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o-Naphthoquinone-Catalyzed Aerobic Oxidation of Amines to (Ket)imines: A Modular Catalyst Approach

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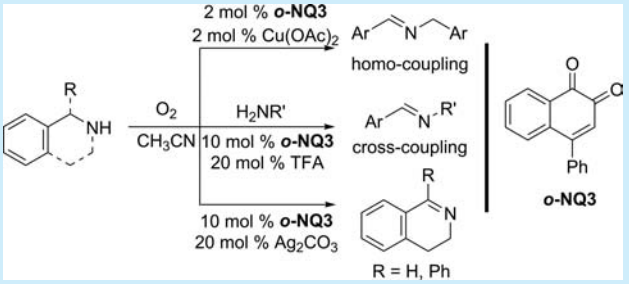
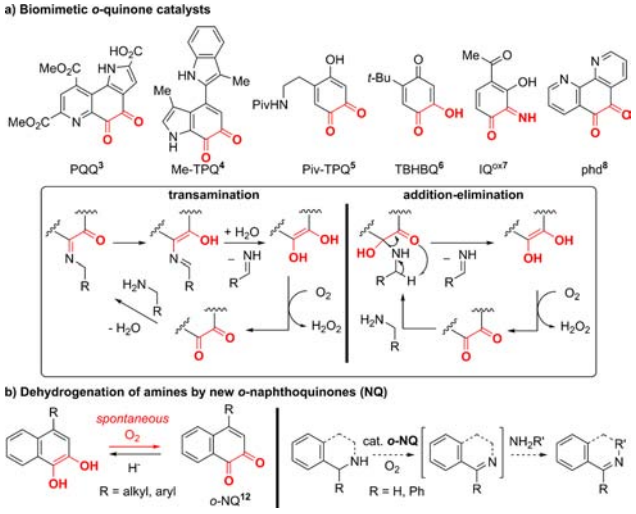
Supporting Information

ABSTRACT: A modular aerobic oxidation of amines to imines has been achieved using an *ortho*-naphthoquinone (***o*-NQ**) catalyst. The cooperative catalyst system of ***o*-NQ** and $Cu(OAc)_2$ enabled the formation of homocoupled imines from benzylamines, while the presence of TFA helped the formation of cross-coupled imines in excellent yields. The current mild aerobic oxidation protocol could also be applied to the oxidation of secondary amines to imines or ketimines with the help of cocatalyst, Ag_2CO_3, with excellent yields.



o-Quinone-catalyzed dehydrogenation of amines mimics the copper amine oxidases (CuAOs) where redox-active organic molecules skillfully utilize the green oxidants such as molecular oxygen or air to promote the imine formation from primary amines.[1] The development of novel *o*-quinone cofactors in CuAOs has received considerable attention from the synthetic community for the past few years, culminating in the successful identification of *o*-quinones for catalytic aerobic oxidation of primary and secondary amines to imines.[2] Taking initiative from natural *o*-quinone cofactors with the two possible CuAOs mechanisms (Scheme 1a), the laboratories of Bruice (pyrroloquinonoline quinone),[3] Itoh (methyl tryptophan tryptophylquinone),[4] Sayre (2,4,5-trihydroxy phenylalanine quinone),[5] and Klinman (butyl-2-hydroxy-1,4-benzoquinone)[6] studied the oxidation of amines using biomimetic model *o*-quinones. However, the first practical use of synthetic *o*-quinones in the dehydrogenation of amines was explored by the laboratories of Largeron[7] and Stahl[8] using IQ^{ox} (*o*-iminoquinone) and TBHBQ, respectively. In 2014, the laboratory of Stahl used the PQQ model 1,10-phenanthroline-5,6-dione (phd) to initiate the dehydrogenation of secondary amines and other N-heterocycles in the presence of cocatalysts, ZnI_2 and pyridium *p*-toluenesulfonic acid.[9] Such a modular catalyst system has been applied to the dehydrogenation of 1,2,3,4-tetrahydroquinolines by using a Ru/Co cocatalyst system.[10] With the aim of identifying new *o*-quinone-based catalysts that display tunable dehydrogenation activity for primary and secondary amines,[11] we examined substituted *o*-naphthoquinone derivatives as possible synthetic *o*-quinone cofactors. In our recent synthetic studies of *o*-naphthoquinones, we found that 4-substituted naphthalene-1,2-diols spontaneously undergo aerobic oxidation to *o*-naphthoquinones in quantitative yields (Scheme 1b).[12] Motivated by the high redox activity of 4-substituted *o*-naphthoquinone derivatives, we envisioned a new biomimetic *o*-naphthoquinone-catalyzed dehydrogenation of amines. Herein, we report a mild and tunable *o*-naphthoquinone-based dehydrogenation of primary amines to furnish diverse homo- and cross-coupled imines. Importantly, the current *o*-naphthoquinone-based dehydrogenation can be applied to secondary amines to give imines and ketimines in excellent yields.

