Letter

Substrate Promiscuity of ortho-Naphthoquinone Catalyst: Catalytic Aerobic Amine Oxidation Protocols to Deaminative Cross-Coupling and N-Nitrosation

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Substrate Promiscuity of *ortho*-Naphthoquinone Catalyst: Catalytic Aerobic Amine Oxidation Protocols to Deaminative Cross-Coupling and *N*-Nitrosation

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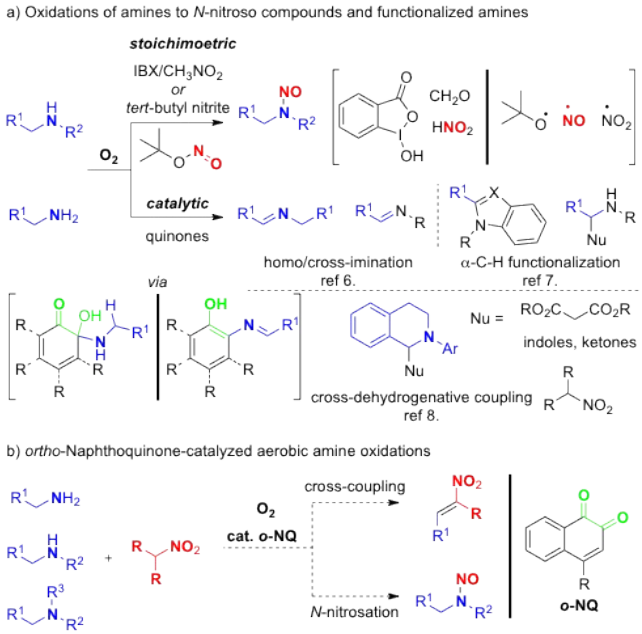
ABSTRACT: *ortho*-Naphthoquinone-based organocatalysts have been identified as versatile aerobic oxidation catalysts. Primary amines were readily cross-coupled with primary nitroalkanes via deaminative pathway to give nitroalkene derivatives in good to excellent yields. Secondary and tertiary amines were inert to *ortho*-naphthoquinone catalysts, however secondary nitroalkanes were readily converted by *ortho*-naphthoquinone catalysts to the corresponding nitrite species that in situ oxidized the amines to the corresponding *N*-nitroso compounds. Without using harsh oxidants in a stoichiometric amount, the present catalytic aerobic oxidation protocol utilizes the substrate promiscuity feature to provide a facile access to amine oxidation products under mild reaction conditions.

KEYWORDS: aerobic oxidation, amines, cross coupling, deaminative reaction, nitroalkanes

Aerobic oxidations of amines to other functional groups are industrially relevant chemical processes with longstanding research interests in the development of efficient catalytic systems.[1] The recent advances in metal-catalyzed oxidation of amine substrates clearly demonstrate the importance of catalyst design methods and optimization processes due to the subtle interaction between substrates and metal catalysts.[2] In contrast, the catalytic use of organic oxidants such as IBX (2-iodoxybenzoic acid)[3] and TBN (*tert*-butyl nitrite)[4] for the oxidation of amines is yet to be achieved (Scheme 1a). The aerobic oxidations of amines have been achieved with various quinone organocatalysts,[5] where the different amine oxidation potentials are exploited to accomplish the cross-imination of amines,[6] oxidative α-C-H functionalization of amines,[7] and cross-dehydrogenative coupling of amines.[8] In addition, the recent quinone organocatalyst systems do not require metal/acid co-catalysts to enhance the reactivity since the quinone organocatalysts display the much improved catalytic reactivities.[6,7,8b,9]



