Heterocyclization Approach for Electrooxidative Coupling of Functional Primary Alkylamines with Aromatics

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Supporting Information Placeholder

ABSTRACT: A new approach for electrooxidative coupling of aromatic compounds and primary alkylamines bearing a functional group such as a hydroxyl group and an amino group was developed. The key to the success of the transformation is heterocyclization of functional primary alkylamines. Treatment of primary alkylamines bearing a functional group with nitriles or their equivalents gives the corresponding heterocycles. The electrochemical oxidation of aromatic substrates in the presence of the heterocycles followed by chemical reaction under non-oxidative conditions gave the desired coupling products.

Amination of aromatic compounds serves as a straightforward and useful route to aromatic amines which are often key components of natural products, medicinal compounds, and functional materials.[1] In particular, C−H amination of aromatic compounds is the state of the art in amination reactions.[2] A variety of methods have been developed based on transition-metals,[3] hypervalent iodines,[4] and radical species,[5] and serve as powerful tools for synthesizing nitrogen containing complex molecules. We have also developed electrochemical[6,7] C−H amination[8] which enables direct introduction of nitrogen functionalities into electron-rich aromatic compounds selectively. However, the introduction of primary alkylamino groups bearing a functional group still remains challenging,[9] although such structures serve as prominent structural motif in various biologically and pharmaceutically active compounds as exemplified in Figure 1.[10] We report here a new strategy for electrooxidative coupling of aromatic compounds and primary alkylamines bearing a functional group such as a hydroxyl group and an amino group.

The conventional approaches using electrochemical oxidation suffer from the following problems: The direct use of alkylamines should be unsuccessful because they are oxidized prior to aromatic substrates (Scheme 1A).[11] The use of *N*-protected alkylamines could suppress such undesired oxidation because protecting groups are usually electron-withdrawing (Scheme 1B). However, the nucleophilitity of an *N*-protected alkylamine toward the radical cation of an aromatic compound would also be decreased in such situations. Furthermore, even if the nucleophilic attack is successful, overoxidation[12] is inevitable because addition of the amine to the aromatic ring will lower its oxidation potential.[13] Also, nucleophilic functional groups bearing an acidic proton such as such as OH and NHR groups might be problematic for the electrooxidative reaction because of their undesired nucleophilic attack on the radical cation of an aromatic compound.

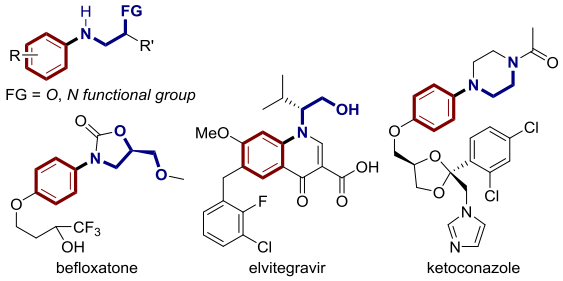
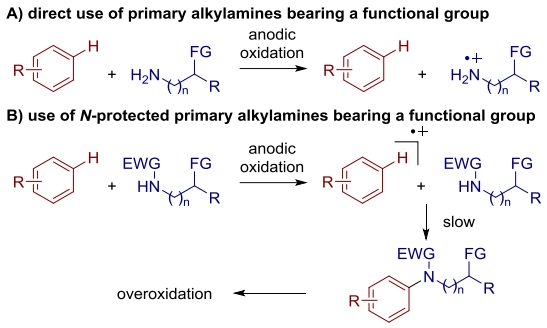


Figure 1. Aromatic compounds bearing functional alkylamino groups.

As we have previously reported, heterocyclic compounds such as pyridine,[8a] *N*-mesylimidazole,[8b] and pyrimidine[8c] are effective as nitrogen sources affording the electrooxidatively inactive cationic intermediates, which can be subsequently converted to the corresponding neutral nitrogen-containing products under non-electrolytic conditions. Consequently, the overoxidation can be avoided.

