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Manganese Oxide Promoted Liquid-Phase Aerobic Oxidative Amidation of Methylarenes to Monoamides Using Ammonia Surrogates[**]

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Selective functionalization of sp^3-hybridized C−H bonds of hydrocarbons, for example alkylarenes, to value-added products is of crucial importance.[1] With regard to oxidation of alkylarenes, there have been many efforts to find efficient catalysts to date.[1,2] For example, toluene, the simplest and readily available alkylarene, has been catalytically converted into oxidized products, such as benzyl alcohol, benzaldehyde, and benzoic acid.[1,2] Currently, benzonitrile and cyanopyridines have been produced by catalytic ammoxidation of toluene and methylpyridines, respectively.[3] These products, namely alcohols, aldehydes, carboxylic acids, and nitriles, are commercially very important as versatile intermediates in the manufacture of pharmaceuticals, agricultural chemicals, perfumes, dyes, solvents, and specialty chemicals.

Primary amides are also a very important class of compounds in chemistry as well as biology.[4] Even at present, ammonolysis of activated carboxylic acid derivatives with ammonia has still been utilized for synthesis of primary amides.[5] However, this antiquated procedure requires reagents in stoichiometric quantities, such as thionyl chloride ($SOCl_2$), and carbodiimides for pre-activation of carboxylic acids. Furthermore, at least equimolar amounts of byproducts are formed not only during the ammonolysis but also the preactivation of carboxylic acids;[5] for example, synthesis of acid chlorides by chlorination of carboxylic acids with $SOCl_2$ produces equimolar amounts of SO_2 and HCl, and ammonolysis of acid chlorides with ammonia also produces an equimolar amount of HCl. Thus, the development of efficient green procedures instead of the above-mentioned antiquated ammonolysis is a subject of urgency.

Until now, several green procedures for synthesis of primary amides have been developed.[6–10] For example, catalytic synthesis of primary amides from nitriles,[7] aldoximes,[8] primary alcohols,[9] aldehydes,[9] and primary amines[10] are attractive procedures. Herein, we demonstrate for the first time that the aerobic oxidative amidation of various kinds of methylarenes using ammonia (or its surrogates) in the presence of amorphous MnO_2 (see the Supporting Information for preparation details) [Eq. (1)].

$$\boxed{\mathrm{Ar{-}CH_3}} \xrightarrow{\mathrm{O_2,\ NH_3\ (or\ its\ surrogate)}} \boxed{\mathrm{Ar{-}CONH_2}} \qquad (1)$$

Initially, various kinds of catalysts were applied to the amidation of toluene (**1a**) to benzamide (**2a**) with urea[11] (Table 1). We found that manganese-based oxides, such as amorphous MnO_2, OMS-2, and β-MnO_2, gave **2a** in moderate to high yields based on the amount of nitrogen (ammonia) in ammonia sources, and that amorphous MnO_2 showed the best result. For example, when the amorphous MnO_2-catalyzed amidation of **1a** was carried out using urea as an ammonia source in 5 atm of O_2 at 150 °C (bath temperature), the corresponding amide **2a** was obtained in 76% yield for 3 h with formation of benzonitrile (**3a**), benzaldehyde, and benzoic acid.[12] $KMnO_4$ and $MnSO_4{\cdot}H_2O$ (precursors for amorphous MnO_2) were not effective, and the desired **2a** was not produced at all. Although Co_3O_4 gave a moderate yield of

Table 1: Aerobic oxidative amidation of toluene (**1a**).[a]

$$\underset{\mathbf{1a}}{\mathrm{Ph{-}CH_3}} \longrightarrow \underset{\mathbf{2a}}{\mathrm{Ph{-}CONH_2}} + \underset{\mathbf{3a}}{\mathrm{Ph{-}CN}}$$