Scheme 1. Biomimetic *o*-Quinones for Dehydrogenation of Amines



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To evaluate the dehydrogenation activity of *o*-naphthoquinone derivatives, we chose *p*-methoxy benzylamine **1a** as a model substrate (Table 1). Upon stirring benzylamine **1a** in the presence of a catalytic amount of various *o*-naphthoquinones,

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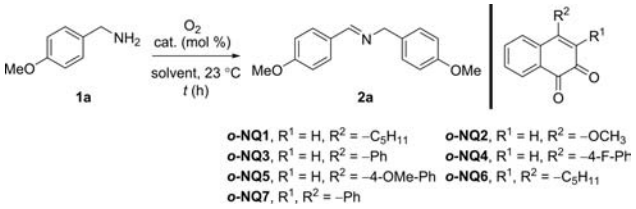
Table 1. Optimization of the Dehydrogenation of Benzyl Amine



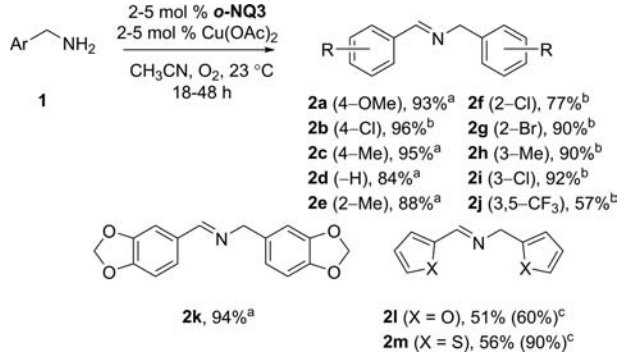
entry	cat. (mol %)	add. (mol %)	solvent, t (h)	yield (%)[b]	
1	***o*-NQ1** (10)	–	CH_3CN	48	39
2	***o*-NQ2** (10)	–	CH_3CN	48	64
3	***o*-NQ3** (10)	–	CH_3CN	48	69
4	***o*-NQ4** (10)	–	CH_3CN	48	47
5	***o*-NQ5** (10)	–	CH_3CN	48	63
6	***o*-NQ6** (10)	–	CH_3CN	48	9
7	***o*-NQ7** (10)	–	CH_3CN	48	29
8	***o*-NQ3** (10)	–	CH_2Cl_2	48	25
9	***o*-NQ3** (10)	–	$PhCH_3$	48	22
10	***o*-NQ3** (10)	–	THF	48	50
11	***o*-NQ3** (10)	–	EtOH	48	28
12	***o*-NQ3** (20)	–	CH_3CN	24	91
13	***o*-NQ3** (5)	–	CH_3CN	48	33
14	***o*-NQ3** (5)	$Cu(OAc)_2$ (5)	CH_3CN	18	99
15[c]	***o*-NQ3** (2)	$Cu(OAc)_2$ (2)	CH_3CN	18	99
16	***o*-NQ3** (1)	$Cu(OAc)_2$ (1)	CH_3CN	60	80
17	***o*-NQ3** (0.5)	$Cu(OAc)_2$ (0.5)	CH_3CN	60	65
18	***o*-NQ3** (2)	$Cu(OAc)_2$ (1)	CH_3CN	18	83
19	***o*-NQ3** (1)	$Cu(OAc)_2$ (2)	CH_3CN	18	43
20[d]	***o*-NQ3** (2)	$Cu(OAc)_2$ (2)	CH_3CN	60	81

