CHEMISTRY
AN ASIAN JOURNAL
ACES
COMMUNICATION

DOI: 10.1002/asia.201402057

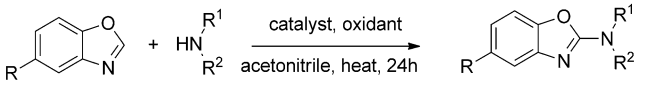
Heterogeneously Porous γ-MnO_2-Catalyzed Direct Oxidative Amination of Benzoxazole through C–H Activation in the Presence of O_2

Provas Pal, Arnab Kanti Giri, Harshvardhan Singh, Subhash Chandra Ghosh,* and Asit Baran Panda*[a]

Abstract: Oxidative amination of azoles through catalytic C–H bond activation is a very important reaction due to the presence of 2-aminoazoles in several biologically active compounds. However, most of the reported methods are performed under homogeneous reaction conditions using excess reagents and additives. Herein, we report the heterogeneous, porous γ-MnO_2-catalyzed direct amination of benzoxazole with wide range of primary and secondary amines. The amination was carried under mild reaction conditions and using molecular oxygen as a green oxidant, without any additives. The catalyst can easily be separated by filtration and reused several times without a significant loss of its catalytic performance. Of note, the reaction tolerates a functional group such as alcohol, thus indicating the broad applicability of this reaction.

The C–N bond formation reaction of aromatic and heteroaromatic compounds is one of the most important and vastly used transformations in synthetic organic chemistry.[1] It is ever demanding simply because of the great interest in nitrogen-containing heteroaromatic molecules in pharmaceutical, biological, and materials sciences.[2] Classically, aryl halides and pseudo halides with amines or their precursors are used for C–N bond formation under transition metal catalysis.[3] The strategies towards the synthesis of C–N bond are palladium-catalysed Buchwald–Hartwig coupling,[4] and copper-catalyzed Ullman and Goldberg coupling.[5] Several groups have also developed Pd-,[6] Cu-,[7] and Rh[8]-catalyzed C–N bond formation with proper ligands. Alternatively, amination of arenes and heteroarenes through catalytic C–H bond activation is developing very fast in recent years.[9] By contrast, limited examples have been reported for oxidative amination of azoles. Mori et al.,[10] Schreiber et al.,[11] and Li et al.[12] independently reported the copper catalyzed amination of azoles under harsh reaction conditions. Daun et al.[13] also reported the amination of azoles in the presence of Ni as a catalyst by using acid and organic peroxide. Miura et al.[14] reported on the amination of azoles under mild condition using chloramine as a nitrogen source instead of amine. Wang et al.[15] reported the iron-catalyzed amination of azoles using DMF as an amine source and stoichiometric amounts of imidazole as an additive. Chang et al.[16] initially reported the use of a stoichiometric amount of silver species and acid as an additive for this reaction; more recently, the same group developed cobalt and manganese-catalyzed amination of azoles in the presence of stoichiometric amounts of T-Hydro (70% *tert*-butyl hydroperoxide in water) as an oxidant and acid as additive.[17] A metal-free approach for the amination of benzoxazole was reported using iodine and tetrabutylammonium iodide as a catalyst in the presence of a stoichiometric amount of peroxide as an oxidant and acid as an additive.[18] However, limitations of these direct aminations of azoles are harsh reaction conditions and the use of both excess peroxide as an oxidant and a Brønsted acid; moreover, all reactions were conducted under homogeneous conditions. Therefore, the development of a more efficient, cheap, and reusable catalyst for amination of azoles is highly desirable.

