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# Chemoselective Organocatalytic Aerobic Oxidation of Primary Amines to Secondary Imines

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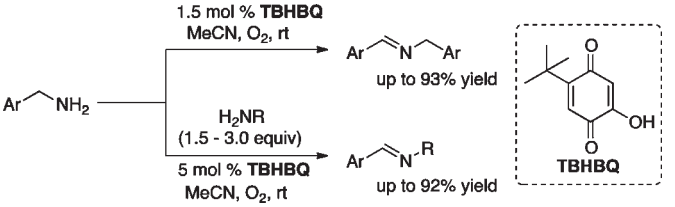
## ABSTRACT




**Biomimetic aerobic oxidation of primary benzylic amines has been achieved by using a quinone catalyst. Excellent selectivity is observed for primary, unbranched benzylic amines relative to secondary/tertiary amines, branched benzylic amines, and aliphatic amines. The exquisite selectivity for benzylic amines enables oxidative self-sorting within dynamic mixtures of amines and imines to afford high yields of cross-coupled imine products.**

Imines are valuable synthetic intermediates,[1] and a range of methods for the preparation of secondary imines from primary or secondary amines is known.[2] Typical strategies employ transition-metal catalysts with a stoichiometric oxidant, and these include methods capable of using molecular oxygen as the terminal oxidant.[2a−c,e−h] In biology, copper amine oxidases mediate aerobic oxidation of primary amines to aldehydes using *ortho*-quinone cofactors, such as topaquinone (TPQ) and lysine tyrosylquinone (LTQ).[3] Biochemical studies suggest that copper is required for biosynthesis of the quinone cofactors, but it is not involved in amine oxidation. Indeed, model quinones have been shown to mediate amine oxidase activity *ex vivo* in the absence of metals, using simple amine substrates.[4] The synthetic scope of such reactions has received little attention; however, and in connection with our broader interest in aerobic oxidation catalysis,[5] we sought to explore this class of reactions. In the present study, we report a highly chemoselective method for aerobic oxidative homo- and heterocoupling of benzylic amines to secondary imines using the TPQ analog, 4-*tert*-butyl-2-hydroxybenzoquinone

(1) For a recent review highlighting the versatility of imine electrophiles, see: Kobayashi, S.; Mori, Y.; Fossey, J. S.; Salter, M. M. *Chem. Rev.* **2011**, *111*, 2626–2704.

(2) For several recent examples, see: (a) Lang, X.; Ji, H.; Chen, C.; Ma, W.; Zhao, J. *Angew. Chem., Int. Ed.* **2011**, *50*, 3934–3937. (b) Murahashi, S.-I.; Okano, Y.; Sato, H.; Nakae, T.; Komiya, N. *Synlett* **2007**, 1675–1678. (c) Zhu, B.; Angelici, R. J. *Chem. Commun.* **2007**, 2157–2159. (d) Choi, H.; Doyle, M. P. *Chem. Commun.* **2007**, 745–747. (e) Wang, J.-R.; Fu, Y.; Zhang, B.-B.; Cui, X.; Liu, L.; Guo, Q.-X. *Tetrahedron Lett.* **2006**, *47*, 8293–8297. (f) Samec, J. S. M.; Éll, A. H.; Bäckvall, J.-E. *Chem.—Eur. J.* **2005**, *11*, 2327–2334. (g) Maeda, Y.; Nishimura, T.; Uemura, S. *Bull. Chem. Soc. Jpn.* **2003**, *76*, 2399–2403. (h) Yamaguchi, K.; Mizuno, N. *Angew. Chem., Int. Ed.* **2003**, *42*, 1480–1483. (i) Nicolaou, K. C.; Mathison, C. J. N.; Montagnon, T. *J. Am. Chem. Soc.* **2004**, *126*, 5192–5201.

(3) For reviews, see: (a) Mure, M. *Acc. Chem. Res.* **2004**, *37*, 131–139. (b) Mure, M.; Mills, S. A.; Klinman, J. P. *Biochemistry* **2002**, *41*, 9269–9278.