[a]Reaction conditions: **1a** (0.4 mmol) in CH_3CN (1 mL) under O_2 balloon. [b]Isolated yield of products after column chromatography. [c]CuCl (7%), $CuCl_2$ (23%), CuOAc (9%). [d]Reaction under ambient air.

the formation of homocoupled imine **2a** was observed at ambient temperature under O_2 atmosphere. The electron-donating substituent at C-4 of *o*-naphthoquinones ***o*-NQ2** improved the dehydrogenation activity, resulting in the formation of **2a** in 64% yield (entry 2) as opposed to 39% when 4-alkyl naphthoquinone ***o*-NQ1** was used (entry 1). The dehydrogenation activity was further improved with the use of 4-phenyl naphthoquinone ***o*-NQ3** to a 69% yield. The investigation into the electronic effect of the phenyl group revealed that the electron-donating group (entry 5) was beneficial as opposed to the electron-deficient group (entry 4). The substituent at C-3 of *o*-naphthoquinones significantly reduced the dehydrogenation activity, possibly due to steric reasons, providing **2a** in 9–29% yields (entries 6–7). The solvent screening revealed CH_3CN as the optimal solvent for the current dehydrogenation protocol (entries 8–11). Next, we examined the catalyst loading. While the use of 20 mol % ***o*-NQ3** led to the desired product **2a** in 91% yield in 24 h (entry 12), the reduced catalyst loading to 5 mol % provided **2a** in 33% yield with a prolonged reaction time of 48 h (entry 13). To improve the dehydrogenation activity of ***o*-NQ3**, we opted for the use of additional promoters as cocatalysts. Gratifyingly, the catalytic use of $Cu(OAc)_2$ significantly enhanced the dehydrogenation activity of ***o*-NQ3**,[13] providing **2a** in >99% yield in the presence of 2 mol % of both ***o*-NQ3** and $Cu(OAc)_2$ (entries 14–17). The optimal ratio between ***o*-NQ3** and $Cu(OAc)_2$ was 1:1 (entries 18–19). Finally, the current dehydrogenation protocol could be carried out under ambient air conditions, but the reaction time increased to 60 h for completion (entry 20).

The optimized dehydrogenation conditions were further evaluated using various benzyl amines (Scheme 2). In general,

Scheme 2. Scope of *o*-NQ3-Catalyzed Aerobic Dehydrogenation of Benzyl Amines



[a]2 mol % catalysts. [b]5 mol % catalysts. [c]Yields using internal standard.

benzyl amines with an electron-donating substituent provided excellent yields of imines in the presence of 2 mol % ***o*-NQ3** and $Cu(OAc)_2$ (**2a**, **2c–e**, **2k**). However, electron-deficient benzyl amines required 5 mol % of catalysts for comparable dehydrogenation activities (**2b**, **2f–j**). In cases of heteroatom-containing amine substrates, the isolated yields of imines (**2l–m**) were in 51–56% yields, possibly due to the facile imine decomposition upon isolation and coordination to the metal center.

Since the current dehydrogenation conditions using ***o*-NQ3** were not applicable to aliphatic primary amines and *sec*-primary amines,[14] we examined the cross-coupling between primary benzyl amines and other unreactive amines. After some optimization studies (see the Supporting Information for detail), we identified optimal conditions for the cross-coupling using 10 mol % ***o*-NQ3** and 20 mol % TFA with 2 equiv of nonoxidizing amines. The result of the ***o*-NQ3**/TFA-catalyzed aerobic cross-coupling of primary amines is illustrated in Table 2. The reaction is quite effective for various *sec*-primary amines (**3a–k**), aliphatic primary amines (**3l**), *tert*-primary amines (**3m**), anilines (**3n**).