In view of easy recycling and high catalytic efficiency, heterogeneous catalysts have been widely used in recent years. During the course of our studies on the catalytic activities of our developed lotus-shaped porous γ-MnO_2,[19] we anticipated that C–H bond activation followed by oxidative C–N bond formation of heteroarenes with amine could be achieved with our catalyst in the presence of a suitable oxidant. We have made a conscious effort to develop C–N bond formation of benzoxazole with an amine. Herein, we report the direct oxidative amination of benzoxazole using a catalytic amount of γ-MnO_2 and molecular oxygen as an oxidant (Scheme 1). To the best of our knowledge, this is the first example of a heterogeneous catalytic method for the direct oxidative amination of benzoxazole under very mild conditions.



Scheme 1. Amination of benzoxazole with an amine.

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Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/asia.201402057.

The synthesis of the catalyst was performed by following a reported procedure in which $MnCO_3$ is generated under hydrothermal conditions using aqueous $MnCl_2$, ammonium carbonate, and citric acid followed by calcination at 350 °C in air (see the Supporting Information for details).[19] The XRD pattern of calcined materials was indexed to hexagonal γ-MnO_2 (JCPDS Card 14-644), as a binary mixture of hexagonal akhtenskite (ε-MnO_2) (~60%) and intergrowth of tetragonal rutile-type-structured pyrolusite (β-MnO_2, ~15%) and orthorhombic ramsdellite (~25%) with different crystalline domain sizes (Figure 1a).[20] Scanning electron microscopy (SEM) images revealed the formation of bunches of uniform lotus flowers made of spindle-shaped petals with about 6 μm length and 2 μm width in the middle (Figure 1b). The petals are porous and the pores were generated due to the evolution of CO_2 during the decomposition of $MnCO_3$ (Figure 1c). The electron diffraction ring patterns and distinct lattice fringes in the high-resolution transmission electron microscopy (HR-TEM) image confirmed that the materials are polycrystalline and highly crystalline (Figure S1, Supporting information). The nitrogen sorption isotherm corresponding to the type IV and H_2-type hysteresis loop confirmed the formation of mesopores in the synthesized porous lotus-shaped γ-MnO_2 samples.

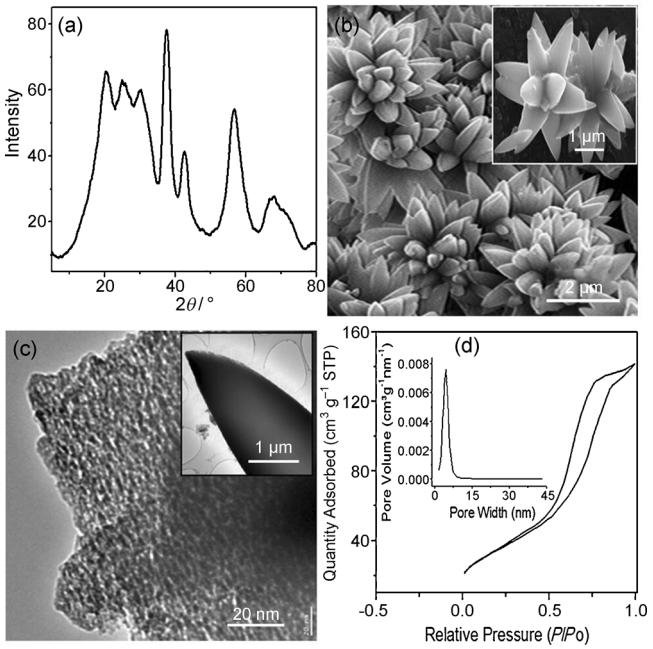
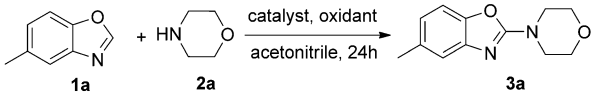


Figure 1. Analysis of the synthesized γ-MnO_2 catalyst by XRD (a), SEM (b), and TEM (c). d) Nitrogen sorption isotherms and BET surface area of the γ-MnO_2 catalyst.

