot 6H_2O$ (15 mol%), 4 Å MS (100 mg), 60 ℃, 24 h. [a] Without $FeCl_3 \cdot 6H_2O$. [b] Replaced $FeCl_3 \cdot 6H_2O$ (15 mol%) with $CaCO_3$ (15 mol%).

Next, the generality of the amine part also had been tested and the result was listed in scheme 3. Most of the tested amines work well for this reaction. In terms of linear aliphatic amines, the reaction efficiency is slightly influenced by the length of the chain. Not only the linear amines but also amines with branch chains are good substrates for this transformation. For example, the *α*-tertiary carbon can be tolerated and good yields were obtained (**4i-4k**). Significantly, even the amine containing a quaternary carbon went smoothly to provide amide in satisfied yield (**4l**). Notably, the reaction scope can be expanded to the salt of N-terminal free peptide as well as amino ester (**4m-4o**). Importantly, no racemization was detected in the oxidative amidation of chiral *α*-amino ester. 15 mol% of $CaCO_3$ instead of $FeCl_3 \cdot 6H_2O$ was used for the amidation of amine salt.



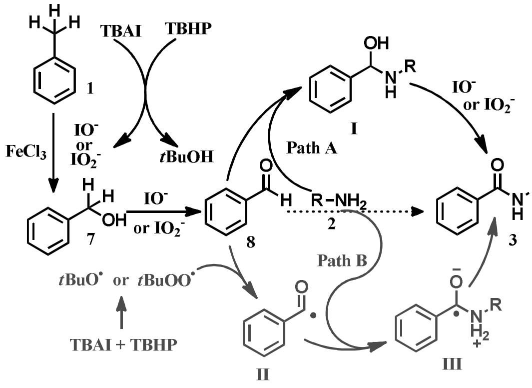
Scheme 4 Reaction conditions: methylarene (5 mmol), **5** (0.24 mmol), water (1.5 mL), TBHP 70 wt % in water (6 equiv), TBAI (30 mol%), $FeCl_3 \cdot 6H_2O$ (15 mol%), 4 Å MS (100 mg), 60 ℃, 24 h.

With the success on primary amines, we go further to test the oxidative amidation of secondary amines. However, the target tertiary amide was obtained in poor yield accompanied by some secondary amide which resulted from a C-N bond cleavage. Interestingly, unlike common secondary amines, morpholine do indeed offer good yield of the target products efficiently. A series of methylarenes were tested and most of them worked well for this reaction (Scheme 4). Electronic effect of substituent has little influence on the reaction efficiency. No matter electron-withdrawing, neutral or –donating groups present on the phenyl ring, the corresponding tertiary amides were obtained in good yields. Steric effect of *ortho* methyl group resulted slight decrease of the yield (**6b**). The amidation of methyl thiophene also proceeded smoothly to give the corresponding amides in high yields (**6h, 6i**).



Scheme 5 Mechanistic studies and control experiments

To understand the reaction mechanism, some control experiments were carried out (Scheme 5). Benzyl alcohol and benzaldehyde would be intermediates (both of them had been detected as side products in the reaction) for this transformation because quantitative yield of N-butylbenzamide **3a** was obtained when either of them was employed as acyl donor under the optimized reaction conditions (Scheme 5 a, b).



Scheme 6 Proposed mechanism

TEMPO (2 equiv) was added to the reaction system with an attempt to probe whether radical was involved in this process (Scheme 5). However, unlike literatures,[5h,6d] no acyl radical was trapped in all of our control experiments (Scheme 5 a, b and c). Interestingly, in the presence of TEMPO, the reaction of toluene and benzyl alcohol was completely inhibited while the reaction of benzaldehyde was kept intact (Scheme 5). This result suggested that the oxidation of toluene and benzyl alcohol might involve radical process. In addition, control experiments disclosed that $FeCl_3$ might play an important role in the oxidation of toluene and benzyl alcohol. Recent studies demonstrated that hypervalent iodine species such as hypoiodite (IO^-) or iodite (IO_2^-) should be the real oxidant for TBHP/TBAI system.[11,12] Based on our experimental results and literatures, we proposed that toluene was oxidized to benzyl alcohol by IO^- or IO_2^- with the assistance of $FeCl_3$.[13] Further oxidation of benzyl alcohol will offer the key intermediate benzaldehyde. Two different pathways had ever been proposed to rationalize oxidative amidation of benzaldehyde (Scheme 6). Li et al. proposed that the oxidative amidation of aldehyde might go through the hemiaminal intermediate, which can be further oxidized to amide (Path A).[6a] On the other hand, very recently, acyl radical was proposed as the key intermediate for the oxidative amidation of aldehyde[6c,6d] and its analogues.[5h] Lei and Lan's DFT calculation illustrated that nucleophilic attack of primary amine toward acyl radical followed by a single electron transfer oxidation and release of proton will also afford the amide (Path B).[5h] According to our experimental results, pathway A is more reasonable while pathway B is unlikely involved.

In summary, we have developed an environmental friendly direct oxidative amidation of methylarenes and free amines in water. Unlike the traditional amide formation strategies, which involving expensive coupling reagents, pre-activated carboxylate derivatives or activated amine surrogates, this protocol employed cheap raw chemicals such as methylarenes and free amines as the starting material to produce high value amides. In addition, water was used as the solvent avoiding using of other organic solvent. With TBHP as the "green" oxidant and cheap, low toxic TBAI and $FeCl_3 \cdot 6H_2O$ as the catalysts, this protocol would be more attractive for pharmaceuticals and other fine chemical synthesis.

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Notes and references

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Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/c000000x/

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