Motivated by the fact that the dehydrogenation of amines was strongly influenced by the additional promoters such as $Cu(OAc)_2$ and TFA, we further investigated the cross-coupling using *o*-aminoaniline (Scheme 3). The synthesis of benzimidazole **4** was accomplished in 86% yield. Additionally, secondary amines such as tetrahydroisoquinoline derivatives were dehydrogenated in the presence of cocatalyst Ag_2CO_3 in excellent yields to give **5a–c**.[15] The dehydrogenation of 9,10-dihydroacridine to acridine **6** was also effected under mild reaction conditions. However, aliphatic amines such as tetrahydroquinoline and indoline were inert under various reaction conditions.[16]

While more studies are needed to cast mechanistic insights into the cooperative catalyst activities between ***o*-NQ3** and cocatalysts (metallic copper(II) salt, acidic TFA, and basic Ag_2CO_3), the current cooperative catalyst system displays the both features of "transamination"[6a,b] and "addition–elimination"[4b,5e,f] mechanistic pathways. Thus, the homocoupling and cross-coupling of primary benzyl amines collectively illustrate

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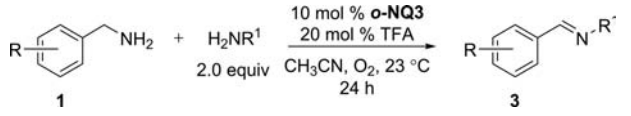
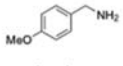
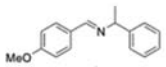
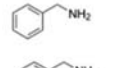
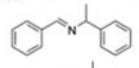
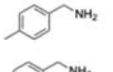
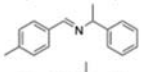
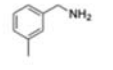
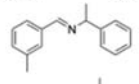
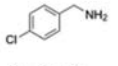
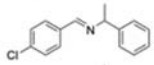
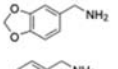
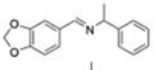
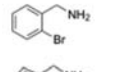
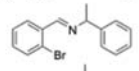
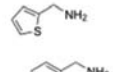
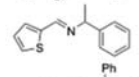
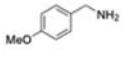
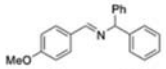
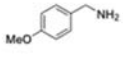
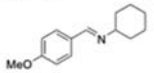
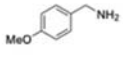
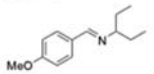
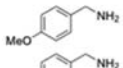
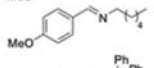
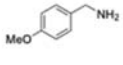
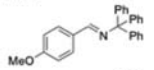
Table 2. *o*-NQ3-Catalyzed Aerobic Cross-Coupling of Amines



entry	1	amine	3	yield (%)[b]
1				**3a**, 92
2				**3b**, 90
3				**3c**, 93
4				**3d**, 95
5				**3e**, 90
6				**3f**, 97
7				**3g**, 91
8				**3h**, 69
9				**3i**, 97
10				**3j**, 87
11				**3k**, 96
12				**3l**, 93
13				**3m**, 92
14				**3n**, 70

[a]Reaction conditions: **1** (0.2 mmol), amines (0.4 mmol) in CH_3CN (1 mL) under O_2 balloon. [b]Isolated yield of products after column chromatography.