The synthesized material showed a reasonably high total surface area of 145 $m^2 g^{-1}$ with a narrow pore-size distribution of 4.2 nm (Figure 1d, inset). It showed two H_2 consumption steps during H_2-TPR (TPR = temperature-programmed reduction) in the temperature range of 150 to 450 °C. The first step with a peak at 304 °C is due to the desorption of surface (O^- and O_2^-) and labile oxygen species,[21] and second step with a peak at 420 °C (Figure S1, Supporting Information) is associated with the evolution of lattice oxygen during the transformation of MnO_2 to the Mn_2O_3 phase.[22] In the first step the material consumed a reasonably high amount of H_2 originating from its texture and surface area; thus, it was expected to display good oxidation properties at low temperature. Analysis by X-ray photoelectron spectroscopy (XPS) revealed the presence of Mn^{+3} species; it is well known that a mixed valency of manganese ions gives rise to oxidation properties.[23] The oxygen adsorption on the surface of the catalyst increased and the formation of O^-, O_2^-, and of labile oxygen increased due to the presence of the mixed valency (Figure S2, Supporting Information). This excess amount of oxygen facilitates the oxidation reaction. As this material contains an excess of low-temperature reducible surface oxygen species, we expected that oxidative C–N bond formation of heteroarenes could be achieved. Accordingly, we began our study with the model reaction of 5-methyl benzoxazole with morpholine to afford 2-(4-morpholinyl)-5-methylbenzoxazole (Table 1).

In an initial attempt, a catalytic amount of γ-MnO_2 together with molecular oxygen as an oxidant and acetic acid as an additive was used in acetonitrile at 50 °C to yield the desired amino benzoxazole product in 84% yield (entry 1, Table 1); however, most of the heterogeneous MnO_2 catalyst was leached out as $Mn(OAc)_2$ after reaction with acetic acid. To prevent the leaching of MnO_2, we replaced acetic acid with a heterogeneous solid acid, that is, mesoporous zirconium phosphate,[24] and a comparable reactivity was ob-

Table 1. Optimization of the reaction conditions.[a]



