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MnO_2 Promoted Sequential C–O and C–N Bond Formation via C–H Activation of Methylarenes: A New Approach to Amides

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ABSTRACT

A novel and efficient approach for the synthesis of amides has been developed through manganese dioxide promoted nondirected C–H activation of methylarenes under mild reaction conditions employing *N*-chloroamines as effective coupling partners.

The development of novel chemical reactions and recuperating the reaction conditions to maximize product selectivity, energy efficiency, and environmental safety remains the main thrust of current chemical research. Hydrocarbons, derived from oil and natural gas, constitute the most inexpensive and readily available feed stocks for chemical industries. Therefore, direct formation of C–C and C–X linkage via carbon–hydrogen (C–H) bond activation of hydrocarbons is of immense importance and has currently emerged as a challenging goal. This idea has been mainly realized by means of chelation-assisted C–H activation[1] and cross-dehydrogenative coupling (CDC)[2] strategy. Although these advances have been extensively explored for C–C and C–O bond formation,[3,4] there is still a dearth of information on C–N bond creation.[5] In this perspective, C–N bond formation and eventual synthesis of amides involving C–H bond activation of alkylarenes remains the cherished target.

The amide is one of the most important functional groups in chemistry, forming the basic building block of a number of natural products, pharmaceuticals, and

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polymers.[6] Amides are commonly formed via reactions of a carboxylic acid with an amine. A number of alternative methods for amide bond formation have been developed including Beckmann rearrangement,[7] aminocarbonylation of aryl halides and alkynes,[8] cross-coupling of formamide with alkyl/aryl halides,[9] oxidative amidation of aldehydes/alcohols,[10] and transamidation.[11] However, more economical, environmentally friendly, resource efficient, and highly selective methods are in demand.[12] Recent developments in the utilization of benzylic C−H bonds[13] inspired us to look into the C−H bond activation of easily available and inexpensive methylarenes to accomplish direct formation of amides. Consequently and as a part of our interest in developing useful synthetic protocols for amides[14] and other systems,[15] we report herein, for the first time, an efficient manganese oxide promoted synthesis of amides via nondirected C−H activation of methylbenzenes (Figure 1).

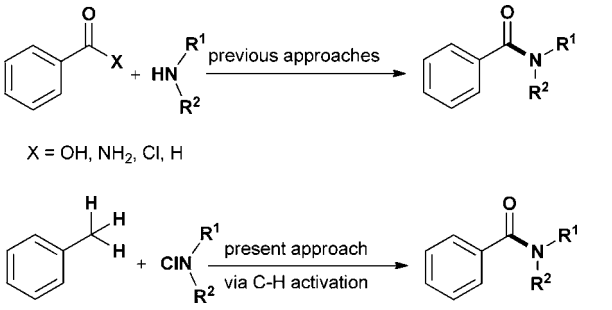
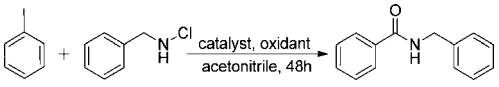


Figure 1. Amide synthesis through C−H activation.

Table 1. Optimization of Reaction Conditions[a]



entry	promoter	oxidant	temp (°C)	yield (%)[b]
1	MnO_2	TBHP	80	75
2	A-MnO_2	TBHP	80	65
3	$Cu(OAc)_2$	TBHP	80	50
4	CuI	TBHP	80	15
5	$CuBr_2$	TBHP	80	30
6	$FeCl_3$	TBHP	80	15
7	$MnCl_2 \cdot 4H_2O$	TBHP	80	trace
8	$Mn(OAc)_2 \cdot 4H_2O$	TBHP	80	trace
9	$NiCl_2 \cdot 6H_2O$	TBHP	80	20
10	TBAI	TBHP	80	55
11		TBHP	80	0
12	MnO_2		80	0
13	MnO_2	$K_2S_2O_8$	80	0
14	MnO_2	$AgNO_3$	80	0
15	MnO_2	TBHP	rt	0
16	MnO_2	TBHP[c]	80	65
17	MnO_2	TBHP	60	40
18	MnO_2	TBHP	100	75

[a] Reaction conditions: *N*-chloroamine (0.5 mmol), alkylarene (5 mmol), oxidant (4 equiv), promoter (1 equiv), and acetonitrile (1.5 mL). [b] Isolated yields after column chromatography. [c] Two equivalent.