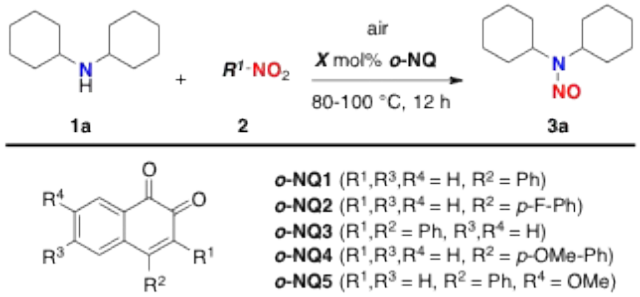
Scheme 1. Aerobic Oxidation of Amines to Other Functional Groups

ortho-Naphthoquinones are stable under acidic and basic conditions, and also possess excellent thermal stability upto 140 °C.[10] The use of *ortho*-naphthoquinones in the aerobic oxidation of amines to imines has been demonstrated in 2016.[11] In 2018, our group disclosed the direct aerobic oxidation of amines to carbonyl compounds in the presence of *ortho*-naphthoquinone catalyst.[12] Encouraged by versatile catalytic modes of *ortho*-naphthoquinones, we investigated the cross-coupling between amines and nitroalkanes. Herein, we

describe the substrate promiscuity of *ortho*-naphthoquinone catalyst that *on demand* activates either amine substrate or nitroalkane substrate. Such substrate promiscuity of catalysts has allowed the deaminative cross-coupling of primary amines and primary nitroalkanes as well as the *N*-nitrosation of secondary and tertiary amines. To the best of our knowledge, the current method is the first catalytic *N*-nitrosation reaction utilizing an aerobic nitrite generation from nitroalkanes under mild reaction conditions. [13] In addition, while nitroalkanes had been utilized in the cross-dehydrogenative coupling of tertiary amines, *N*-phenyltetrahydroisoquinolines,[8] the deaminative cross-coupling of primary amines with nitroalkanes has not been examined.

The *N*-nitrosation of secondary amine **1a** was investigated using *ortho*-naphthoquinone catalysts (***o*-NQ**) and nitroalkanes **2**, where the catalytic generation of nitrite species was postulated by the reaction between nitroalkanes and *ortho*-naphthoquinones (Table 1). While the initial experimentation using the reaction solvents such as THF, CH_3CN, and $PhCH_3$ failed to provide the desired *N*-nitroso product **3a**, the use of 15 equiv of nitromethane **2a** as solvent led to the formation of **3a** in 17% yield (entry 1). The subsequent evaluation of other nitroalkanes **2b-2d** quickly suggested 2-nitropropane **2d** as an optimal nitroso source, leading to **3a** in 80% yield (entry 2-4). Next, the catalyst structure-activity relationship studies revealed the *ortho*-naphthoquinone catalyst (***o*-NQ2**) with a 4-FPh group as the choice of catalyst, providing **3a** in 89% yield (entry 5-8). The use of 10 mol% ***o*-NQ2** slightly lowered the isolated yield of **3a** to 77% (entry 9), illustrating the optimal catalyst loading as 15 mol%. The reaction at 80 °C resulted in the significant reduction of the catalytic activity (entry 10), and the use of oxygen balloon did not particularly influence the catalytic activity (entry 11). The employment of less amount of the nitroso source **2d** was effective (entry 12), the feature suited for the large-scale reactions. The control experiments also confirmed the critical role of oxygen (entry 13) and ***o*-NQ2** (entry 14) for the catalytic activity and the generation of nitrosating species, respectively.