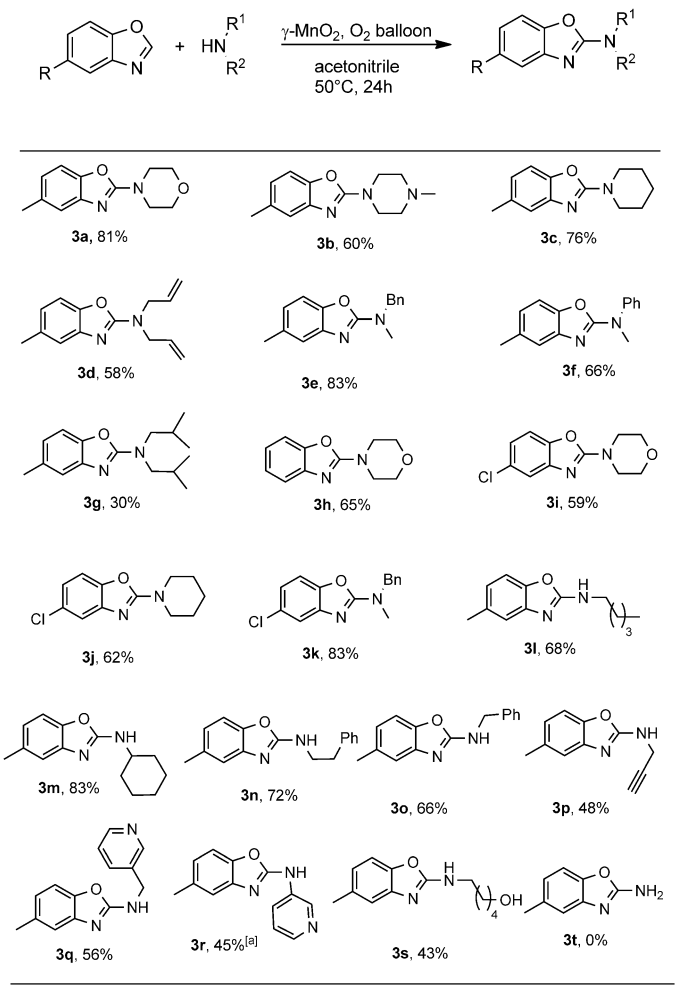
1a 2a 3a

Entry	Catalyst [mg]	Oxidant	Additive	T [°C]	Conversion[b] [%] (yield %)[c]
1	25	O_2	AcOH	50	92 (84)
2	25	O_2	m-ZrP	50	89 (82)
3	25	O_2	–	50	86 (81)
4	25	O_2	–	80	88 (82)
5	25	O_2	–	25	20
6	10	O_2	–	50	45
7	50	O_2	–	50	88
8	25	air	–	50	18
9	25	O_2	–	50	89[d]
10	25	O_2	–	50	68[e]
11	25	O_2	–	50	42[f]
12	25	O_2	–	50	88[g]
13	25	O_2	–	50	18[h]
14	25	O_2		50	0[i]

[a] Unless otherwise stated, all reactions were carried out under the following conditions: acetonitrile (2 mL), **1a** (0.5 mmol), **2a** (1.2 equiv), catalyst γ-MnO_2 (25 mg), oxygen atmosphere, 50 °C, 24 h. [b] NMR conversion. [c] Isolated yield. [d] 48 h. [e] 12 h. [f] 4 h. [g] Bubbling with molecular oxygen. [h] Commercial MnO_2. [i] Synthesized Mn_2O_3. m-ZrP = mesoporous zirconium phosphate.

served (entry 2). Leaching of manganese did not occur as confirmed by inductively coupled plasma-atomic emission spectrometry (ICP-AES) measurements of the reaction mixture. To examine the role of the solid acid, we have carried out the same reaction in the absence of zirconium phosphate. To our delight, a similar conversion and yield were obtained (entry 3). Next, we varied the reaction temperature. A similar conversion was observed in refluxing acetonitrile, while the yield was significantly decreased at room temperature (25 °C, entries 4–5). Subsequently, variation of catalyst loading was tested (entry 6–7), and it was found that an amount of 25 mg of catalyst is optimal for this reaction. When we used air as an oxidant a significant drop in yield was observed (entry 8). Next, we carried out reactions at different reaction times (entries 9–11), and we found that a minimum of 24 h is required for the reaction to reach the highest conversion. Screening a range of solvents revealed that acetonitrile led to better results as compared to those obtained with solvents such as THF, DMSO, toluene, ethyl acetate, and dichloromethane (see the Supporting Information). Bubbling of oxygen into reaction mixture did not improve the yield significantly (entry 12). When we used commercial MnO_2 and synthesized Mn_2O_3 instead of our synthesized γ-MnO_2, the desired aminated benzoxazole product was obtained in a yield of only 18% and 0%, respectively (entries 13–14).

With the optimized conditions (entry 3) in hand, we explored the substrate scope of this reaction. Under the optimized conditions, amination of benzoxazole with various primary and secondary amine was performed (Scheme 2). These reactions afforded the corresponding 2-amino benzaoxazole products in moderate to good yields. The reaction of 5-methyl benzoxazole with cyclic secondary amines like morpholine, piperidine, and 1-methylpiperazine afforded the corresponding amination products **3a–3c** in high yields. Acyclic secondary amines like diallyl amine, *N*-methyl benzyl amine, and *N*-methyl aniline also reacted very smoothly to afford corresponding amination products **3d–3f** in high yields. However, sterically hindered acyclic secondary amines like diisobutyl amine led to the corresponding product **3g** with a much lower yield (30%). Benzoxazole bearing an electron-withdrawing chloride group and unsubstituted benzoxazole reacted smoothly with morpholine and other seconday amines to produce the corresponding aminated products **3h–3k**. We next examined the scope of the amination of 5-methyl benzoxazole with primary amines. To our delight, amination of benzoxazole with a variety of primary amines such as cyclohexyl amine, *n*-pentyl amine, 2-phenylethyl amine, and benzyl amine also worked well, affording the products **3l–3o** in yields of 66–83%. Of note, propargyl amine could also be used as a facile substrate for the amination reaction to give product **3p**. Amination with pyridine-3-methylamine worked smoothly to yield **3q** in 56%, and 3-amino pyridine gave a promising yield of 45% of the aminated product **3r** at an elevated temperature. It is important to note that a functional group such as alcohol is tolerated to give **3s** in a moderate yield, thus indicating