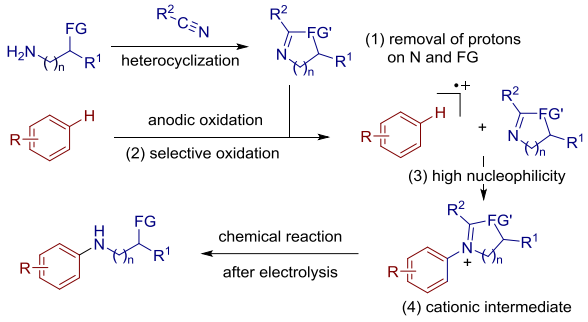
In analogy, we envisaged that an initial heterocyclization of a functional primary alklamine might solve the current challenge as well (Scheme 2). Treatment of primary alkylamines bearing a functional group with nitriles (RCN) or their equivalents gives the corresponding heterocycles.[14] In particular, favorable 5-membered and 6-membered ring formation takes place if the functional group is attached at an appropriate position. In the presence of the resulting heterocycles, aromatic substrates can be electrochemically oxidized to give their radical cations, which reacts with the heterocycles to generate the corresponding cationic intermediates. The cationic intermediates can be chemically converted to the desired cross-coupling products under non-oxidative conditions.

Scheme 1. Conventional approaches to the introduction of functional alkylamines using electrochemical oxidation



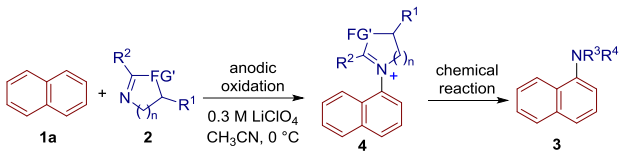
The following points of this approach should be stressed: (1) the formation of the heterocycles removes protons in the amino and the functional groups, which might disturb the electrochemical reaction, (2) the oxidation potential[15] of the heterocycles is higher than those of the corresponding alkylamines because of the sp^2-hybridization of nitrogen atoms, enabling selective oxidation of aromatic substrates, (3) the hetereocycles have sufficient nucleophilicity toward the radical cations of aromatic compounds,[16] and (4) the resulting cationic intermediates, which can be stable enough to accumulate, are not oxidized because of strong electron-withdrawing effect of a positive charge.

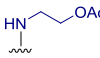
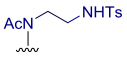
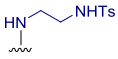
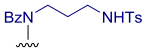
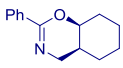
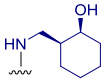
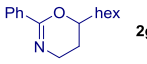
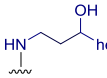
Scheme 2. Present approach for electrooxidative coupling of functional primary alkylamines with aromatics



We first examined the reaction of naphthalene (**1a**) (E_{ox}=1.52 V, vs. Ag/Ag^+) with 2-methyloxazoline (**2a**) (E_{ox}=1.73 V, vs. Ag/Ag^+) which can be derived from 2-hydroxylethylamine (Table 1, entry 1). The anodic oxidation led to the formation of a corresponding cationic intermediate **4a**, which was characterized by ^1H NMR (See SI). Hydrolysis with *aq* $NaHCO_3$ gave 1-(2-acetoxylethylamino)naphthalene (**3aa**) in 75% yield. Furthermore, treatment of the cationic intermediate with ethylenediamine gave 1-(2-hydroxylethylamino)naphthalene (**3aa'**) in 79% yield (entry 2). As shown in table 1, the present method is applicable to C−H amination with various functionalized primary alkylamines. 2-Hydroxy-2-phenylethylamine was also effective (entry 3). The use of a 6-membered-ring heterocycle **2c** which can be derived from 3-hydroxyl-1-propylamine also gave the amination product **3ad** in a good yield (entry 4). Heterocycles derived from ethylenediamine **2d** and 1,3-diaminopropane **2e** gave the corresponding amination products in good yields (entries 5-7). Heterocycles derived from cyclohexane-fused 3-hydroxyl-1-propylamine **2f** (entry 8) and long chain primary alkylamine bearing a hydroxyl group at 3-position **2g** (entry 9) gave the corresponding amination products in good yields.