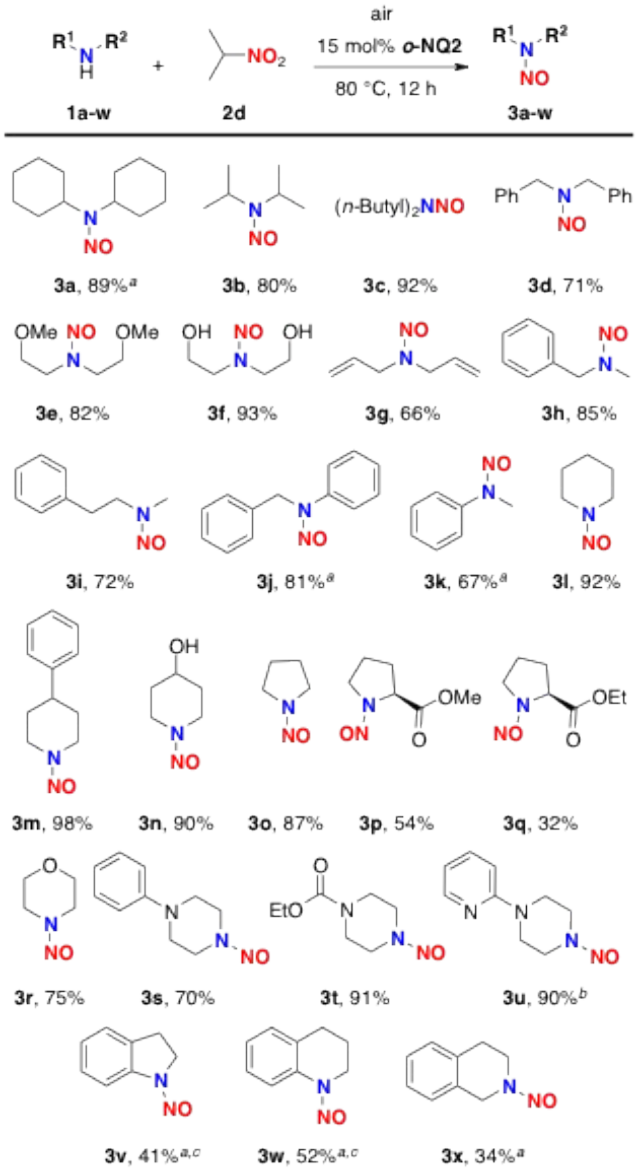
Table 1. Optimization of Catalytic *N*-Nitrosation of Amine[a]



entry	cat (mol%)	R^1-NO_2	yield (%)[b]	comment
1	***o*-NQ1** (15)	**2a**, Me	17	—
2	***o*-NQ1** (15)	**2b**, Et	50	—
3	***o*-NQ1** (15)	**2c**, Pr	33	—
4	***o*-NQ1** (15)	**2d**, *i*-Pr	80	—
5	***o*-NQ2** (15)	**2d**, *i*-Pr	89	—
6	***o*-NQ3** (15)	**2d**, *i*-Pr	48	—
7	***o*-NQ4** (15)	**2d**, *i*-Pr	10	—
8	***o*-NQ5** (15)	**2d**, *i*-Pr	trace	—
9	***o*-NQ2** (10)	**2d**, *i*-Pr	77	—
10	***o*-NQ2** (15)	**2d**, *i*-Pr	20	80 °C
11	***o*-NQ2** (15)	**2d**, *i*-Pr	92	O_2 balloon
12	***o*-NQ2** (15)	**2d**, *i*-Pr	88	10 equiv *i*-$PrNO_2$
13	***o*-NQ2** (15)	**2d**, *i*-Pr	26	Under Ar
14	—	**2d**, *i*-Pr	0	No ***o*-NQ** cat

[a]Reaction conditions: **1a** (0.2 mmol), **2** (3.0 mmol), 15 mol% of ***o*-NQ** in air at 80-100 °C for 12 h. [b]Isolated yields of **3a** after column chromatography.

