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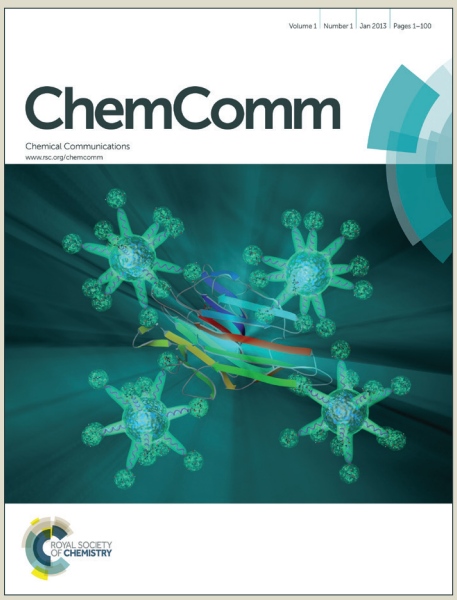





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# A cascade synthesis of quinazolinones and quinazolines using α-$MnO_2$ catalyst and *tert*-butyl hydroperoxide (TBHP) as oxidant

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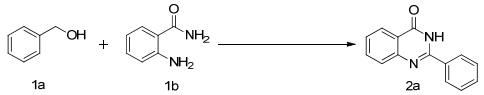
**Heterogeneously catalyzed synthesis of quinazolinones or quinazolines is reported in this study. An α-$MnO_2$ catalyst is found to be highly active and selective in the oxidative cyclization of anthranilamides or aminobenzylamines with alcohols using TBHP as oxidant. This protocol exhibits broad substrate scope, and is operationally simple without additive.**

There is considerable interest in cascade organic synthesis using heterogeneous catalysts,[1] such as metal oxides, metals and zeolites, the merits of which include easy catalyst separation, recycling and high synthetic efficiency even under flow conditions.[2] Quinazolinone and its derivatives are important compounds,[3] and have been widely used in hypnotic, sedative, and anti-inflammatory reagents.[4] Among the various synthetic efforts,[5] the direct oxidative cyclization forming N-heterocyclic rings has attracted more attention on account of abundantly available reactants, such as anthranilamides and alcohols. However, it requires a catalyst to be highly active and selective toward the dehydrogenation of C–H bond and N–H bond in one-pot, which usually leads to poor selectivity. Many studies have reported on the catalytic synthesis of quinazolinones from aldehydes and amides using the catalysts of $FeCl_3$,[6] $I_2$,[4b] $Pd(OAc)_2$,[7] $Ru(PPh_3)_3(CO)(H)_2$[8] and $[Cp^*IrCl_2]_2$.[9] However, little attention has been paid to the heterogeneously catalyzed approaches, primarily due to lack of efficient catalysts.

With the advance of nanoscience, many new nanocrystalline oxides have been synthesized and used as catalysts.[10] Depending on the reaction conditions and crystalline morphologies, some oxides may show very different catalytic behaviors. Manganese oxide is one of such classes, and is commonly used as stoichiometric oxidant, but in some cases as excellent catalysts.[11] We have recently reported the α-$MnO_2$ catalyst and TBHP oxidant is efficient in the oxidative self-coupling of amines to imines forming C=N bond at room temperature.[2b] In our continuous exploration of catalytic system of α-$MnO_2$ catalyst and TBHP oxidant, we find that this system can be used in the dehydrogenation of C–H bond and N–H bond in one-pot, and realize the direct oxidative cyclization of anthranilamides with alcohols. A wide range of quinazolinones and quinazolines are synthesized with 71-99% yields. This study