Table 1. Electrooxidative coupling of naphthalene with various heterocycles



entry	2		chemical reaction	NR^3R^4	product	yield (%)
1		**2a**	A		**3aa**	75
2		**2a**	B		**3aa'**	79
3		**2b**	B		**3ab'**	67
4		**2c**	B		**3ac'**	74[a]
5		**2d**	A		**3ad**	64
6		**2d**	B		**3ad'**	80
7		**2e**	A		**3ae**	90
8		**2f**	B		**3af'**	65
9		**2g**	B		**3ag'**	85

The electrochemical oxidation reactions were carried with **1** (0.2 mmol) and 0.6 mmol of **2** in a 0.3 M solution of $LiClO_4$ in CH_3CN at 0 ºC unless otherwise stated, and the resulting solution was subjected to the chemical reaction: A, *aq* $NaHCO_3$; B, ethylenediamine. [a] 1.0 mmol of **2c** was used.

The scope of the aromatic substrates was examined using 2-methyloxazoline (**2a**) as a coupling partner (Figure 2). In the reaction with *o*-iodoanisole (**1b**), the alkylamino group was introduced at the para position selectively without affecting the iodo group (Figure 2, **3ba**, **3ba'**). In the case of *p*-iodoanisole (**1c**), the alkylamino group was introduced at the ortho position selectively (**3ca**, **3ca'**). The reactions of anisoles bearing various functional groups such as ester (**1d**), amide (**1e**), cyano (**1f**), and *t*-butyl (**1g**) groups at the para position gave the corresponding amination products without affecting such functionality (**3da**-**3ga**). In the case of a phenol derivative which has two aromatic rings (**1h**), the more electron-rich aromatic ring was selectively functionalized without affecting the electron-deficient aromatic ring (**3ha**). Polycyclic aromatic hydrocarbons such as phenanthrene (**1i**) and 9,9-dimethylfluorene (**1j**) gave the corresponding amination products **3ia** and **3ja**, respectively in good yields. Furthermore, heteroaromatic compounds such as indole and benzothiophene derivatives **1k** and **1l** also gave the corresponding amination products **3ka** and **3la**, respectively Small molecule drugs such as aniracetam (**1m**) and fenofibrate (**1n**) gave the corresponding amination products **3ma** and **3na**, respectively without affecting other functional groups.

Regioselectivity of the amination can be predicted based on the DFT calculations.[8a,17] The alkylamines are introduced to the carbon bearing hydrogen with the largest coefficient of the lowest

unoccupied molecular orbital (LUMO) of the radical cations of the aromatic substrates (Figure 3).

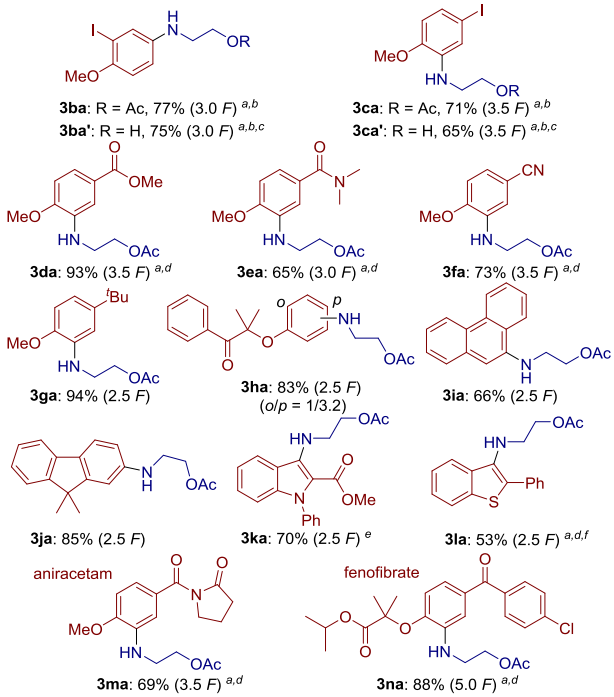


Figure 2. Electrooxidative coupling of various aromatic and heteroaromatic compounds with 2-methyloxazoline. Aromatic substrate **1** (0.2 mmol) was oxidized electrochemically in the presence of 0.6 mmol of **2a** in a 0.3 M solution of $LiClO_4$ in CH_3CN at room temperature unless otherwise stated, and the resulting solution was treated with *aq* $NaHCO_3$. [a]1.0 mmol of 2-methyloxazoline was used. [b]1.0 M solution of $LiClO_4$ was used. [c]The reaction mixture obtained by the electrolysis was treated with ethylenediamine. [d] 0.2 M solution of $Mg(ClO_4)_2$ was used. [e] 0.3 M solution of $NaClO_4$ was used. [f] Electrolysis was carried out at 50 ºC.