(4) For selected examples, see: (a) Eckert, T. S.; Bruice, T. C. *J. Am. Chem. Soc.* **1983**, *105*, 4431–4441. (b) Itoh, S.; Mure, M.; Ogino, M.; Ohshiro, Y. *J. Org. Chem.* **1991**, *56*, 6857–6865. (c) Ohshiro, Y.; Itoh, S. *Bioorg. Chem.* **1991**, *19*, 169–189. (d) Lee, Y.; Sayre, L. M. *J. Am. Chem. Soc.* **1995**, *117*, 3096–3105. (e) Mure, M.; Klinman, J. P. *J. Am. Chem. Soc.* **1995**, *117*, 8698–8706. (f) Mure, M.; Klinman, J. P. *J. Am. Chem. Soc.* **1995**, *117*, 8707–8718. (g) Itoh, S.; Takada, N.; Haranou, S.; Ando, T.; Komatsu, M.; Ohshiro, Y.; Fukuzumi, S. *J. Org. Chem.* **1996**, *61*, 8967–8974. (h) 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. (i) Ling, K.-Q.; Kim, J.; Sayre, L. M. *J. Am. Chem. Soc.* **2001**, *123*, 9606–9611. (j) Mure, M.; Wang, S. X.; Klinman, J. P. *J. Am. Chem. Soc.* **2003**, *125*, 6113–6125. (k) Murakami, Y.; Yoshimoto, N.; Fujieda, N.; Ohkubo, K.; Hasegawa, T.; Kano, K.; Fukuzumi, S.; Itoh, S. *J. Org. Chem.* **2007**, *72*, 3369–3380.

(5) (a) Stahl, S. S. *Angew. Chem., Int. Ed.* **2004**, *43*, 3400–3420. (b) Stahl, S. S. *Science* **2005**, *309*, 1824–1826. (c) Wendlandt, A. E.; Suess, A. M.; Stahl, S. S. *Angew. Chem., Int. Ed.* **2011**, *50*, 11062–11087. (d) Campbell, A. N.; Stahl, S. S. *Acc. Chem. Res.* DOI: 10.1021/ar2002045.

10.1021/ol301095j 
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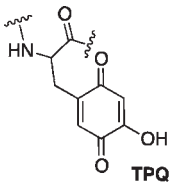
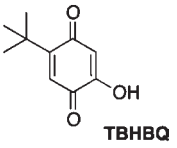
(TBHBQ), as the catalyst.[6] Like the amine oxidases noted above, the reactions proceed effectively in the absence of Cu or another redox-active cocatalyst.