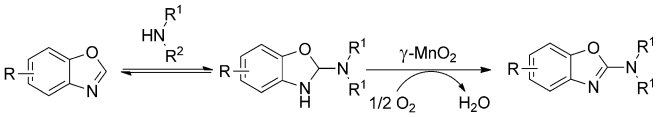
Scheme 2. Reaction scope of the amination of benzoxazole. Reactions were carried out with benzoxazole (0.5 mmol), amine (1.2 equiv), γ-MnO_2 (25 mg) in acetonitrile (1 mL) at 50 °C for 24 h under oxygen atmosphere. All yields reported are isolated yields. [a] At 100 °C.

a broad applicability of this reaction. We sought to extend our facile amination method to the synthesis of primary amines using several ammonia sources such as ammonium hydroxide, ammonium chloride, and ammonium carbonate, but to our disappointment no reaction product **3t** could be obtained. We have tested other substrates like *N*-ethylbenzimidazole, benzothiazole, and benzofuran under the optimized conditions and also at higher temperature (125 °C) and increased catalyst loading; however, no or very poor yield of aminated product was obtained (see Table S2, Supporting Information). This might be due to the higher pK_a values of C_2–H of the other substrates compared to that of benzoxazole. Catalyst γ-MnO_2 showed promising recyclability for a model reaction, that is, amination of 5-methyl benzoxazole with morpholine (Table S3, Supporting Information). For the first two runs, the catalytic activity remained the same, while for further cycles a decrease in catalytic activity was observed. We observed breaking of petals in the catalyst by SEM after the fourth cycle (Figure S3, Support-

ing Information). Furthermore, a decrease in surface area was observed ($S_{BET} = 125\ m^2 g^{-1}$). This could be the main reason for the gradual deactivation of the catalyst. After the reaction, the catalyst was separated through simple filtration. Notably, negligible amounts (<1 ppm) of leached Mn was observed, as assessed from the ICP-AES analysis of the filtrate. To examine if the leached catalyst is responsible for the observed catalytic activity, we have carried out the amination reaction after removal of the solid catalyst by filtration. No appreciable amination was observed after 24 h, thus suggesting that heterogeneous porous γ-MnO_2 is the true active catalyst (Table S3, Supporting Information).

While the reaction mechanism has not been elucidated yet, we have carried out some experiments to gain some insight into the potential mechanism. When we carried out the experiments in the presence of a radical scavenger (TEMPO)[25] under the standard reaction conditions, the desired product was still obtained with a similar yield (79%). This result indicates that the reaction does not proceed through a free-radical pathway. Unlike Chang et al.,[17] we have not observed a ring-opened amidine intermediate in the ^{1}H NMR spectrum of the crude reaction mixture during the reaction. Based on previously reported mechanistic studies on the amination of azoles and our observations during the course of the present study, we propose a tentative mechanism for this reaction (Scheme 3), in which the amine as a nucleophile first reacts with benzoxazole to form 2-amino benzoxazolidine, which then re-aromatizes in the presence of oxygen as an oxidant and γ-MnO_2 as a catalyst.[16]

In summary, we have developed the first heterogeneous catalytic system for the direct amination of benzoxazole with amines using molecular oxygen as an oxidant. A wide range of both primary and secondary amines were reacted



Scheme 3. Proposed reaction mechanism for the amination of benzoxazole.

with benzoxazole to synthesize 2-amino benzoxazole derivatives, which are important skeletons in several biologically active compounds. The C–N bond formation reactions were performed using oxygen, an environmentally benign and green oxidant. The catalyst is reusable and can easily be separated from the reaction mixture. Applications of this methodology to the synthesis of more complex 2-amino azoles and direct aminations of other heteroaromatic compounds are currently under investigation in our group.