**Table 1**. Synthesis of quinazolinones.[a]




| Entry | Catalyst | Solvent | Yield [%][b] |
|---|---|---|---|
| 1 | α-$MnO_2$ | PhCl | 71 |
| 2 | β-$MnO_2$ | PhCl | 67 |
| 3 | δ-$MnO_2$ | PhCl | 40 |
| 4 | γ-$MnO_2$ | PhCl | 54 |
| 5 | OMS-2 | PhCl | 63 |
| 6 | $Mn_3O_4$ | PhCl | 46 |
| 7 | $Fe_2O_3$ | PhCl | 20 |
| 8 | CuO | PhCl | 23 |
| 9 | $Cu_2O$ | PhCl | 45 |
| 10 | $Co_3O_4$ | PhCl | 21 |
| 11 | $CeO_2$ | PhCl | 6 |
| 12 | Zn/α -$MnO_2$ | PhCl | 48 |
| 13 | Co/α-$MnO_2$ | PhCl | 51 |
| 14 | Ni/α-$MnO_2$ | PhCl | 57 |
| 15 | Mg/α-$MnO_2$ | PhCl | 49 |
| 16 | Cu/α-$MnO_2$ | PhCl | 46 |
| 17 | α-$MnO_2$-150 | PhCl | 81 |
| 18 | α-$MnO_2$-250 | PhCl | 59 |
| 19 | α-$MnO_2$-350 | PhCl | 51 |
| 20[c] | α-$MnO_2$-150 | PhCl | 11 |
| 21[d] | α-$MnO_2$-150 | PhCl | 0 |
| 22 | - | PhCl | 0 |
| 23 | α-$MnO_2$-150 | Acetonitrile | 17 |
| 24 | α-$MnO_2$-150 | Dichloromethane | 77 |
| 25 | α-$MnO_2$-150 | Dimethyl sulphoxide | 13 |
| 26 | α-$MnO_2$-150 | Tetrahydrofuran | 10 |

[a] Reaction conditions, 1.5 mmol 1a, 0.5 mmol 1b, 2 mmol TBHP, 0.0[illegible] mmol catalyst, 80 °C, 12 h, 2 mL solvent. [b] GC yields by internal standard (n-dodecane) based on amine. [c] In 0.3 MPa $O_2$ and 120 °C. [d] Without TBHP.

demonstrates that α-$MnO_2$ and TBHP consist of an efficient oxidative dehydrogenation catalytic system for C–H bond and N–H bond transformation.

The initial studies were carried out using the reaction of benzyl alcohol and anthranilamide in the presence of 10 mol% catalyst and 1.3 eqv. TBHP at 80 °C. Among the screened manganese oxides, α-$MnO_2$ offered 71% yield (Table1, entry 1), which surpassed other manganese oxides (Table1, entries 2-6). Other metal oxides, which are frequently used as oxidation catalysts, gave much lower yields (Table 1, entries 7-11). We tried to increase the catalytic activity by heteroatom-doping of α-$MnO_2$ (M/α-$MnO_2$, M denotes heteroatom) or thermal annealing of α-$MnO_2$ in Ar (α-$MnO_2$-T, T denotes temperature).[12] Both operations on α-$MnO_2$ were intended to create more active sites and thus increase activities.[13] However, in a contrary, doping α-$MnO_2$ with Zn, Co, Ni, Mg, and Cu elements resulted in even lower yields (Table 1, entries 12-16). The annealing temperature has strong effect on the catalytic performance. The yields over α-$MnO_2$-250 and α-$MnO_2$-350 were lower than that over the pristine α-$MnO_2$ (Table 1, entries 18-19). α-$MnO_2$-150 exhibited the best catalytic performance with 81% yield (Table 1, entry 17). After reaction, the catalyst can be separated by centrifugation and reused for several times with no apparent loss of catalytic performance (Figure S1). The SEM and TEM images of α-$MnO_2$ revealed the catalyst has nanoflower morphology (Figure S2). The inductively coupled plasma-mass analysis revealed that no Mn species were leached in the reaction mixture, indicating the catalyst is robust and the reaction is heterogeneous in nature. Thermal annealing under inert conditions removes some surface oxygen and creates more vacancy sites, which may function as substrate activation sites. However, due to the variable valence and structure of manganese oxides, the annealing at much higher temperature (>150 °C) may induce phase reconstruction and result in lower activity.

