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Catalytic Dehydrogenative Dual Functionalization of Ethers: Dealkylation–Oxidation–Bromination Accompanied by C–O Bond Cleavage via Aerobic Oxidation of Bromide

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A catalytic dehydrogenative dual functionalization (DDF) of ethers via oxidation, dealkylation, and α-bromination by the aerobic oxidation of bromide was developed to obtain the corresponding α-bromo ketones in high yields. In particular, the reaction of substituted tetrahydrofurans as cyclic ethers provided 3,3-dibromo tetrahydrofuran-2-ols in high yields selectively through the double α-bromination.

The functionalization of organic molecules is a very important strategy for the synthesis of various heteroatom-containing functional compounds. The increasing demand for more complex structures has underscored the need for more functionalizations to construct the desired moieties in molecules. In the past, multi functionalization was an economical and efficient methodology for the direct installation of functional groups in molecules.[1] In recent years, various dual functionalizations, such as saturated dual functionalization, which involves the conversion of unsaturated hydrocarbon into saturated hydrocarbon of functionalization acceptors by the addition of functional groups (Figure 1, upper left),[2] and the hybrid orbital retained dual functionalization, which retains the binding mode on the carbon-carbon bond in functionalization acceptors, have been accomplished (Figure 1, upper middle).[3] On the other hand, to the best of our knowledge, there are few reports of dehydrogenative dual functionalization (DDF), which involves the rehybridization of sp^3 orbital into sp^2 orbital by the installation of functional groups (Figure 1, upper right). Xiao and co-workers reported the dehydrogenative coupling of tetrahydroisoquinolines in the presence of an iridium catalyst to obtain corresponding quinolone derivatives (Figure 1a).[4] Moreover, the stoichiometric oxidation-chlorination of alcohols using trichloroisocyanuric acid by Studer et al.[5] and the oxidation-iodination of alcohols with hypoiodous acid, which was generated from NaI and aq. H_2O_2 in the presence of excess of H_2SO_4, by Barluenga et al.[6] were reported (Figure 1b).

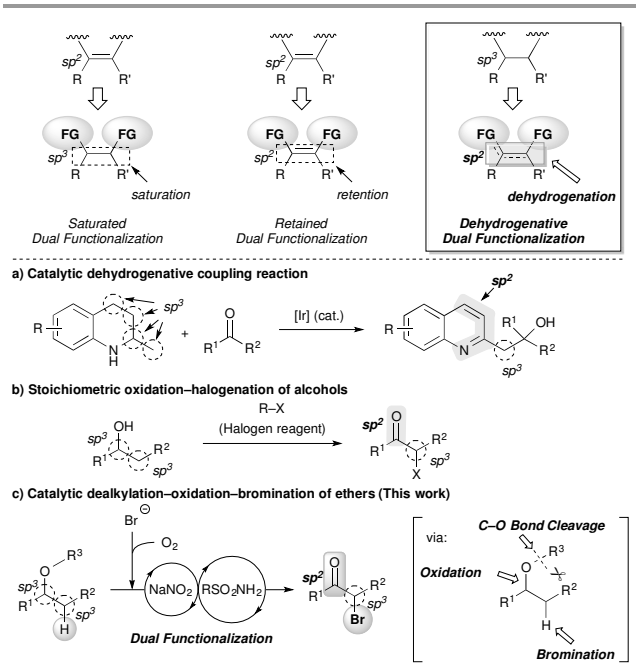

Figure 1. Dual functionalization for organic molecules.

We succeeded in tandem oxidation of ethers through dealkylation and oxidation[7] via umpolung of bromide using alkali metal bromide and a strong oxidant (e.g. Oxone®: $2KHSO_5 \bullet KHSO_4 \bullet K_2SO_4$)[8] to obtain ketones in gratifying yields. In this context, we came up with an idea that the catalytic DDF of ethers by a three-step tandem reaction, that is, oxidation-dealkylation-bromination, via aerobic umpolung of bromide would efficiently provide α-bromo ketones, which are biologically active molecules[9] and versatile building blocks for the synthesis of functional materials and natural products[10]

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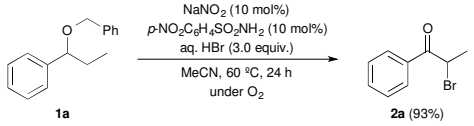
(Figure 1c). One very important piece of information regarding the transition metal-free aerobic oxidation of bromide is that a catalytic amount of sodium nitrite promotes the oxidation of bromide through the generation of NO_2 under O_2.[11] We report herein the DDF of acyclic and cyclic ethers using the sodium nitrite and 4-nitrobenzenesulfonamide co-catalyst system via the aerobic umpolung of bromide.