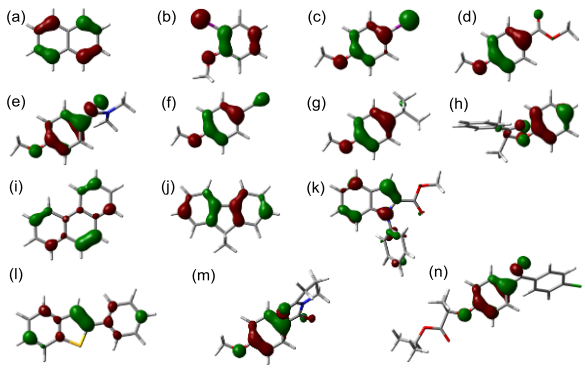
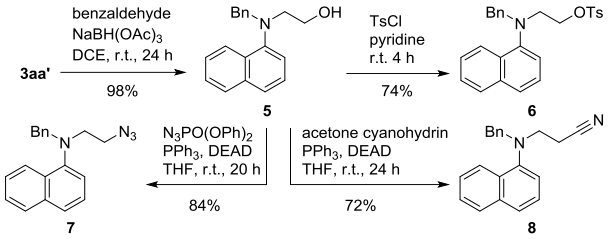


Figure 3. The lowest unoccupied molecular orbitals (β-LUMOs) of radical cations of (a) **1a**,[8a] (b) **1b**,[8a] (c) **1c**,[8a] (d) **1d**, (e) **1e**, (f) **1f**, (g) **1g**, (h) **1h**, (i) **1i**, (j) **1j**, (k) **1k**, (l) **1l**, (m) **1m**, and (n) **1n** obtained by DFT calculations.

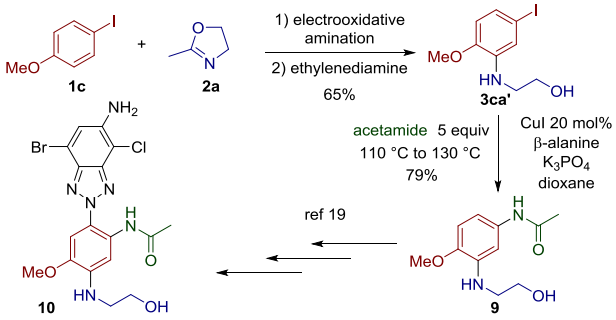
It is also noteworthy that the hydroxyl group attached to the alkylamino group in the products can be used for further transformations. For example, after benzyl protection of the amino group, the hydroxyl group was successfully converted to various functional groups such as tosylate, azide, and cyano groups as shown in Scheme 3.

Scheme 3. Transformation of the hydroxyl group in the alkylamino group



Chemical synthesis of mutagens is very important in confirming their structures and evaluating their activity. To demonstrate the utility of the present C−H amination method, we synthesized a key intermediate **9** for the synthesis of a mutagen **10** isolated from blue cotton-adsorbed materials in the Nikko River in Japan (Scheme 4).[18] The electrochemical oxidation of *p*-iodoanisole (**1c**) in the presence of 2-methyloxazoline (**2a**) followed by the treatment with ethylenediamine gave the corresponding amination product **3ca'**. The iodo group, which was not affected during the electrolysis, was then successfully converted to -NHAc group using a copper catalyst to give desired **9**. The previous synthesis of **9** reported in the literature[18] requires 6 steps with the overall yield of only 7% because protection and deprotection steps are necessary. In contrast, the present approach provides a short and straightforward route to **9** with the overall yield of 51%.

Scheme 4. Synthesis of mutagen 10



In summary, we have developed an effective method for C-H amination of aromatic compounds with functionalized primary alkylamines via heterocyclization based on the rational reaction design. The method is highly chemoselective and provides a metal- and chemical-oxidant-free route to the *N*-alkylaniline derivatives bearing oxygen and nitrogen functionalities in the alkyl group, which can be used for further transformations.