To fulfill the aim to activate the methyl C−H bond of toluene, an initial study using toluene and benzylamine as reactants was made using $CuBr_2$ and TBHP in acetonitrile at 80 °C for 24 h, which gave rise to 40% yield of the amidation product. Other copper salts were also screened to improve the yield, but they did not surpass $CuBr_2$. However, when $CuBr_2$ was applied to the reactions involving

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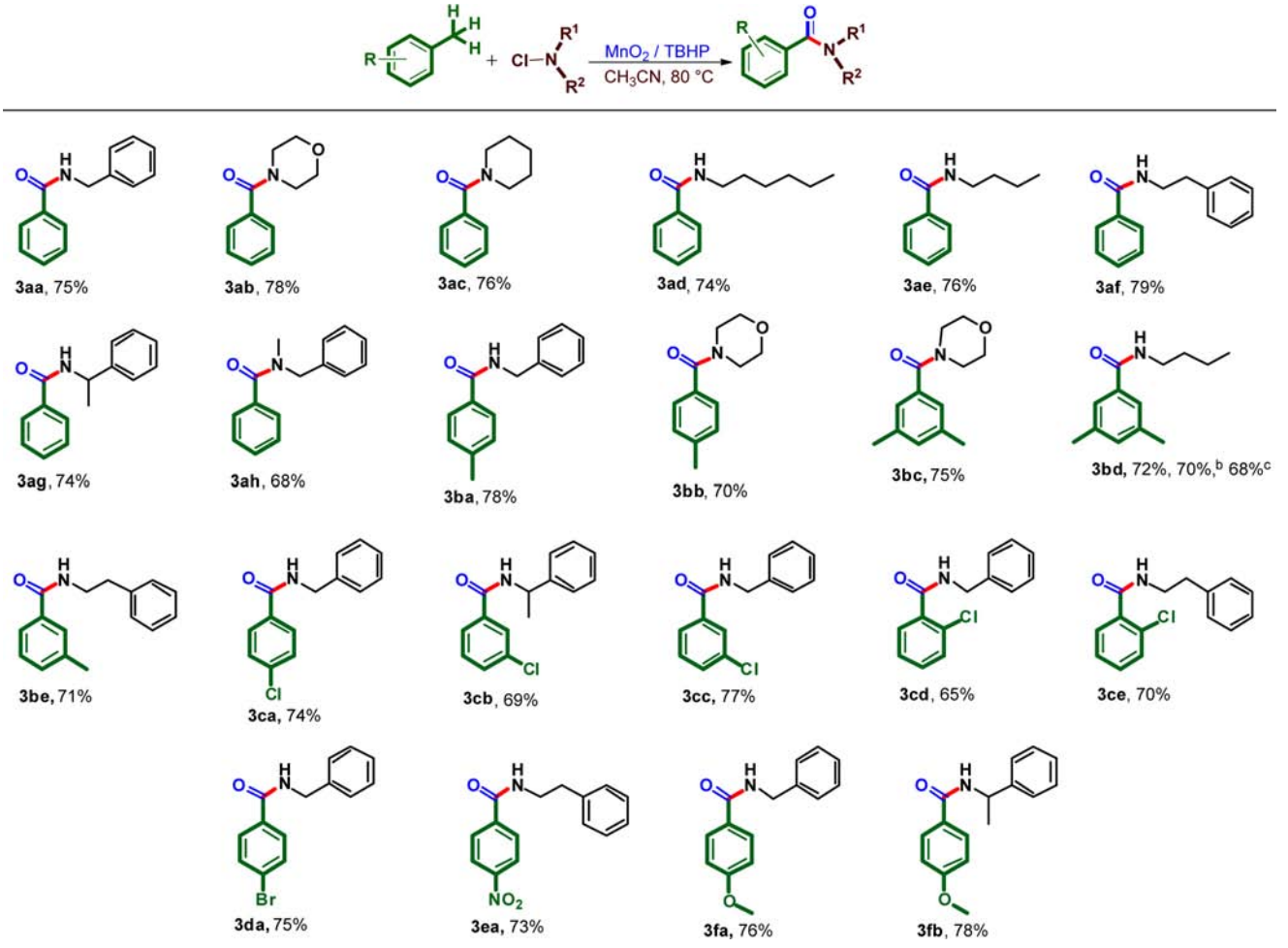
Scheme 1. Substrate Scope of the Reaction[a]



[a] Reaction conditions: *N*-chloroamine (0.5 mmol), alkylarene (5 mmol), oxidant (4 equiv), MnO_2 (1 equiv), and acetonitrile (1.5 mL). Isolated yields reported after column chromatography. [b] Second recycle. [c] Third recycle.

secondary amines such as morpholine and piperidine, it failed to provide the corresponding amides. Considering the oxidation activity[16] of manganese salts, it was then thought to be worthwhile to attempt Mn salts. The replacement of $CuBr_2$ with MnO_2 for the reaction of morpholine with toluene succeeded well, giving the corresponding amide, but that of benzylamine witnessed formation of benzamide as a byproduct. Considering the high reactivity of the nitrogen–halogen bond,[17] we next envisioned to employ *N*-chloroamines as a source of amine partner. To our utmost pleasure, we obtained the desired amides from *N*-chloroamines of both benzylamine and morpholine without the formation of any byproduct. Now a detailed investigation was carried out to optimize the reaction conditions by varying different parameters such as promoter, oxidizing agent, and temperature using a model reaction of toluene and *N*-chlorobenzylamine, and the findings are given in Table 1.