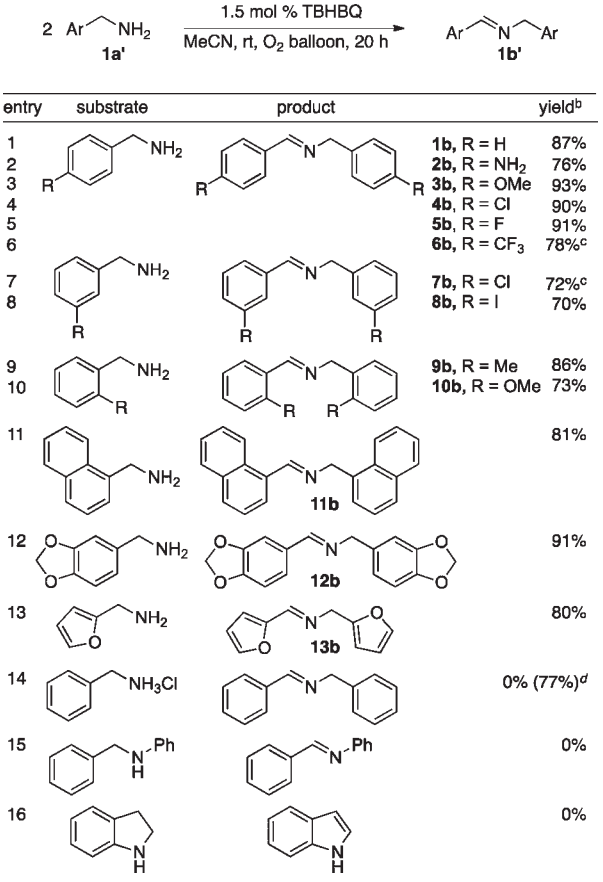




Important precedents to our work include the use of quinones as stoichiometric reagents[7] and catalysts[8] in the oxidation of primary amines to aldehydes and ketones and as electrocatalysts for the oxidation of primary amines to secondary imines[9] and amines.[10] And, during preparation of this manuscript, Largeron et al. reported a study very similar to the one presented here using an iminoquinone catalyst in combination with a copper cocatalyst, which facilitates aerobic reoxidation of the quinone.[11]

Building upon the work of Mure and Klinman,[4e,f] we evaluated the oxidation of benzylamine **1a** to *N*-benzylidenebenzylamine **1b** with TBHBQ. Efficient oxidation takes place with 1.5 mol % TBHBQ in a number of solvents, including 1,4-dioxane, THF, DMF, and MeCN (76%, 76%, 76%, and 87% yields, respectively) at room temperature under 1 atm of $O_2$. The reactions can be carried out with ambient air as the oxidant, but the reactions are slower. For example, 26% of unreacted **1a** was observed after 24 h.

Under the optimized conditions, a range of *ortho*-, *meta*-, and *para*-substituted benzylamines undergo oxidation to their secondary imine dimers under these conditions (Table 1). Electon-rich amines, such as *p*-methoxybenzylamine (93%, entry 3) and piperonylamine (91%, entry 12), and some electron-deficient amines, such as *p*-chlorobenzylamine (90%, entry 4) and *p*-fluorobenzylamine (91%, entry 5), are readily converted to the secondary imines in high yields. More electron-deficient benzylamines, such as *p*-trifluoromethylbenzylamine (78%, entry 6) and *m*-chlorobenzylamine (72%, entry 7), oxidize more slowly and require 48 h for complete conversion. The observation that electron-withdrawing substituents react more slowly is evident from an initial-rate study of substrates **1a**–**3a**, **5a**, and **6a**, from which a substantial negative Hammett correlation was determined ($\rho = -1.3$; see Supporting Information).

**Table 1.** Quinone-Catalyzed Aerobic Oxidation of Primary Benzylic Amines[a]




[a] Conditions: amine substrate (1.0 mmol), TBHBQ (0.015 mmol, 1.5 mol %), $O_2$ balloon, MeCN (3.5 mL), rt, 20 h. [b] Yield determined by $^1$H NMR spectroscopy versus internal standard. [c] Reaction time was 48 h. [d] Carried out in the presence of 1.0 equiv of $Et_3N$.

The free amino group of *p*-aminobenzylamine does not inhibit dimerization; however, the yield is slightly lower than some of the other derivatives (76%, entry 2). As noted above, halogen substituents, including *m*-iodobenzylamine, are well tolerated (entries 4, 5, 7, and 8, respectively). Sterically bulky groups, such as 1-naphthyl (81%, entry 11), and *ortho* substitution on the aromatic ring (entries 9, 10) cause only a slight diminution in yield. The heterocycle furfurylamine (80%, entry 13) undergoes oxidative dimerization, but 2- and 4-(aminomethyl)pyridines are not efficient substrates (not shown). The hydrochloride salt of benzylamine does not react, but good reactivity can be recovered upon addition of a Brønsted base, such as $Et_3N$ (entry 14).

Secondary amines, such as *N*-phenylbenzylamine and indoline (Table 1, entries 15, 16), and tertiary amines, such as $Et_3N$ and *N*,*N*-dimethybenzylamine (not shown), are not oxidized under the reaction conditions. This selectivity for primary amines is readily explained by the reaction mechanism (Scheme 1), which has been elucidated in previous biochemical model studies.[3] Condensation of the primary amine **1a** with TBHBQ leads to the iminoquinone

(6) For previous reports by Mure and Klinman describing the use of TBHBQ in enzyme model studies, see refs 4e, 4f.