First, we chose the transformation of *O*-benzyl 1-phenyl propyl ether (**1a**) into α-bromopropiophenone (**2a**) as an example of aerobic DDF using $NaNO_2$ catalyst and screened for the optimum additive and solvent (Table S1, Supporting Information).

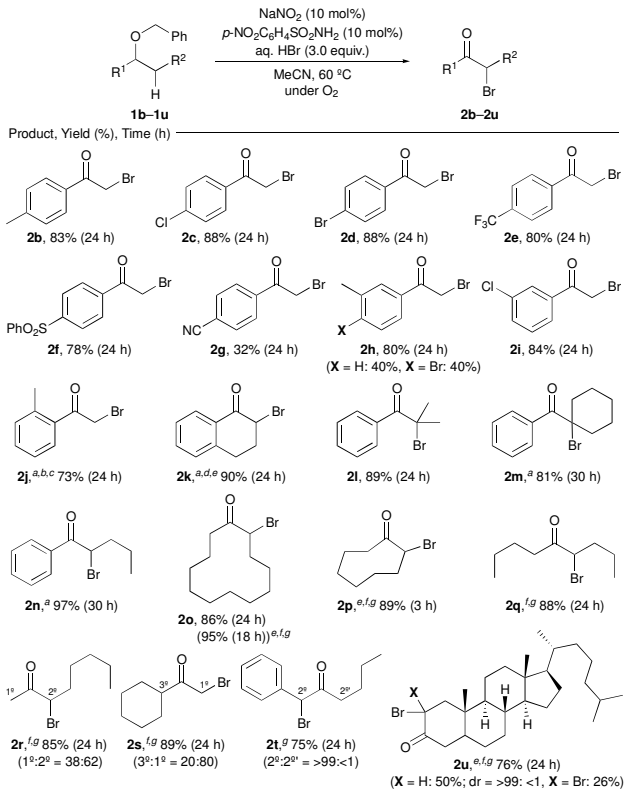


Scheme 1. Screening for DDF of **1a** via aerobic oxidation of bromide.

The optimum conditions for the reaction were **1a**, aq. HBr (3.0 equiv.), $NaNO_2$ (10 mol%), and *p*-$NO_2C_6H_4SO_2NH_2$ (10 mol%) in MeCN at 60 ºC under O_2, which **2a** in 93% yield (Scheme 1).

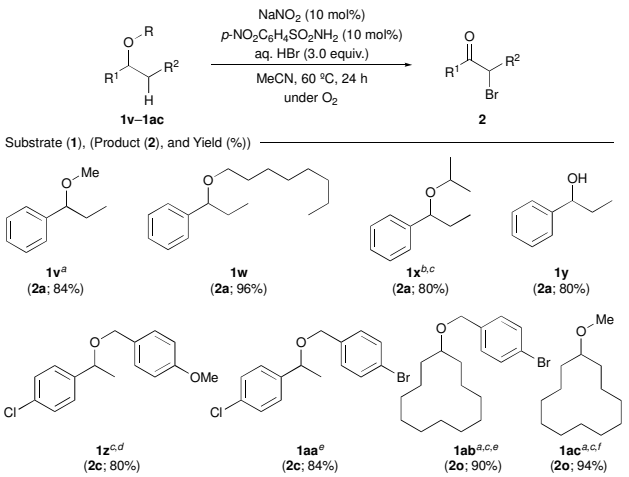
To explore the substrate scope for DDF, *O*-benzyl ethers (**1**) were examined under the optimum conditions (Table 1). When *para-*, *meta-,* and *ortho*-substituted *O*-benzyl α-methyl benzyl ethers (**1b**–**1j**) were used in this reaction, corresponding products (**2b**–**2j**) were obtained in high yields (73–88% yield). In the case of **1h**, a mixture with the concurrent bromination of the benzene ring product (**2h**: X = Br) was provided. *O*-Benzyl α-alkyl benzyl ethers (**1k**–**1n**) also gave the desired products (**2k**–**2n**) in high yields (81–97%), respectively. The reaction of more reactive *O*-benzyl aliphatic ethers (**1o**–**1u**) gave α-bromo ketones (**2o**–**2u**) in satisfactory yields under *p*-$NO_2C_6H_4SO_2NH_2$-catalyst-free conditions.[12] Complicated regioselective dual functionalization with asymmetric *O*-benzyl ethers (**1r**–**1u**) efficiently proceeded to furnish α-bromo ketones (**2r**–**2u**) in high yields (73–89%) with moderate to high regioselectivities (rr = 38:62 to >99:<1).