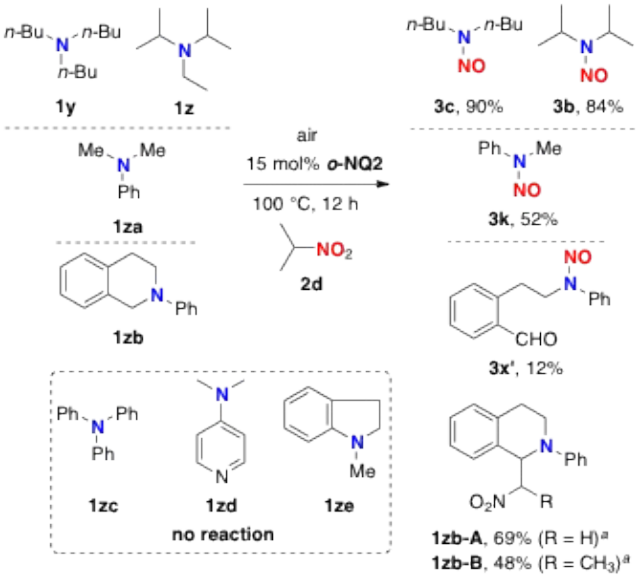
The substrate scope of secondary amines for the optimized catalytic *N*-nitrosation conditions was illustrated in Scheme 2. While our model amine **1a** required slightly higher reaction temperature of 100 °C for the effective *N*-nitrosation, most of the tested secondary amines could be oxidized at 80 °C. Thus, dialkyl-substituted *N*-nitroso amines **3b-3d** were obtained in 71-92% yields. Functional group tolerance was also demonstrated in the synthesis of *N*-nitroso amines **3e-3g**, where alcohol, ether, and alkene moieties were well tolerated. The demethylation of *N*-methyl amines did not occur under the oxidation conditions, resulting in the formation of the corresponding *N*-nitroso compounds **3h-3i** in 72-85% yields. The subjection of aniline derivatives required the reaction temperature of 100 °C, however the desired products **3j-3k** were obtained without benzylic oxidation and demethylation. Cyclic amines were also smoothly oxidized to the corresponding *N*-nitroso compounds in excellent yields. Thus, piperidine derivatives provided the corresponding *N*-nitroso piperidines **3l-3n** in 90-98% yields at 80 °C. The pyrrolidine derivatives were also oxidized to give **3o-3q**, however the proline alkyl esters **2p-2q** displayed the functional group compatibility issue upon freeing them from the commercially available **2**•HCl salts.[14] The formations of *N*-nitroso morpholine **3r** and piperazines **3s-3u** were accomplished, where 1-(pyridin-2-yl)piperazine **2u** was subjected to a 1 gram scale using 5 mol% of ***o*-NQ2** catalyst with 10 equiv of 2-nitropropane **2d** to give **3u** in 90% yield. The current catalytic *N*-nitrosation reaction possesses the substrate limitation for indoline **2v**, tetrahydroquinoline **2w**, and tetrahydroisoquinoline **2x**, where the aniline moiety displayed the low reactivity to give **3v and 3w** in 41-52% yields, and the competing imine formation during the formation of **3x**.[15]



Scheme 2. Catalytic Aerobic *N*-Nitrosation of Secondary Amines

[a]Reaction at 100 °C. [b]Reaction using 1 gram of **2u**, 5 mol% ***o*-NQ2** and 10 equiv of **2d**. [c]Reaction under O_2 balloon.