(7) (a) Corey, E. J.; Achiwa, K. *J. Am. Chem. Soc.* **1969**, *91*, 1429–1432. (b) Klein, R. F. X.; Bargas, L. M.; Horak, V.; Navarro, M. *Tetrahedron Lett.* **1988**, *29*, 851–852.

(8) For an example involving C–H bond oxidation, see: (a) Ohshiro, Y.; Itoh, S.; Kurokawa, K.; Kato, J.; Hirao, T.; Agawa, T. *Tetrahedon Lett.* **1983**, *24*, 3465–3468. For examples involving C–C bond activation, see: (b) Itoh, S.; Kato, N.; Ohshiro, Y.; Agawa, T. *Tetrahedron Lett.* **1984**, *25*, 4753–4756. (c) Mure, M.; Suzuki, A.; Itoh, S.; Ohshiro, Y. *J. Chem. Soc., Chem. Commun.* **1990**, 1608–1611.

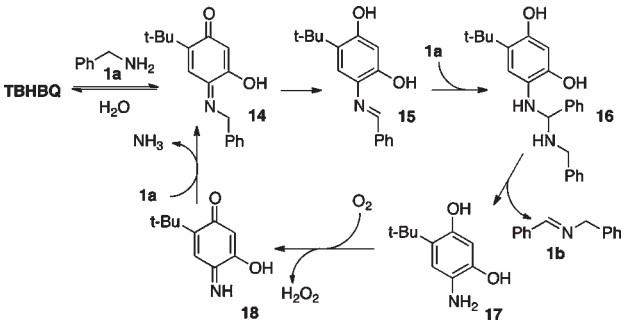
(9) Largeron, M.; Chiaroni, A.; Fleury, M.-B. *Chem.—Eur. J.* **2008**, *14*, 996–1003.

(10) Largeron, M.; Fleury, M.-B. *Org. Lett.* **2009**, *11*, 883–886.

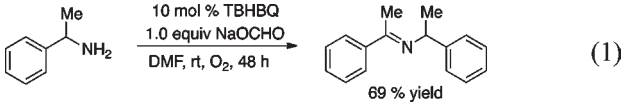
(11) Largeron, M.; Fleury, M.-B. *Angew. Chem., Int. Ed.* **2012**, 10.1002/anie201200587.

intermediate **14**. Tautomerization of this species to form **15** results in the net two-electron oxidation of the amine. Addition of a second equivalent of amine **1a** to imine **15** generates an aminal that can react further to liberate the product **1b** and reduced aminohydroquinone **17**. Aerobic oxidation of **17** generates iminoquinone **18**, which can undergo transimination with substrate **1a** to liberate $NH_3$ and close the catalytic cycle.

**Scheme 1.** Proposed Mechanism of Quinone-Catalyzed Aerobic Oxidation of Primary Amines




Aliphatic primary amines are not oxidized by TBHBQ under these reaction conditions, probably because this quinone is not sufficiently oxidizing to promote the reaction. The sec-primary amine α-methylbenzylamine is also not oxidized under these mild reaction conditions. In this case, the lack of reactivity must be a steric effect because the α-C−H bond should be weaker than that of the parent benzylamine. Reactivity is observed under more forcing conditions, using 10 mol % TBHBQ. With 1.0 equiv of sodium formate as a Brønsted base in DMF, a 69% yield of the imine dimer is obtained after 48 h (eq 1).

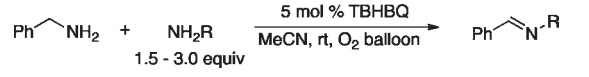


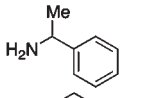
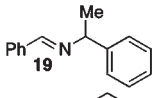
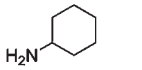
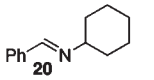
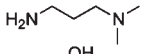
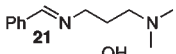
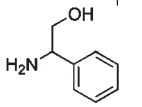
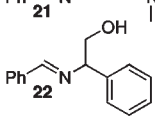
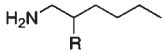
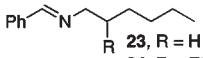
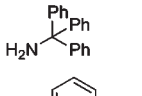
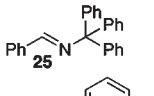
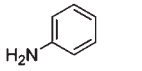
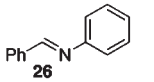