Table 1. DDF of benzyl ethers **1** via aerobic oxidation of bromide.



[a]$NaNO_2$ (20 mol%). [b]aq. HBr (4.0 equiv.). [c]In MeCN:H_2O (10:1). [d]In MeCN:H_2O (9:1). [e]At 50 ºC. [f]aq. HBr (2.0 equiv.). [g]Absence of *p*-$NO_2C_6H_4SO_2NH_2$.

Table 2. DDF of ethers **1** via aerobic oxidation of bromide.



[a]Absence of *p*-$NO_2C_6H_4SO_2NH_2$. [b]aq. HBr (4.0 equiv.). [c]At 50 ºC. [d]aq. HBr (5.0 equiv.). [e]$NaNO_2$ (20 mol%). [f]aq.HBr (2.0 equiv.) for 18 h.

Next, we extensively investigated the scope of co-catalyzed DDF with various ethers (Table 2). Interestingly, *O*-aliphatic ethers bearing Me (**1v** and **1ac**), *n*-octyl (**1w**), and *i*-propyl (**1x**) groups, alcohol (**1y**), and substituted benzyl ethers (**1z**, **1aa**, and **1ab**) instead of a benzyl group also gave corresponding α-bromo ketones (**2a**, **2c**, and **2o**) in high yields (80–94%), respectively. In some cases where *O*-aliphatic ethers were also used in the present reaction, the absence of *p*-$NO_2C_6H_4SO_2NH_2$ catalyst was effective to obtain the desired products.

Furthermore, to show the advantage of this methodology, we demonstrated the DDF of five-membered cyclic ethers, tetrahydrofurans (**3**) via the aerobic oxidation of bromide (Table 3). Unexpectedly, 3,3-dibromo-2-substituted tetrahydrofuran-2-ol (**4**) was selectively obtained in high yield by modification of the amount of aq. HBr (5.0 equiv.), whereas the reaction under optimum conditions for acyclic ethers furnished oxidized products.[13]

Various tetrahydrofurans bearing a substituent on the aromatic ring (**3a**–**3k**) also gave the corresponding products (**4a**–**4k**) in high yields (83–99%), respectively, except for **4f** and **4h**.

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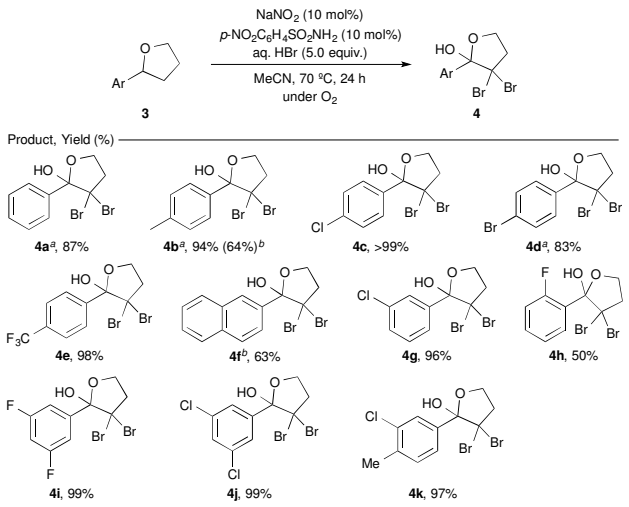
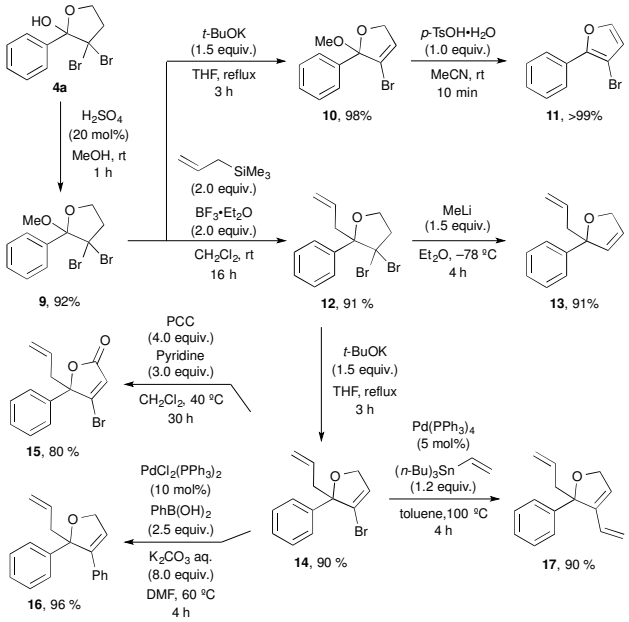
Table 3. DDF of tetrahydrofurans **3** via aerobic oxidation of bromide.