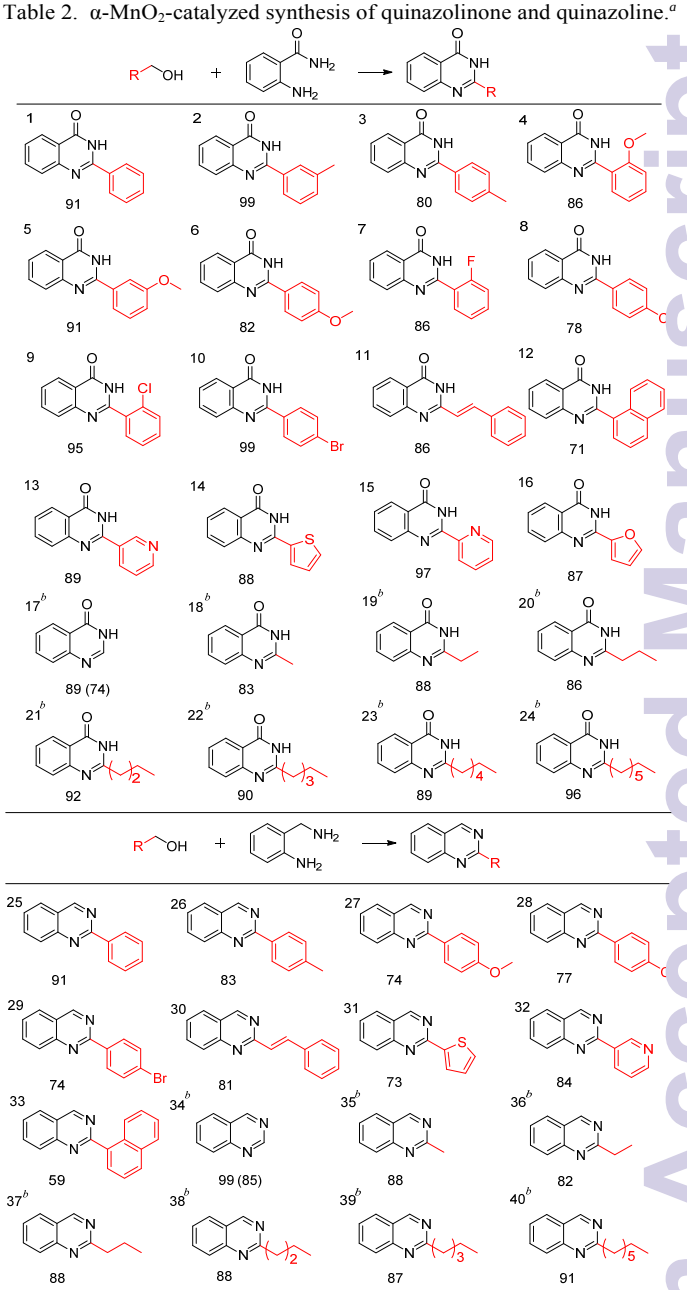
Replacement of TBHP with molecular oxygen gave only 11% yield (Table 1, entry 20). $H_2O_2$ is an instable oxidant, and quickly decomposes over α-$MnO_2$ during the reaction at room temperature. As a result, no conversion is observed with the use of $H_2O_2$ as oxidant. In contrast, only 1.3 eqv. of TBHP relative to alcohol is required with the utilization efficiency at least 77%. The control tests show that both TBHP and α-$MnO_2$ is indispensable in this reaction (Table 1, entries 21-22).

Next we evaluated the effect of solvent. Chlorobenzene is the best solvents among acetonitrile, dichloromethane, dimethyl sulphoxide and tetrahydrofuran (Table 1, entries 23-26).

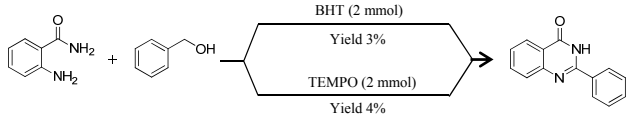
Encouraged by these initial results, we then chosen α-$MnO_2$-150 as the catalyst and PhCl as the solvent to investigate the substrate scope. A wide range of quinazolinones were synthesized with good yields (Table 2). Electron-donating and -withdrawing substituents (–$CH_3$, –$OCH_3$, –F, –Cl, –Br) on the phenyl group of aromatic alcohols have minor effect, affording 82-99% quinazolinones yields (Table 2, entries 1-10). The olefinic C=C bond survives under the reaction conditions in the case of cinnamyl alcohol (Table 2, entry 11). 1-Naphthalenemethanol is relatively inert to be oxidized due to steric hindrance (Table 2, entry 12). Heteroatoms may poison the noble metal site because of strong coordination. However, in the present study, heterocyclic alcohols could be efficiently transformed into the desired products with high yields (Table 2, entries 13-16). Furthermore, inert aliphatic alcohols were converted with reasonably good yields (Table 2, entries 17-24).