(1)

The exquisite selectivity for primary benzylic amines suggested that selective heterocoupling could be achieved by combining a benzylic amine with a less readily oxidized amine. Upon increasing the catalyst loading to 5 mol %, cross-coupled products were formed in very good yields, often with excellent selectivities (Table 2). The coupling of benzylamine and α-methylbenzylamine is facile (89%, entry 1), forming *N*-benzylidene-α-methylbenzylamine **19** as the exclusive product. Linear and branched aliphatic amines, such as cyclohexylamine (91%, entry 2), hexylamine (83%, entry 5), and 2-ethylhexylamine (85%, entry 6), are also good substrates for cross-product formation, though in the latter cases small amounts of *N*-benzylidenebenzylamine are also observed.

Primary amines that contain a tertiary amine (92%, entry 4) or primary alcohol (80%, entry 4) undergo effective heterocoupling with benzylamine, with no background oxidation of the tertiary amine or primary alcohol fragment. These observations highlight a potential advantage of the organocatalytic oxidation method described here, as transition-metal catalysts are unlikely to demonstrate comparable chemoselectivity. The sterically hindered tritylamine serves as an effective coupling partner (78%, entry 7), with the product crystallizing out of the reaction mixture. Aniline affords *N*-benzylidene aniline in good yield after 48 h (76%, entry 8), provided a second 5 mol % portion of the catalyst is added after 24 h.

**Table 2.** Quinone-Catalyzed Aerobic Cross-Coupling of Primary Amines[a]




| entry | amine | equiv | product | yield[b] |
|---|---|---|---|---|
| 1 |  | 2.0 |  **19** | 89% |
| 2 |  | 3.0 |  **20** | 91% |
| 3 |  | 1.5 |  **21** | 92%[c] |
| 4 |  | 2.0 |  **22** | 80%(5.5%)[c,d] |
| 5 |  | 2.0 |  **23**, R = H | 83%(6.5%)[c,d] |
| 6 | | 2.0 | **24**, R = Et | 85%(2.0%)[c,d] |
| 7 |  | 2.0 |  **25** | 78%[e] |
| 8 |  | 3.0 |  **26** | 76%(11%)[c,d] |

[a] Conditions: benzylamine (1.0 mmol), amine (1.5−3.0 mmol), TBHBQ (0.05 mmol), $O_2$ balloon, MeCN (3.5 mL), rt, 20−48 h. [b] Yield determined by $^1$H NMR spectroscopy versus internal standard. [c] After 24 h an additional aliquot of TBHBQ (5.0 mol %) was added, and the reaction was run for a total of 48 h. [e] Isolated yield.

In order to explore the origin of the excellent cross-product selectivity, two heterocoupling reactions were monitored by $^1$H NMR spectroscopy (Figure 1). In the reaction of benzylamine with 2.0 equiv of α-methylbenzylamine (Figure 1A), the time course reveals the parallel formation of homo- and heterocoupled products **1b** and **19** at early stages of the reaction. As the reaction progresses, the homocoupled product **1b** is progressively consumed, and the reaction converges to exclusive formation of **19** at the end of the reaction. A different profile is evident in the reaction of benzylamine and 2.0 equiv of aniline (Figure 1B). In this case, the time course reveals that the homocoupled dimer **1b** is formed exclusively and accumulates in good yield at early stages of the reaction ($t$ < 300 min). This observation is consistent with the tolerance of an aromatic amine in the oxidative homocoupling reactions

noted above (cf. Table 1, entry 2). At longer reaction times, the homodimer **1b** is slowly converted into the cross-product **26**.