ASSOCIATED CONTENT

Supporting Information. Experimental procedures and spectroscopic data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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REFERENCES

(1) (a) Lawrence, S. A., Eds. *Amines: Synthesis, Properties and Applications*; Cambridge University Press: Cambridge, 2004. (b) Rappoport, Z., Eds. *The Chemistry of Anilines, Parts 1 and 2*; John Wiley & Sons: New York, 2007. (c) Scholz, U.; Schlummer, B. Arylamines. In *Science of Synthesis*; Georg Thieme Verlag: Stuttgart, 2007, *31b*, 1565. (d) Ricci, A., Eds. *Amino Group Chemistry: From Synthesis to the Life Sciences*; Wiley-VCH: Weinheim, 2008.

(2) (a) Collet, F.; Dodd, R. H.; Dauban, P. *Chem. Commun*. **2009**, *48*, 5061. b) Stokes, B.; Driver, T. G. *Eur. J. Org. Chem*. **2011**, *22*, 4071. c) Louillat, M. L.; Patureau, F. W. *Chem. Soc. Rev*. **2014**, *43*, 901.

(3) (a) Kim, J. Y.; Park, S. H.; Ryu, J.; Cho, S. H.; Kim, S. H.; Chang, S. *J. Am. Chem. Soc*. **2012**, *134*, 9110. (b) Boursalian, G. B.; Nagi, M. Y.; Hojczyk, K. N.; Ritter, T. *J. Am. Chem. Soc.* **2013**, *135*, 13278. (c) Yu, D. G.; Suri, M.; Glorius, F. *J. Am. Chem. Soc.* **2013**, *135*, 8802. (d) Shang, M.; Sun, S. Z.; Dai, H. X.; Yu, J.-Q. *J. Am. Chem. Soc*. **2014**, *136*, 3354.

(4) (a) Kim, H. J.; Kim, J.; Cho, S. H.; Chang, S.; *J. Am. Chem. Soc.* **2011**, *133*, 16382. (b) Ban, X.; Pan, Y.; Lin, Y.; Wang, S.; Du, Y.; Zhao, K. *Org. Biomol. Chem*. **2012**, *10*, 3606. (c) Souto, J. A.; Zian, D.; Muñiz, K. *J. Am. Chem. Soc*. **2012**, *134*, 7242. (d) Alla, S. K.; Kumar, R. K.; Sadhu, P.; Punniyamurthy, T. *Org. Lett*. **2013**, *15*, 1334.

(5) (a) Allen, L. J.; Cabrera, P. J.; Lee, M.; Sanford, M. S. *J. Am. Chem. Soc*. **2014**, *136*, 5607. (b) Foo, K.; Sella, E.; Thome, I.; Eastgate, M. D.; Baran, P. S. *J. Am. Chem. Soc.* **2014**, *136*, 5279. (c) Zhou, L.; Tang, S.; Qi, X.; Lin, C.; Liu, K.; Liu, C.; Lan, Y.; Lei, A. *Org. Lett*. **2014**, *16*, 3404.

(6) (a) Moeller, K. D. *Tetrahedron* **2000**, *56*, 9527. (b) Sperry, J. B.; Wright, D. L. *Chem. Soc. Rev*. **2006**, *35*, 605. (c) Yoshida, J.; Kataoka, K.; Horcajada, R.; Nagaki, A. *Chem. Rev*. **2008**, *108*, 2265. (d) Ogawa, K. A.; Boydston, A. J. *Chem. Lett.* **2015**, *44*, 10.

(7) Recent examples of electroorganic chemistry: (a) Ashikari, Y.; Shimizu, A.; Nokami, T.; Yoshida, J. *J. Am. Chem. Soc.* **2013**, *135*, 16070. (b) Redden, A.; Perkins, R. J.; Moeller, K. D. *Angew. Chem., Int. Ed*. **2013**, *52*, 12865. (c) Ogawa, K. A.; Boydston, A. J. *Org. Lett*. **2014**, *16*, 1928. (d) Elsler, B.; Schollmeyer, D.; Dyballa, K. M.; Franke, R.; Waldvogel, S. R. *Angew. Chem., Int. Ed*. **2014**, *53*, 5210. (e) Rosen, B. R.; Werner, E. W.; O'Brien, A. G.; Baran, P. S. *J. Am. Chem. Soc*. **2014**, *136*, 5571. (f) Chen, J.; Yan, W. Q.; Lam, C. M.; Zeng, C. C.; Hu, L. M.; Little, R. D. *Org. Lett.* **2015**, *17*, 986.