[a]At 60 °C. [b]aq. HBr (3.0 equiv.).

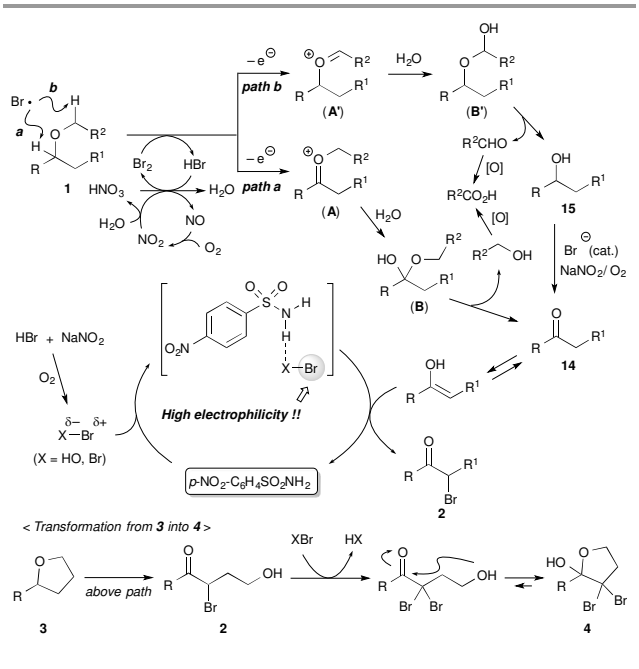
To demonstrate the synthetic utility of 3,3-dibromo-2-aryl tetrahydrofuran-2-ol (**4**) formed in the present reaction, we investigated the derivatization of **4a** into various furan derivatives (Scheme 2). **4a** was converted into acetal **9** in 92% yield through the interconversion with MeOH under acidic conditions. The reaction of **9** with *t*-BuOK gave 3-bromo-2,5-dihydrofuran (**10**) in 98% yield. Aromatization of **10** using *p*-TsOH•H_2O provided 3-bromofuran (**11**) in quantitative yield.



Scheme 2. Transformation of **4a** into various furan derivatives.

Treatment of **9** with allyltrimethylsilane in the presence of a Lewis acid proceeded via C–C bond formation to obtain alkyl-substituted furan (**12**) in high yield. **12** was smoothly converted into 2,5-dihydrofuran with a quaternary carbon center (**13**) via the formation of carbene species, and into 3-bromo-2,5-dihydrofuran with a quaternary carbon center (**14**) by β-elimination. **14** underwent further transformations to give various 2,5-dihydrofurans bearing functional groups, such as lactone (**15**), styrene (**16**), and diene (**17**), in good yields (80–96%), respectively.

To elucidate the reaction mechanism in the DDF of ethers via the aerobic oxidation of bromide, various supporting experiments were conducted (Supporting Information) and the results indicated the following: 1) the DDF proceeded in a stepwise manner through the dealkylation of ethers, the oxidation of alcohols, and the α-bromination of ketones (Figure S1); 2) the oxidation of alcohols was catalyzed by HBr in the present reaction, whereas the dealkylation and the α-bromination of ketones occurred stoichiometrically to give the corresponding products selectively (Scheme S1, Eqs. S1–S3); 3) the role of sulfonamide catalyst promoted the α-bromination of ketones by activation of a bromo source via hydrogen bonding interaction without the formation of *p*-$NO_2C_6H_4SO_2NBr_2$, a high-performance bromo source[12,13] (Scheme S1, Eq S3 and Figure S2). In addition, this reaction with **1a** (Table 1, entry 10) gave benzaldhyde and benzoic acid, as co-products together with the desired product.[14]



Scheme 3. Plausible reaction mechanism.