Scheme 3. Scope of *o*-NQ3-Catalyzed Dehydrogenation of Various Amines

the possibility of a "transamination" mechanism, where the high selectivity for unhindered primary benzylamines was observed.[8] One possible role of TFA in the formation of cross-coupled imines and benzimidazole is to facilitate the hydrolysis of imines for the dynamic equilibrium of imine species. In contrast, the dehydrogenation of secondary amines suggests the possible involvement of hemiacetal intermediates that typically requires basic conditions for the abstraction of a H atom as shown in Scheme 1.[10,11a]

In summary, we have developed the highly modular aerobic dehydrogenation protocols for primary and secondary amines. With the discovery of new biomimetic *o*-naphthoquinones, mild and efficient homo- and cross-couplings of amines were achieved with the help of cocatalysts such as acids and bases. While there exists room for improvement in terms of amine substrate scope to nonbenzylic amines and catalyst loading to <5 mol %, the fact that the reactivity of ***o*-NQ3** could be modulated using cocatalysts makes the current method attractive for the synthesis of various heterocycles. Our current research efforts are directed to detailed mechanistic studies and expanding the chemistry to other amine substrates.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02697.

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

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) For reviews, see: (a) *Principles and Applications of quinoproteins*; Davidson, V. L., Ed.; Dekker: New York, 1993. (b) Klinman, J. P. *J. Biol. Chem.* **1996**, *271*, 27189−27192. (c) Mure, M. *Acc. Chem. Res.* **2004**, *37*, 131−139. (d) Klinman, J. P.; Bonnot, F. *Chem. Rev.* **2014**, *114*, 4343−4365.

(2) For recent reviews, see: (a) Largeron, M.; Fleury, M.-B. *Science* **2013**, *339*, 43−44. (b) Chen, B.; Wang, L.; Gao, S. *ACS Catal.* **2015**, *5*, 5851−5876. (c) Wendlandt, A. E.; Stahl, S. S. *Angew. Chem., Int. Ed.* **2015**, *54*, 14638−14658.

(3) (a) Eckert, T. S.; Bruice, T. C.; Gainor, J. A.; Weinreb, S. M. *Proc. Natl. Acad. Sci. U. S. A.* **1982**, *79*, 2533−2536. (b) Eckert, T. S.; Bruice, T. C. *J. Am. Chem. Soc.* **1983**, *105*, 4431−4441. (c) Sleath, P. R.; Noar, J. B.; Eberlein, G. A.; Bruice, T. C. *J. Am. Chem. Soc.* **1985**, *107*, 3328−3338. (d) Rodriguez, E. J.; Bruice, T. C. *J. Am. Chem. Soc.* **1989**, *111*, 7947−7956.

(4) (a) Itoh, S.; Ogino, M.; Haranou, S.; Terasaka, T.; Ando, T.; Komatsu, M.; Ohshiro, Y.; Fukuzumi, S.; Kano, K. *J. Am. Chem. Soc.* **1995**, *117*, 1485−1493. (b) Itoh, S.; Takada, N.; Haranou, S.; Ando, T.; Komatsu, M.; Ohshiro, Y.; Fukuzumi, S. *J. Org. Chem.* **1996**, *61*, 8967−8974. (c) Itoh, S.; Kawakami, H.; Fukuzumi, S. *J. Am. Chem. Soc.* **1997**, *119*, 439−440. (d) Itoh, S.; Takada, N.; Ando, T.; Haranou, S.; Huang, X.; Uenoyama, Y.; Ohshiro, Y.; Komatsu, M.; Fukuzumi, S. *J. Org. Chem.* **1997**, *62*, 5898−5907. (e) Itoh, S.; Kawakami, H.; Fukuzumi, S. *Biochemistry* **1998**, *37*, 6562−6571. (f) Itoh, S.; Taniguchi, M.; Fukuzumi, S. *Chem. Commun.* **2000**, 329−330.