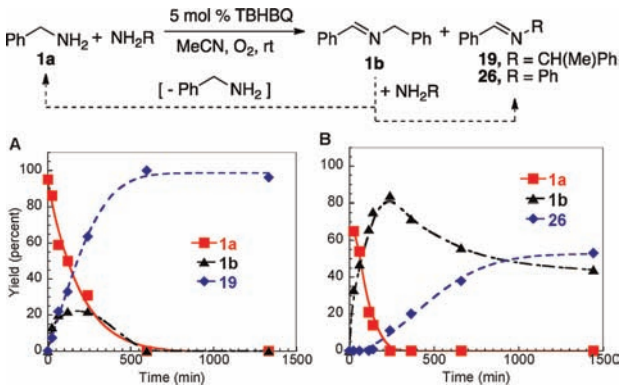
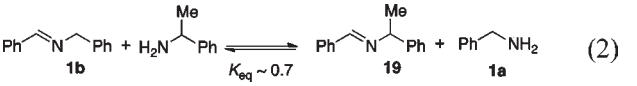



**Figure 1.** A $^1$H NMR time course of the TBHBQ-catalyzed oxidation of (A) benzylamine and methylbenzylamine and (B) benzylamine and aniline. Reaction conditions: benzylamine (0.28 M), α-methylbenzlamine or aniline (0.57 M), TBHBQ (0.014 M), trimethoxybenzene (internal standard, 0.078 M), MeCN-$d_3$, $O_2$ balloon, rt.

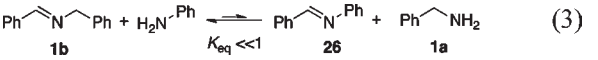
The cross-coupling results depicted in Figure 1 can be rationalized by three considerations: (1) the relative nucleophilicity of the two amines with the catalytic intermediate **15**, (2) equilibrium exchange of the amine substrates with the secondary imine products, and (3) the relative reactivity of the amine substrates toward oxidation.

The parallel formation of **1b** and **19** in Figure 1A suggests that benzylamine and α-methylbenzylamine can react with catalytic intermediate **15** to afford the homo- and heterocoupled dimers, respectively. Control experiments show that **1b** and **19** equilibrate readily under the reaction conditions in the presence of the amine substrates (eq 2), and the equilbrium constant ($K_{eq} \approx 0.7$) shows a slight preference for **1b**. The substantially higher reactivity of benzylamine toward oxidation by TBHBQ (see above), however, causes the equilibrium mixture to be driven toward formation of the heterocoupled product **19**.



(2)

Similar considerations rationalize the reactivity observed with benzylamine and aniline in Figure 1B. Exclusive formation of homodimer **1b** early in the reaction is readily explained by the higher reactivity of benzylamine relative to aniline with imine-hydroquinone intermediate **15**. Formation of *N*-benzylidene aniline **26** at longer reaction times is relatively sluggish. Formation of **26** via condensation of aniline with **1b** is thermodynamically unfavorable ($K_{eq} \ll 1$; eq 3). Nevertheless, its formation can be driven by continuous oxidation of the benzylamine generated, albeit in small quantities, from this exchange reaction.



(3)

The ability of a dynamic equilibrium mixture of species to converge toward a single product by consumption of one of the species has been termed "self-sorting."[12] With the pair of substrates shown in Figure 1A, oxidatively promoted self-sorting overcomes the slight thermodynamic preference of **1b** over **19**, enabling exclusive formation of **19**. With the substrate pair in Figure 1B, the kinetically preferred product may be obtained in good yield at short reaction times, or oxidative self-sorting can be exploited to obtain the otherwise strongly disfavored product. This oxidative strategy to achieve imine self-sorting is complementary to other approaches being pursued in the field of dynamic covalent chemistry[13–15] (e.g., through the use of templates) to promote selective product formation within an equilibrating mixture.

In summary, we have identified a highly chemoselective method for the aerobic oxidative coupling of primary benzylic amines to afford secondary imines, and dynamic self-sorting of the imine products enables selective formation of heterocoupled imines. The mild reaction conditions, the functional group compatibility, the use of $O_2$ as the oxidant, and the low catalyst loadings compare favorably with previously reported metal-catalyzed methods.

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**Supporting Information Available.** Experimental procedures, product characterization data, and $^1$H and $^{13}$C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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