The success of the above experiments drove us to further apply the method to the quinazolines synthesis using aminobenzylamines and alcohols. Various alcohols, including aromatic alcohols, heterocyclic alcohols and aliphatic alcohols, are all transformed into the corresponding quinazolines with 59-91% yields (Table 2, entries 25-40).

Table 2. α-$MnO_2$-catalyzed synthesis of quinazolinone and quinazoline.[a]

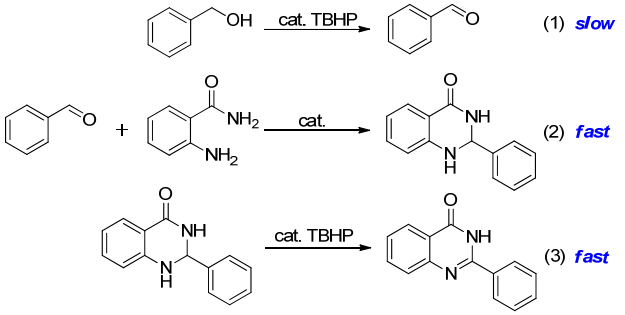



[a] Reaction conditions: 0.5 mmol amines, α-$MnO_2$-150 (10 mol%), 2 mmol TBHP, 1.5 mmol alcohols, 2 mL chlorobenzene, 80 °C, 16 h. GC yields by internal standard (n-dodecane) based on amine. Data in the parentheses indicate isolated yields. [b] Two mL of alcohol were used.




Scheme 1. Control experiments in the presence of radical inhibitors.

The reaction mechanism was further studied. Benzaldehyde was generated during the reaction as detected by GC. In the presence of the α-$MnO_2$ catalyst and TBHP, a reaction of benzaldehyde and anthranilamide generated **2a**. While, without the catalyst and TBHP, 2,3-dihydroquinazolinone was obtained.[14] These results indicate that aldehyde and 2,3-dihydroquinazolinone should be the reaction intermediates. The addition of (2,2,6,6-tetramethylpiperidin-1-yl)oxy (TEMPO) and butylated hydroxytoluene (BHT) as a radical inhibitor greatly inhibited the reaction (Scheme 1), indicating the radical process nature.[15] Based on the above-mentioned results, we propose a reaction route (Figure 1). First, benzyl alcohol is oxidized to benzaldehyde (step 1). Then, benzaldehyde reacts with anthranilamide to form 2,3-dihydroquinazolinone (step 2), which is then oxy-dehydrogenated over catalyst to **2a** (step 3). Oxy-dehydrogenation of alcohol is the rate-determining step since the step has the lowest reaction rate ($3.0 \times 10^{-5}$ M $s^{-1}$). Oxy-dehydrogenation of 2,3-dihydroquinazolinone was not affected by the presence of BHT, indicating this step does not involve radical mechanism. Catalytic reactions may take place on surface defect sites of α-$MnO_2$, the property of which is altered during doping with other metals and thermal annealing. The TBHP radical generated on defect site, probably forming TBHP-$MnO_2$ adduct, oxidizes alcohol to aldehyde, and then dihydroquinazolinone to **2a**.[2b, 16]




| rate ($10^{-5}$ $MS^{-1}$) | no BHT | 1 equiv. BHT |
|---|---|---|
| $r_1$ | 3 | 0.9 |
| $r_2$ | 8.5 | not applicable |
| $r_3$ | 11 | 11 |

Figure 1. Rates of each step at 80 °C with and without 1 eqv BHT in 30 min. Reaction conditions: 0.5 mmol substrate, 1 mmol TBHP, 0.5 mmol BHT, 0.05 mmol catalyst, 2 mL chlorobenzene.

## Conclusions

In summary, a robust and reusable α-$MnO_2$ catalyst is shown to be highly active for the cascade synthesis of quinazolinones or quinazolines from anthranilamides or aminobenzylamines with alcohols. The α-$MnO_2$ could be reused without loss of its high catalytic performance. In general, the simple, cost-effective and efficient protocol is expected to contribute to its utilization for the synthesis of various products.

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## Notes and references

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Electronic Supplementary Information (ESI) available: the experimental section and characterization data. See DOI: 10.1039/c000000x/

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