Based on these mechanistic experiments, we proposed a reaction mechanism, as depicted in Scheme 7. First, Br_2 is generated in situ by the aerobic oxidation of bromide with $NaNO_2$.[11,15] A bromo radical converted from Br_2 concertedly abstracts the H atom (H_a or H_b) at α-position of ethers (**1**) to generate α-radical intermediate. A more stable α-radical than another one is proncipally formed (path a) and oxonium intermediate (**A**) formed by one-electron oxidation is transformed into ketones (**14**) via formation of hemiacetal (**B**)

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by addition of H_2O immediately. By contrast, ganaration of another α-radical (path b) is provided alcohols (**15**) via formation of **A'** and **B'** intermediates by above reaction mechanism. However, **15** is oxidized by aerobic oxidation with a catalytic amount of bromide to obtain corresponding ketones (**14**) (Scheme S1, Eq. S2). The α-bromination of **14** via oxidation of bromide provides α-bromo ketones (**2**). In the α-bromination, it is important to add p-$NO_2C_6H_4SO_2NH_2$ catalyst to promote the α-bromination of **14** by activation of a bromo source. In the reaction of cyclic ethers (**3**), a second bromination of **2** followed by intramolecular cyclization gives **4** after the formation of **2** through the above reaction mechanism.

In conclusion, we developed a catalytic DDF of ethers via dealkylation–oxidation–α-bromination by the aerobic oxidation of bromide to obtain the corresponding α-bromo ketones and 3,3-dibromo tetrahydrofuran-2-ols in high yields. This DDF is expected to further expand fine organic reactions. The development of this catalytic system in aerobic transformation and the application of this oxygen-containing heterocycles are underway in our laboratory.

Notes and references

1 For reviews on multi functionalization, see: a) A. Minatti, K. Muñiz, *Chem. Soc. Rev.* **2007**, *36*, 1142-1152; b) E. M. Beccalli, G. Broggini, M. Martinelli, S. Sottocomola, *Chem. Rev.* **2007**, *107*, 5318-5365, c) S. E. Allen, R. R. Walvoord, R. Padolla-Salinas, M. C. Kozlowski, *Chem. Rev.* **2013**, *113*, 6234-6458; d) X. Zeng, *Chem. Rev.* **2013**, *113*, 6864-6900; e) Y. Shimizu, M. Kanai, *Tetrahedron Lett.* **2014**, *55*, 3727-3737; f) D. Qiu, J. Shi, Y. Li, *Synlett* **2015**, *26*, 2194-2198.

2 Selected recent report for the reductive dual functionalization: a) E. M. Beccalli, G. Broggini, S. Gazzola, A. Mazza, *Org. Biomol. Chem.* **2014**, *12*, 6767-6789; b) K. Mori, S. Sueoka, T. Akiyama, *Chem. Lett.* **2009**, *38*, 628-629; c) Y. Nakao, E. Morita, H. Idei, T. Hiyama, *J. Am. Chem. Soc.* **2011**, *133*, 3264-3267; d) S. J. Heffernan, J. P. Tellam, M. E. Queru, A. C. Silvanus, D. Benito, M. F. Mahon, A. J. Hennessy, B. I. Andrews, D. R. Carbery, *Adv. Synth. Catal.* **2013**, *355*, 1149-1159; e) H. K. Munch, J. E. Rasmussen, G. Popa, J. B. Christensen, K. J. Jensen, *Chem. Commun.* **2013**, *49*, 1936-1938; f) Y. Nishihara, M. Suetsugu, D. Saito, M. Kinoshita, M. Iwasaki, *Org. Lett.* **2013**, *15*, 2418-2421; g) F. Hu, Y. Xia, Z. Liu, Chen, Ma, Y. Zhang, J. Wang, *Org. Biomol. Chem.* **2014**, *12*, 3590-3593; h) G. Fumagalli, P. T. G. Rabet, S. Boyd, M. F. Greaney, *Angew. Chem. Int. Ed.* **2015**, *54*, 11481-11484; i) R. Yao, G. Rong, B. Yan, L. Qiu, X. Xu, *ACS Catal.* **2016**, *6*, 1024-1027; j) G.-Q. Xu, C.-G. Li, M.-Q. Liu, J. C. Y.-C. Luo, P.-F. Xu, *Chem. Commun.* **2016**, *52*, 1190-1193.