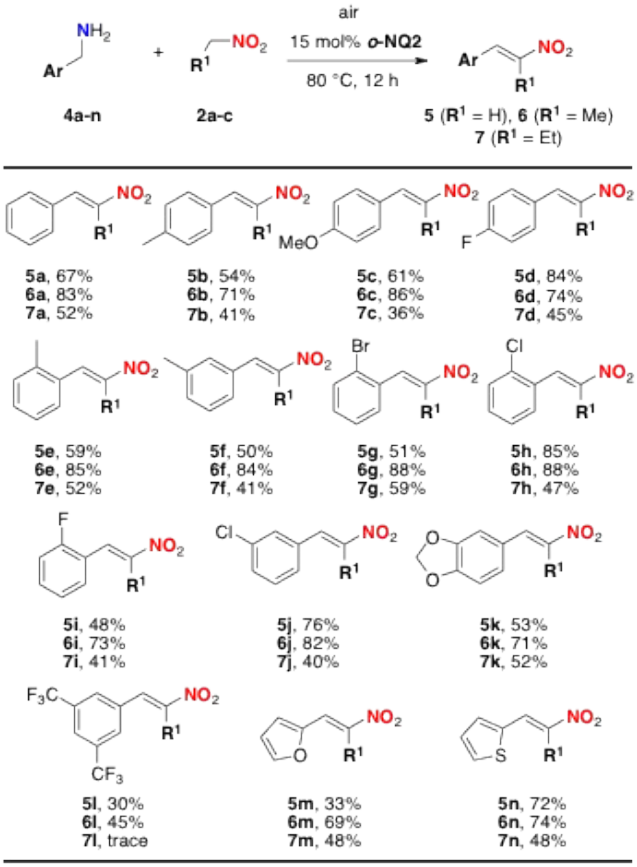
The *N*-nitrosation of tertiary amines was next investigated since the secondary amines with strong nucleophilicity collectively displayed the better oxidation capability. Gratifyingly, the optimized *N*-nitrosation conditions for secondary amines were also applicable to tertiary amines (Scheme 3). Given that the demethylation of *N*-nitroso secondary amines did not occur, the *N*-quaternization of sterically congested tertiary amines followed by dealkylation was rather surprising. Thus, tributylamine **1y** was smoothly *N*-nitrosonated to give **3c** using 2-nitropropane **2d** in 90% yield.[16] *N,N*-Diisopropylethylamine **1z** selectively deethylated to give the corresponding *N*-nitroso compound **3b** in 84% yield. The use of *N,N*-dimethylaniline derivative **1za** also provided **3k** in 52% yield. However, unlike acyclic tertiary amines the use of cyclic tertiary amine, *N*-phenyltetrahydroisoquinoline **1zb**, provided the *N*-nitroso product **3x'** in 12% yield due to the competing imine hydroysis. Thus, the utilization of nitromethane **2a** and nitromenthane **2b** for the oxidation of *N*-phenyltetrahydroisoquinoline **1zb** led to the cross-dehydrogenation products **1zb-A** and **1zb-B** in 48-69% yields.[8] The *N*-nitrosation of triphenylamine **1zc**, *N,N*-dimethylaminopyridine **1zd**, and *N*-methylindoline **1ze** failed, probably due to the weak nucleophilicity of the amine moieties.