Entry	Catalyst	Ammonia source	Yield [%][b]	
			2a	**3a**
1	amorphous MnO_2	urea	76	4
2	OMS-2	urea	24	3
3	β-MnO_2	urea	20	8
4[c]	$KMnO_4$	urea	<1	3
5[c]	$MnSO_4{\cdot}H_2O$	urea	<1	<1
6	Co_3O_4	urea	19	57
7	CeO_2	urea	<1	<1
8	$Ru(OH)_x/Al_2O_3$	urea	<1	8
9	amorphous MnO_2	aqueous ammonia	64	3
10	amorphous MnO_2	$(NH_4)_2CO_3$	50	2
11	amorphous MnO_2	NH_4HCO_3	58	3
12	amorphous MnO_2	$HCOONH_4$	60	3
13	amorphous MnO_2	CH_3COONH_4	17	11
14	amorphous MnO_2	$(NH_4)_2HPO_4$	47	4
15	amorphous MnO_2	NH_4NO_3	21	1
16	amorphous MnO_2	NH_4Cl	7	5

[a] Reaction conditions: **1a** (2 mL), catalyst (100 mg), nitrogen source (amount of nitrogen: 0.25 mmol), 150 °C (bath temperature), O_2 (5 atm), 3 h. [b] Yields were determined by GC using naphthalene as an internal standard and based on the amount of nitrogen (ammonia) in ammonia sources. The main byproducts were benzaldehyde and benzoic acid (for more detail, see the Supporting Information, Table S1). [c] Mn salts (0.25 mmol).

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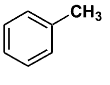
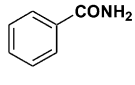
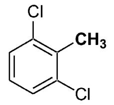
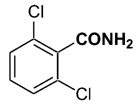
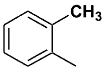
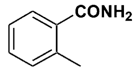
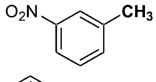
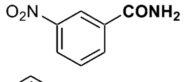
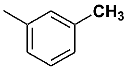
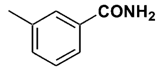
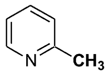
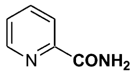
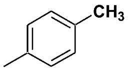
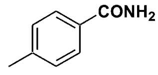
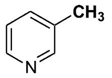
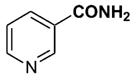
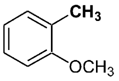
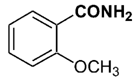
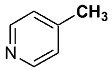
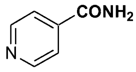
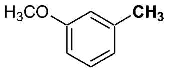
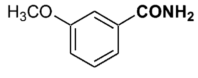
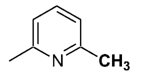
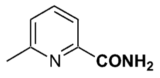
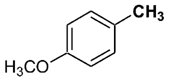
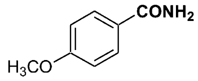
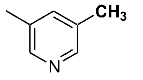
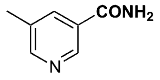
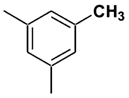
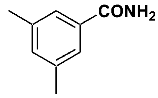
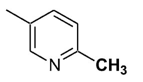
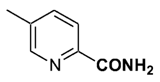
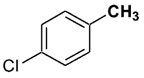
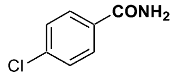
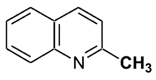
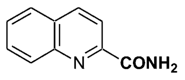
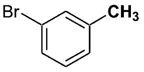
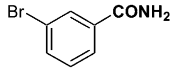
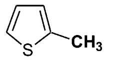
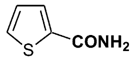
2a, a large amount of benzoic acid was produced. $Ru(OH)_x/Al_2O_3$[10b] and CeO_2 did not afford **2a** under the conditions described in Table 1. Apart from urea, aqueous ammonia, $(NH_4)_2CO_3$, NH_4HCO_3, $HCOONH_4$, and NH_4HPO_4 could act as effective ammonia sources for the present amorphous MnO_2-catalyzed amidation, giving **2a** in 47–64 % yields (Table 1).

To verify whether the observed catalysis is derived from solid amorphous MnO_2 or leached manganese species, the amidation of **1a** was carried out under the conditions described in Table 1. Amorphous MnO_2 was removed from the reaction mixture by hot filtration at 0.5 h. Then, urea was again added to filtrate, and the resulting mixture was heated at 150 °C in 5 atm of O_2. In this case, no further production of **2a** and **3a** was observed. It was confirmed by inductively coupled plasma atomic emission spectroscopy (ICP-AES) analysis that no manganese species was detected in the filtrate (below 0.008 %). All these facts can rule out any contribution to the observed catalysis from manganese species that leached into the reaction solution, and the observed catalysis is intrinsically heterogeneous.[13] Furthermore, the MnO_2 catalyst recovered after the amidation could be reused without an appreciable loss of its high catalytic performance (see entries 2, 3, 10, 11, and 18 in Table 2).