3 Selected recent report for the retained dual functionalization: a) T. Morishita, H. Fukushima, H. Yoshida, J. Ohshita, A. Kumai, *J. Org. Chem.* **2008**, *73*, 5452-5457; b) A. Chartoire, C. Comoy, Y. Fort, *Org. Biomol. Chem.* **2011**, *9*, 1839-1845; c) J. Kwak, Y. Ohk, Y. Jung, S. Chang, *J. Am. Chem. Soc.* **2012**, *134*, 17778-17788; d) K. Moriyama, K. Ishida, H. Togo, *Chem. Commun.* **2015**, *51*, 2273-2276; e) B. Zhou, Z. Chen, Y. Yang, W. Ai, H. Tang, Y. Wu, W. Zhu, Y. Li, *Angew. Chem. Int. Ed.* **2015**, *54*, 12121-12126; f) R. A. Dhokale, S. B. Mhaske, *Org. Lett.* **2016**, *18*, 3010-3013.

4 D. Talwar, A. Gonzalez-de-Castro, H. Y. Li, J. Xiao, *Angew. Chem. Int. Ed.* **2015**, *54*, 5223-5227.

5 Y. Jing, C. G. Daniliuc, A. Studer, *Org. Lett.* **2014**, *16*, 4932-4935.

6 J. Barluenga, M. Marco-Arias, F. González-Bobes, A. Ballesteros, J. M. González, *Chem. Commun.* **2004**, 2616-2617.

7 K. Moriyama, Y. Nakamura, and H. Togo, *Org. Lett.* **2014**, *16*, 3812-3815.

8 a) K. Moriyama, Y. Izumisawa, and H. Togo, *J. Org. Chem.* **2011**, *76*, 7249-7255; b) K. Moriyama, M. Takemura, and H. Togo, *Org. Lett.* **2012**, *14*, 2414-2417; c) K. Moriyama, K. Ishida, and H. Togo, *Chem. Commun.* **2012**, *48*, 8574-8576; d) K. Moriyama, M. Takemura, and H. Togo, *J. Org. Chem.* **2014**, *79*, 6094-6104; e) K. Moriyama, T. Sugiue, C. Nishinohara, H. Togo, *J. Org. Chem.* **2015**, *80*, 9132-9140; f) K. Moriyama, C. Nishinohara, T. Sugiue, H. Togo, *RSC Advance.* **2015**, *5*, 85872-85878.

9 a) G. Arabaci, X.-C. Guo, K. D. Beebe, K. M. Coggeshall, D. Pei, *J. Am. Chem. Soc.* **1999**, *121*, 5085-5086; b) G. Arabaci, T. Yi, H. Fu, M. E. Porter, K. D. Beebe, D. Pei, *Bioorg. Med. Chem. Lett.* **2002**, *12*, 3047-3050; c) S. Conde, D. L. Pérez, A. Martínez, C. Perez, F. J. Moreno, *J. Med. Chem.* **2003**, *46*, 4631-4633.

10 a) N. De Kimpe, R. Verhé *The Chemistry of α-Haloketones, α-Heteroaldehydes, and α-Haloimines*, Wiley, Nuw York, 1999; b) A. W. Erian, S. M. Sherif, H. M. Gaber, *Molecules* **2003**, *8*, 793-865.

11 a) R. Mu, Z. Liu, Z. Yang, Z. Liu, L. Wu, Z.-L. Liu, *Adv. Synth. Catal.* **2005**, *347*, 1333-1336; b) M. Uyanik, R. Fukatsu, K. Ishihara, *Chem. Asian J.* **2010**, *5*, 456-460.

12 Treatment of p-$NO_2C_6H_4SO_2NH_2$ with aq. HBr and $NaNO_2$ in MeCN under O_2 at 60 ^oC for 24 h did not provide p-$NO_2C_6H_4SO_2NBr_2$.

13 W. Z. Yu, F. Chen, Y. A. Cheng, Y.-Y. Yeung, *J. Org. Chem.* **2015**, *80*, 2815-2821.

14 This reaction of **1a** under the optimized conditions (Scheme 1) provided benzaldehyde (38% yield) and benzoic acid (37%) as byproduct together with **2a**.

15 F. Minisci, O. Porta, F. Recupero, C. Punta, C. Gambarotti, M. Pierini, L. Galimberti, *Synlett*, **2004**, 2203-2205.