Scheme 3. Catalytic Aerobic *N*-Nitrosation of Tertiary Amines

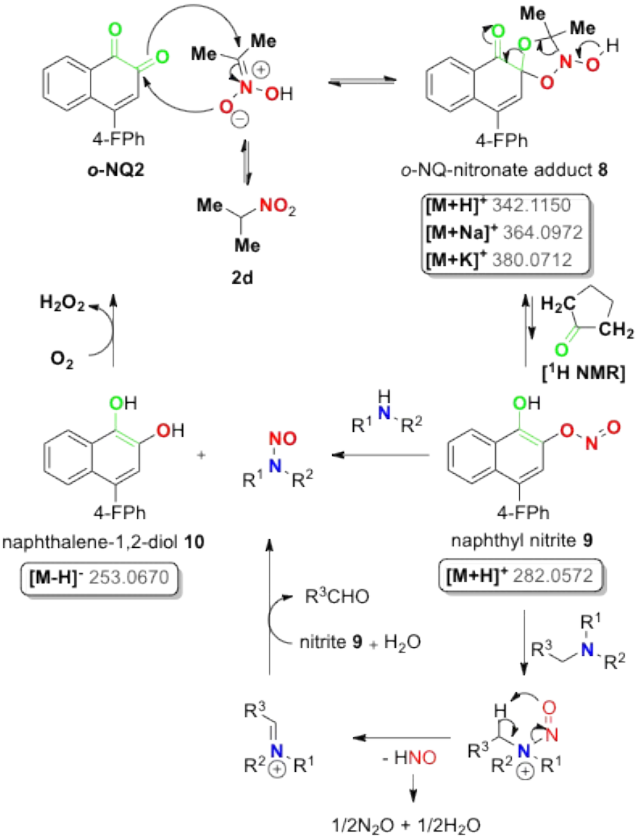
[a]Reaction under O_2 ballon

We next turned our attention to the use of primary amines under the aerobic oxidation conditions since the *ortho*-naphthoquinone catalysts rapidly reacted with primary amines to provide imines and carbonyl compounds.[11,12] While the nitroalkanes could competitively react with the *ortho*-naphthoquinone catalysts,[17] it was anticipated that in the absence of strong nucleophiles the *N*-nitrosation pathway might slow down, leading to the preferential oxidation pathway of primary amines by the *ortho*-naphthoquinone catalysts. The successful deaminative cross-coupling between primary amines and nitroalkanes by the *ortho*-naphthoquinone catalyst, ***o*-NQ2**, is presented in Scheme 4. Thus, the various primary aryl amines with different electronic and steric features smoothly reacted with nitroalkanes **2a-2c**, providing the desired cross-coupled products **5-7** in a synthetically useful level. In general, the use of nitroethane **2b** provided better yields compared to nitromethane **2a** and nitropropane **2c**. Interestingly, the major byproduct of the reactions with nitromethane **2a** was 1,3-dinitropropane derivatives from the conjugate addition of **2a** to nitroalkenes **5**.[18] The low reactivity of nitropropane **2c** could be reasoned by the inefficient formation of nitronate species in the absence of an added base.[19] While the current aerobic deaminative cross-coupling reaction possesses room for further improvement in the alkyl amines,[20] the discovery of a novel coupling method combined with the simplicity of this reaction will help diversifying the cross-coupling strategies.



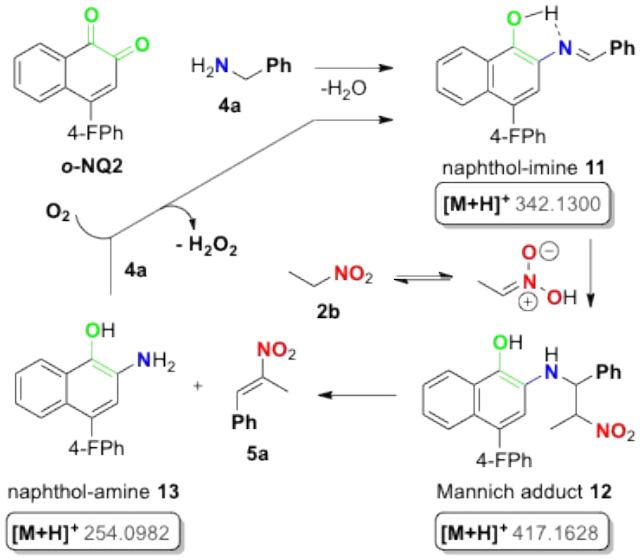
Scheme 4. Catalytic Aerobic Deaminative Cross-Coupling between Primary Amines and Nitroalkanes

The substrate promiscuity of the *ortho*-naphthoquinone catalyst suggests two different reaction modes of nitroalkanes: electrophilic nitrosating species and nucleophilic nitronate species. Thus, nitroalkanes (**2d**, *p*Ka 16.9) are readily converted to the corresponding nitronates in the presence of amines **1** (Scheme 5). The formation of adduct **8** between the ***o*-NQ2** and the nitronate of **2d** has been established from the HRMS-ESI experiments (see the Supporting Information for detail). The subsequent Nef-type rearrangement[21] of the adduct **8** could generate a naphthyl nitrite **9** that acts as a nitrosating agent for the amines **1**.[22] Our HRMS-ESI experiment also confirmed the formation of the naphthyl nitrite **9** as $[M+H]^+$ ion. In our control experiment using nitrocyclopentane instead of 2-nitropropane, the formation of cyclopentanone was observed,[23] demonstrating the Nef-type rearrangement. The *N*-nitrosation of primary amines typically leads to the unstable primary *N*-nitrosamines that could isomerize to diazonium compounds.[17] The secondary and tertiary amines, however, readily underwent the desired *N*-nitrosation. In particular, the use of tertiary amines led to the nitrosoammonium ion that subsequently lost HNO by a *syn* cyclic transition state to iminium intermediates.[24] However, the fact that a cyclic tertiary amine (*i.e* **3x'**) was not *N*-nitrosated under our optimized conditions suggested the possibility of direct H-transfer mechanism between the ***o*-NQ2** catalyst and the tertiary amine, leading to the α-C-H functionalization of tertiary amine.[8b] The nitroxyl is known to rapidly decomposed to nitrous oxide and water by a bimolecular pathway. The *syn* cyclic transition state may explain the facile *N*-nitrosation of acyclic tertiary amines as opposed to the cyclic tertiary amines[25] such as *N*-phenyltetrahydroisoquinoline **1zb** and *N*-methylindoline **1ze** in Scheme 3. The possibility of radical reactions, involving nitric oxide radical species, has been ruled out because the catalytic aerobic *N*-nitrosation reaction occurred smoothly in the presence of radical inhibitors such as TEMPO and 1,1-diphenylethylene.[26] The aerial oxidation of naphthalene-1,2-diol derivatives **10** to *ortho*-naphthoqunones has been established by our previous works.[10a]