DOI: 10.1021/acs.orglett.6b02697
Org. Lett. 2016, 18, 5174−5177

(5) (a) Lee, Y.; Sayre, L. M. *J. Am. Chem. Soc.* **1995**, *117*, 3096−3105. (b) Lee, Y.; Sayre, L. M. *J. Am. Chem. Soc.* **1995**, *117*, 11823−11828. (c) Lee, Y.; Huang, H.; Sayre, L. M. *J. Am. Chem. Soc.* **1996**, *118*, 7241−7242. (d) Ling, K.-Q.; Kim, J.; Sayre, L. M. *J. Am. Chem. Soc.* **2001**, *123*, 9606−9611. (e) Lee, Y.; Ling, K.-Q.; Lu, X.; Silverman, R. B.; Shepard, E. M.; Dooley, D. M.; Sayre, L. M. *J. Am. Chem. Soc.* **2002**, *124*, 12135−12143. (f) Qiao, C.; Ling, K.-Q.; Shepard, E. M.; Dooley, D. M.; Sayre, L. M. *J. Am. Chem. Soc.* **2006**, *128*, 6206−6219. (g) Zhang, Y.; Ran, C.; Zhou, G.; Sayre, J. M. *Bioorg. Med. Chem.* **2007**, *15*, 1868−1877.

(6) (a) Mure, M.; Klinman, J. P. *J. Am. Chem. Soc.* **1995**, *117*, 8698−8706. (b) Mure, M.; Klinman, J. P. *J. Am. Chem. Soc.* **1995**, *117*, 8707−8718.

(7) (a) Largeron, M.; Fleury, M.-B. *J. Org. Chem.* **2000**, *65*, 8874−8881. (b) Largeron, M.; Neudorffer, A.; Fleury, M.-B. *Angew. Chem., Int. Ed.* **2003**, *42*, 1026−1029. (c) Largeron, M.; Chiaroni, A.; Fleury, M.-B. *Chem. - Eur. J.* **2008**, *14*, 996−1003. (d) Largeron, M.; Fleury, M.-B. *Org. Lett.* **2009**, *11*, 883−886. (e) Largeron, M. *Electrochim. Acta* **2009**, *124*, 5505−5508. (f) Largeron, M.; Fleury, M.-B.; Strolin Benedetti, M. *Org. Biomol. Chem.* **2010**, *8*, 3796−3800. (g) Largeron, M.; Fleury, M.-B. *Angew. Chem., Int. Ed.* **2012**, *51*, 5409−5412. (h) Nguyen, K. M. H.; Largeron, M. *Chem. - Eur. J.* **2015**, *21*, 12606−12610.

(8) Wendlandt, A. E.; Stahl, S. S. *Org. Lett.* **2012**, *14*, 2850−2853.

(9) Wendlandt, A. E.; Stahl, S. S. *J. Am. Chem. Soc.* **2014**, *136*, 506−512.

(10) Wendlandt, A. E.; Stahl, S. S. *J. Am. Chem. Soc.* **2014**, *136*, 11910−11913.

(11) For recent examples, see: (a) Yuan, H.; Yoo, W.-J.; Miyamura, H.; Kobayashi, S. *J. Am. Chem. Soc.* **2012**, *134*, 13970−13973. (b) Yuan, H.; Yoo, W.-J.; Miyamura, H.; Kobayashi, S. *Adv. Synth. Catal.* **2012**, *354*, 2899−2904. (c) Jawale, D. V.; Gravel, E.; Shah, N.; Dauvis, V.; Li, H.; Namboothri, I. N. N.; Doris, E. *Chem. - Eur. J.* **2015**, *21*, 7039−7042. (d) Qin, Y.; Zhang, L.; Lv, J.; Luo, S.; Cheng, J.-P. *Org. Lett.* **2015**, *17*, 1469−1472.

(12) Kim, H.; Takizawa, S.; Oh, K. *Org. Biomol. Chem.* **2016**, *14*, 7191−7196.

(13) The catalytic activity of $Cu(OAc)_2$ was already demonstrated in the previous aerobic oxidation protocol for *o*-naphthoquinones in ref 12.

(14) The use of hexylamine and 1-phenylehtylamine under the optimized dehydrogenation conditions led to the imine formation in >1% and >5%, respectively.

(15) A base is needed for the dehydrogenation of secondary amines; see the Supporting Information for the base screening results.

(16) Under the forcing condition at 80 °C, 5−10% conversions were obtained. Thus, no catalytic activity was observed.

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