Next, the scope of the amorphous MnO_2-catalyzed amidation was examined. As shown in Table 2, various kinds of structurally diverse methylarenes could be converted into the corresponding primary amides (or nitriles) in moderate to high yields (based on ammonia). Xylenes (**1b**–**1d**) gave toluamides in moderate to high yields. In the case of *o*-xylene (**1b**), *o*-tolunitrile was formed as a main product because of the slow hydration of *o*-tolunitrile owing to the steric effect of the *ortho* methyl group.[14] In the amidation of toluene derivatives, the electronic effect of substituents was not significant; toluene derivatives with electron-donating as well as electron-withdrawing groups gave good yields of the corresponding primary amides and nitriles. In the case of halogen-substituted methylarenes (**1i**–**1k**), the desired amides and nitriles were obtained without dehalogenation. Thus, it would be possible to utilize these halogen functional groups for further modification of the amide (or nitrile) molecules. The amidation of methylpyridine and quinoline derivatives (**1m**–**1s**) also efficiently proceeded to afford the corresponding primary amides in moderate to high yields. Furthermore, methylthiophene (**1t**) could be converted into the corresponding thiophenecarboxamide.

In the case of methylarenes with two or more methyl groups (**1b**–**1d**, **1h**, and **1p**–**1r**), the amidation selectively

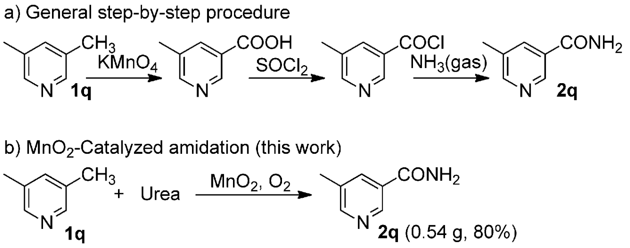
Table 2: Scope of the MnO_2-promoted amidation of methylarenes.[a]

Entry	Substrate		Product		Yield [%][b]	Entry	Substrate		Product		Yield [%][b]
1		**1a**		**2a**	76(4)	15		**1k**		**2k**	37(33)
2[c]		**1a**		**2a**	72(7)						
3[d]		**1a**		**2a**	71(8)						
4		**1b**		**2b**	15(70)	16		**1l**		**2l**	70(<1)
5		**1c**		**2c**	53(9)	17		**1m**		**2m**	86(10)
						18[c]		**1m**		**2m**	77(13)
6		**1d**		**2d**	64(6)	19		**1n**		**2n**	72(2)
7		**1e**		**2e**	66(21)	20		**1o**		**2o**	78(8)
8		**1f**		**2f**	38(3)	21		**1p**		**2p**	48(37)
9		**1g**		**2g**	90(6)	22		**1q**		**2q**	87(9)
10[c]		**1g**		**2g**	85(7)						
11[d]		**1g**		**2g**	83(7)						
12		**1h**		**2h**	50(16)	23		**1r**		**2r**	50(9)[e]
13		**1i**		**2i**	54(1)	24		**1s**		**2s**	81(16)
14		**1j**		**2j**	53(1)	25		**1t**		**2t**	59(12)

[a] Reaction conditions: Methylarene (2 mL), amorphous MnO_2 (100 mg), urea (amount of nitrogen: 0.25 mmol), 150 °C (bath temperature), O_2 (5 atm), 3 h. [b] Yields were determined by GC using naphthalene or biphenyl as an internal standard and based on the amount of nitrogen (ammonia) in urea. The values in the parentheses were yields of the corresponding nitriles. The main byproducts were aldehydes and carboxylic acids (for more detail, see the Supporting Information, Table S2). [c] The first reuse experiments. [d] The second reuse experiments. [e] 6-Methyl-3-pyridinecarboxamide and 6-methyl-3-pyridinecarbonitrile were also formed in 1 % and 4 % yields, respectively.