Experimental Section

Synthesis of lotus-shaped porous γ-MnO_2

In a typical synthetic procedure, a solution of $(NH_4)_2CO_3$ (4 g, 25 mmol) in H_2O (20 mL) was added to 20 mL of a pre-mixed solution of $MnCl_2$ (analytical reagent grade, 2 g, 10.1 mmol) and citric acid (2 g, 10.4 mmol). The clear solution was then transferred to a 60 mL Teflon-lined stainless steel autoclave, sealed, and heated for 12 h at 150 °C. After that, the mixture was allowed to cool to room temperature and the resultant precipitates were collected, thoroughly washed with water and ethanol, and finally dried at 90 °C. Finally, the dried powder was calcined at 350 °C for 6 h. The catalyst was characterized by XRD, SEM, TEM, BET surface area, and H_2-TPR.

Representative procedure for the amination of benzoxazole

A two-neck, 10 mL round-bottomed flask fitted with a reflux condenser was charged with 5-methylbenzoxazole (0.5 mmol, 1.0 equiv) and catalyst γ-MnO_2 (25 mg). The reaction vessel was then evacuated and refilled with oxygen. Subsequently, morpholine (0.6 mmol, 1.2 equiv) and acetonitrile (1.0 mL) were added under oxygen atmosphere, and an oxygen balloon was fitted at the top of the condenser. The reaction mixture was then stirred for 24 h at 50 °C. The crude mixture was filtered through a plug of celite and washed with EtOAc (25 mL). The organic layer was washed with water and brine, dried over $MgSO_4$, and then concentrated under reduced pressure. The resulting residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc = 10:1) to afford 2-(4-morpholinyl)-5-methylbenzoxazole (**3a**, 81%) as a white solid.

Acknowledgements

CSIR-CSMCRI Communication No. 156/2013. The authors acknowledge the Department of Science and Technology (DST), India, (SR/S1/IC-33/2011) for financial support. The authors also acknowledge the Analytical Discipline and Centralized Instrumental Facility of CSMCRI for materials characterization. PP,AKG and HS are thankful to CSIR and UGC for research fellowships. PP, AKG and HS are also thankful to AcSIR for providing the PhD degree.

Keywords: amination · benzoxazole · C–H activation · heterogeneous catalysis · manganese

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Received: February 14, 2014
Published online: ■■ ▮▮, 0000

COMMUNICATION

Amination

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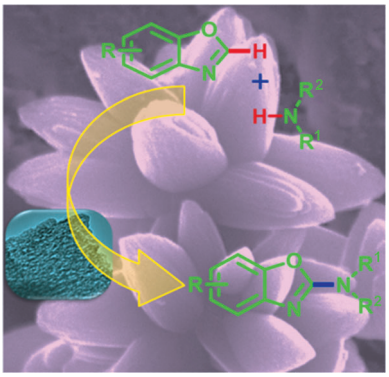
Heterogeneously Porous γ-MnO_2-Catalyzed Direct Oxidative Amination of Benzoxazole through C−H Activation in the Presence of O_2



Sorry for being so direct: The heterogeneously catalyzed direct amination of benzoxazole with a wide range of primary and secondary amines, using molecular oxygen as a green oxidant under mild reaction conditions, is reported. The catalyst can easily be separated by filtration and reused. The 2-aminobenzoxazole products are important skeletons in several biologically active compounds.