The screening was initiated using different metal salts such as $Cu(OAc)_2$, $CuBr_2$, CuI, $FeCl_3$, and $NiCl_2 \cdot 6H_2O$ using TBHP as an oxidant. All of these trials led us to finish off MnO_2 as the most suitable promoter for successful activation of benzylic C–H bonds to give the targeted amide in reasonably high yield. CuI, $CuBr_2$, and $FeCl_3$ gave poor yields (entries 4–6), but $Cu(OAc)_2$ performed satisfactorily (entry 3). The use of amorphous MnO_2 (A-MnO_2) was less effective (entry 2) as compared to MnO_2, whereas other manganese salts such as $MnCl_2 \cdot 4H_2O$ and $Mn(OAc)_2 \cdot 4H_2O$ proved worthless (entries 7 and 8). After identification of MnO_2 as the most effective promoter, the studies were next directed toward the optimization

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of molar proportion of TBHP and reaction temperature. The reaction temperature of 80 °C and 4 equiv of TBHP were found to be appropriate to bring about the utmost conversion. Decreasing the molar ratio of TBHP resulted in decrease of the yield. Changing TBHP to other oxidizing agents such as $K_2S_2O_8$ and $AgNO_3$ was also unsuccessful. TBHP in decane solution gave similar yields, but on prolongation, it gave rise to the formation of carboxylic acid, too. Effects of solvent on the reaction were not studied in detail.

After having established the reaction conditions, various alkylarenes and *N*-chloroamines were subjected to the reaction to assess the scope and versatility of the methodology, and the outcome is summarized in Scheme 1. Toluene derivatives such as *p*-xylene, *m*-xylene, *o*-chlorotoluene, *p*-chlorotoluene, *m*-chlorotoluene, *p*-bromotoluene, *p*-nitrotoluene, and mesitylene worked well and were effectively converted into the corresponding amides in high yields. Doubly methyl-substituted arenes such as *p*-xylene and *m*-xylene and triply methyl-substituted mesitylene were selectively converted to their corresponding monosubstituted amides. With regard to *N*-chloroamines, cyclic amines like morpholine and piperidine *N*-chloroamines underwent the reaction smoothly, giving tertiary amides. *N*-Chloroamines derived from aliphatic primary amines, such as *n*-hexylamine, *n*-butylamine, benzylamine, 2-phenethylamine, and 1-phenethylamine, as well as those obtained from aliphatic secondary amines such as *N*-methylbenzylamine also reacted nicely to afford the corresponding secondary and tertiary amides. Steric effects were not predominant, and their effect on the reaction yield was minimal. While recyclable studies were conducted, MnO_2 being heterogeneous in nature was recovered simply by filtration and was recycled up to three times without any significant loss in its activity after washing with acetone. The XRD patterns of fresh and recycled MnO_2 match well with each other (Supporting Information).

Based on literature survey and isolation of products, a plausible mechanism is outlined (Figure 2). Toluene is oxidized by TBHP/MnO_2 to benzaldehyde, which by subsequent action of TBHP generates an acyl radical.[18] Chloroamine on decomposition gives a nitrogen-centered radical,[17a] which then reacts with the acyl radical to afford the amide eventually.

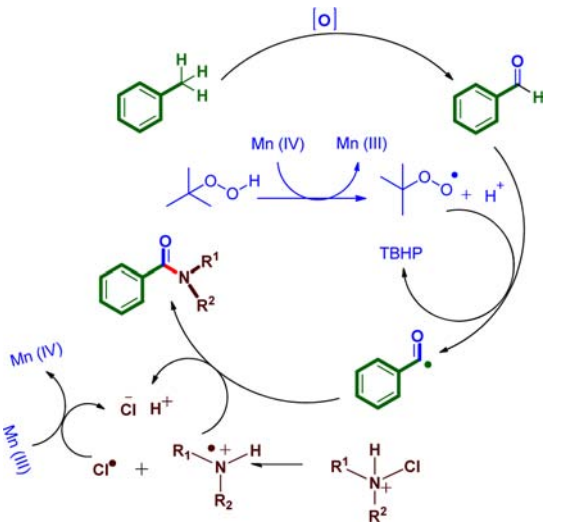

Figure 2. Proposed mechanism.

In summary, we have developed a novel MnO_2 promoted approach for the synthesis of amides through a nondirected C−H bond activation of alkylarenes using *N*-chloroamines as suitable amine partners.

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Supporting Information Available. General information, experimental procedure, spectral data, and copies of ^1H and ^{13}C NMR spectra for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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