Scheme 5. Proposed Catalytic Cycle for the *N*-Nitrosation of Amines Based on HRMS-ESI Analysis

As for the aerobic deaminative cross-coupling between primary nitroalkanes and benzylamines, the *ortho*-naphthoquinone catalyst ***o*-NQ2** deaminates the primary benzylamines **4a** via the corresponding imine intermediate **11**[27] that *in situ* condenses with the nitroalkanes **2a-2c** (pKa 16.7-17.2) to give the nitroalkenes **5-7** (Scheme 6). Our HRMS-ESI experiments identified the corresponding intermediate species **11-13**, establishing a new cross-coupling strategy to the nitroalkenes.[28] It should be noted that the deaminative cross-coupling reaction occured smoothly in the absence of any added acids or bases.[29]



Scheme 6. Proposed Catalytic Cycle for the Deaminative Cross-Coupling Based on HRMS-ESI Analysis

In summary, we have discovered the unique substrate promiscuity behavior of *ortho*-naphthoquinone catalysts under aerobic oxidation conditions. The *ortho*-naphthoquinone catalysts can selectively activate two different substrates, nitroalkanes and amines, to the respective oxidation products: *N*-nitrosation of amines and deaminative cross-coupling between benzylamine derivatives and nitroalkanes. The catalytic generation of nitrite-like species has been achieved for the first time, and given the synthetic utility of *N*-nitroso amines[30] this newly discovered aerobic *N*-nitrosation protocol should open up new opportunities in an industrial setting. In addition, the development of the deaminative cross-coupling reaction between benzylamines and nitroalkanes has significantly broadened the choice of cross-coupling substrates. As a result of these exciting discoveries, our current efforts are directed to further exploring the promiscuity behavior of organocatalysts that can *on demand* switch the activation modes.

ASSOCIATED CONTENT

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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Notes

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Supporting Information.

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures and characterization data for all new compounds (PDF)

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14. The **2**•HCl salts were freed by treating them with aq. K_2CO_3, and extracted with using ethyl acetate. After removing the solvent, the prolinates were used directly. The low chemical yields for *N*-nitrosation might be due to the decomposition/loss of prolinates upon the experimental handling of prolinates under basic conditions.

15. The formation of 3,4-dihydroisoquinoline, an imine derived from **3x,** was observed in 30% yield under the optimized *N*-nitrosation conditions.

16. Upon using other nitroalkanes, no side reaction was observed. However, the reaction conversion was low (**3c**, 35% yield using CH_3NO_2 and 47% yield using $CH_3CH_2NO_2$ after 12 h).

17. The *N*-nitrosation of aromatic primary amines, for example benzylamines (including α-branched benzylamines), provided the corresponding *N*-nitro amines in low yields (>10%) due to the inherent thermal instability of products. For the diazotization of primary amines via *N*-nitroso compounds, see: Moumne, R.; Lavielle, S.; Karoyan, P. Efficient Synthesis of β^2-Amino Acid by Homologation of α-Amino Acids Involving the Reformatsky Reaction and Mannich-Type Imminium Electrophile. *J. Org. Chem.* **2006**, *71*, 3332-3334.

18. The formation of (1,3-dinitropropan-2-yl)benzene, a tandem Michael addition of CH_3NO_2 to nitroalkene product **5a**, could be improved to 60% under slightly modified conditions. This reaction will be reported elsewhere.

19. The second-order rate constants were influenced by the steric bulkiness of alkyl groups of nitronates, see: Bu, T.; Lemek, T.; Mayr, H. Nucleophilicities of Nitroalkyl Anions. *J. Org. Chem*. **2004**, *69*, 7565-7576.