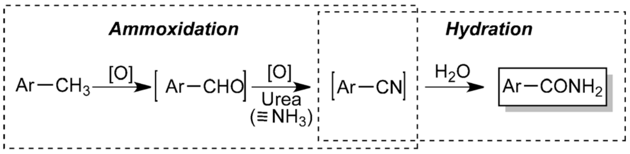
took place at one methyl group, giving the corresponding monoamides in all cases. Notably, the amidation of 2,5-lutidine (**1r**) mostly took place on the methyl group at 2 position, which is most likely due to the coordination of the pyridine group on active sites (or their neighbor).[7h]

To show the usefulness of the present MnO_2-catalyzed amidation of methylarenes, the larger-scale synthesis of 5-methylnicotinamide (**2q**) was carried out. Compound **2q** is very useful as an inhibitor of poly(ADP-ribose) synthetase,[15] and have generally been synthesized by the step-by-step procedure form **1q**; for example: 1) oxygenation of **1q** with $KMnO_4$ to the corresponding monocarboxylic acid; 2) reaction of the monocarboxylic acid with $SOCl_2$ to form the corresponding acid chloride; and 3) ammonolysis of the acid chloride (Scheme 1 a).[16] Without any decrease in the performance in comparison with the small-scale transformation in Table 2, the MnO_2-catalyzed larger scale amidation of **1q** also efficiently carried out. After the amidation was completed, the spent MnO_2 catalyst was separated by filtration and washed with ethanol and acetone. Ethanol and acetone were first removed by evaporation, and then the remaining substrate **1q** was recovered by distillation under reduced pressure (>90% recovery).[12] The solid residue was rinsed with diethyl ether, giving analytically pure **2q** (0.54 g, 80% yield of isolated product based on ammonia, >98% purity; Scheme 1 b).



Scheme 1. Synthesis of 5-methylnicotinamide (**2q**) from 3,5-lutidine (**1q**): a) General step-by-step procedure and b) MnO_2-catalyzed amidation (this study; 80% yield of isolated product). Reaction conditions for amidation: **1q** (30 mL), amorphous MnO_2 (2 g), urea (2.5 mmol), 150 °C (bath temperature), O_2 (5 atm), 4 h.

The reaction profile for the amidation of **1a** showed that the formation of not only the corresponding amide **2a** but also **3a**, benzaldehyde, and benzoic acid during the transformation (Supporting Information, Figure S1). When the transformation of **1a** was carried out in the presence of amorphous MnO_2 (without ammonia surrogates), toluene was oxidized to benzaldehyde and benzoic acid (Supporting Information, Scheme S1). We confirmed that amorphous MnO_2 showed high catalytic activities for the amidation of benzaldehyde with urea (Supporting Information, Scheme S2).[11] The reaction profile for the amidation of benzaldehyde showed that **3a** was initially formed followed by the formation of **2a**. Furthermore, amorphous MnO_2 showed high catalytic activities for the hydration of **3a** (Supporting Information, Scheme S2). When the transformation of benzoic acid with urea was carried out under the conditions described in Table 2 (in 1,4-dioxane), the corresponding primary amide **2a** was hardly produced, suggesting that the present amidation does not proceed through condensation (direct ammonolysis) of carboxylic acid with ammonia (that is, benzoic acid is a byproduct). Therefore, the present MnO_2-catalyzed amidation possibly proceeds through the sequence of ammoxidation of methylarenes to nitriles (via aldehydes), followed by hydration to form the corresponding primary amides (Scheme 2).



Scheme 2. Possible reaction path for amidation of methylarenes.

In summary, we have successfully developed a novel procedure for synthesis of primary amides by the MnO_2-catalyzed aerobic oxidative amidation of methylarenes with ammonia surrogates. A wide range of methylarenes could selectively be converted into the corresponding monoamides (or nitriles) even in the case of methylarenes with two or more methyl groups. The observed catalysis for the present amidation was truly heterogeneous, the product isolation was very easy, unreacted substrates could easily be recovered and recycled, rather inexpensive manganese-based oxides could be utilized, and the MnO_2 catalyst could be reused without an appreciable loss of its high performance.

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[11] It was confirmed by a separate experiment that urea decomposed to ammonia under similar conditions.

[12] Although a large amount of **1a** is used for the amidation (ca. 75 equiv of **1a** with respect to ammonia), we believe that this is not a serious problem because the remaining **1a** can easily be recovered by simple distillation and recycled for the next reaction.

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