20. Currently, the quinone-catalyzed amine oxidation protocols are not applicable to alkyl amines, possibly due to the imine-enamine isomerization of catalyst-amine adducts.

21. For a review, see: Ballini, R.; Petrini, M. The Nitro to Carbonyl Conversion (Nef Reaction): New Perspectives for a Classical Transformation. *Adv. Synth. Catal.* **2015**, *357*, 2371-2402.

22. For a review, see: Wang, P. G.; Xian, M.; Tang, X.; Wu, X.; Wen, Z.; Cai, T.; Janczuk, A. J. Nitric Oxide Donors: Chemical Activities and Biological Applications. *Chem. Rev.* **2002**, *102*, 1091-1134.

23. While the use of nitrocyclopentane provided the desired *N*-nitroso compound **3a** in 20% yields after 12 h at 100 °C, the formation of Nef-type reaction product, cyclopentanone from nitrocyclopentane, could be monitored by the NMR spectra of the crude reaction mixture (see the Supporting Information for detail).

24. The loss of HNO is the rate limiting step above pH 3.8 and is preceded by a rapid equilibrium nitrosation-denitrosation, see: Gowenlock, B. G.; Hutchison, R. J.; Little, J.; Pfab, J. Nitrosative Dealkylation of Some Symmetric Tertiary Amines. *J. Chem. Soc. Perkin Trans.2*, **1979**, 1110-1114.

25. The use of wet nitropropane did not facilitate the *N*-nitrosation of tertiary amines, supporting the intramolecular HNO elimination, see: (a) Smith, P. A. S.; Loeppky, R. N.; Nitrosative Cleavage of Tertiary Amines. *J. Am. Chem. Soc.* **1967**, *89*, 1147-1157. (b) Leoppky, R. N.; Tomasik, W. Stereoelectronic Effects in Tertiary Amine Nitrosation: Nitrosative Cleavage vs. Aryl Ring Nitration. *J. Org. Chem.* **1983**, *48*, 2751-2757.

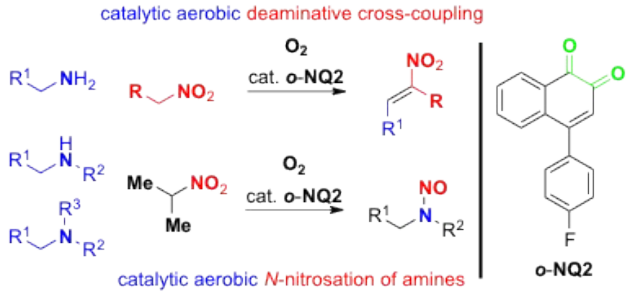
26. The use of 1 equiv of TEMPO under the optimized *N*-nitrosation conditions resulted in the formation of **3a** in 85% yield (89% in the absence of TEMPO).

27. (a) Filarowski, A. Intramolecular Hydrogen Bonding in *o*-Hydroxyaryl Schiff Bases. *J. Phys. Org. Chem.* **2005**, *18*, 686-698. (b) Makal, A.; Schilf, W.; Kamienski, B.; Szady-Chelmieniecka, A.; Grech, E.; Wozniak, K. Hydrogen Bonding in Schiff Bases – NMR, Structural and Experimental Charge Density Studies. *Dalton Trans.* **2011**, *40*, 421-430.

28. The formation of homo-imine adducts has been observed from the crude reaction mixtures with low conversion by ^{1}H NMR in <5% yields.

29. A control experiment using benzaldehyde instead of benzylamine under the optimized reaction conditions did not provide the nitroalkene product at all, suggesting the critical role of ***o*-NQ2** in the deaminative cross-coupling reaction.

30. For a review, see: Huang, J.; Chen, Z.; Yuan, J.; Peng, Recent Advances in Highly Selective Applications of Nitroso Compounds. *Asian, J. Org. Chem*. **2016**, *5*, 951-960.


catalytic aerobic deaminative cross-coupling
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