(8) (a) Morofuji, T.; Shimizu, A.; Yoshida, J. *J. Am. Chem. Soc.* **2013**, *135*, 5000. (b) Morofuji, T.; Shimizu, A.; Yoshida, J. *J. Am. Chem. Soc*. **2014**, *136*, 4496. (c) Morofuji, T.; Shimizu, A.; Yoshida, J. *Chem. Eur. J*. **2015**, *21*, 3211. (d) Waldvogel, S. R.; Möhle, S. *Angew. Chem., Int. Ed*. **2015**, *54*, 6398.

(9) Elegant methods for introducing primary alkylamines to aromatic compounds based on directed C−H activation were reported. (a) Shin, K.; Baek, Y.; Chang, S. *Angew. Chem., Int. Ed.* **2013**, *52*, 8031. (b) Ng, K. H.; Zhou, Z.; Yu, W. Y. *Chem. Comm*. **2013**, *49*, 7031. (c) Tran, L. D.; Roane, J.; Daugulis, O. *Angew. Chem., Int. Ed*. **2013**, *52*, 6043. (d) Xue, Y.; Fan, Z.; Jiang, X.; Wu, K.; Wang, M.; Ding, C.; Yao, Q.; Zhang, A. *Eur. J. Org. Chem*. **2014**, 7481.

(10) (a) Warot, D.; Berlin, I.; Patat, A.; Durrieu, G.; Zieleniuk, I.; Puech, A. J. *J. Clin. Pharmacol.* **1996**, *36*, 942. (b) Simura, K.; Kodama, E.; Sakagami, Y.; Matsuzaki, Y.; Watanabe, W.; Yamataka, K.; Watanabe, Y.; Ohata, Y.; Doi, S.; Sato, M.; Kano, M.; Ikeda, S.; Matsuoka, M. *J. Virol*. **2008**, 764. (c) Amado, J. A.; Pesquera, C.; Gonzalez, E. M.; Otero, M.; Freijanes, J.; Alvarez, A. *Postgrad. Med. J*. **1990**, *66*, 221.

(11) Oxidation potential of alkylamines is generally low. Bourdelande, J. L.; Gallardo, I.; Guirado, G. *J. Am. Chem. Soc.* **2007**, *129*, 2817.

(12) (a) Bockmair, G.; Fritz, H. P. *Electrochim. Acta.* **1976**, *21*, 1099. (b) Raoult, E.; Sarrazin, J.; Tallec, A. *J. Appl. Electrochem.* **1984**, *14*, 639. (c) Ogibin, Y. N.; Ilovaiskii, A. I.; Nikisin, G. I. *Russ. Chem. Bull*. **1994**, *43*, 1536. (d) Purgato, F. L. S.; Ferreira, M. I. C.; Romero, J. R. *J. Mol. Catal. A: Chem.* **2000**, *161*, 99. (e) Halas, S. M.; Okyne, K.; Fry, A. J. *Electrochim. Acta* **2003**, *48*, 1837.

(13) Oxidation potential of acetanilide is lower than that of benzene. (a) Bordwell, F. G.; Algrim, D. J.; Harrelson, J. A. *J. Am. Chem. Soc.* **1988**, *110*, 5903. (b) Fukuzumi, S.; Ohkubo, K.; Suenobu, T.; Kato, K.; Fujitsuka, M.; Ito, O. *J. Am. Chem. Soc.* **2001**, *123*, 8459.

(14) (a) Bellamy, E.; Bayh, O.; Hoarau, C.; Trecourt, F.; Queguiner, G.; Marsais, F. *Chem. Commun*. **2010**, *46*, 7043. (b) Ge, H.; Liu, P.; Li, X.; Sun, W.; Li, J.; Yang, B.; Shi, Z. *Tetrahedron*, **2013**, *69*, 6591. (c) Trieu, T. H.; Dong, J.; Shi, X. X.; Lu, X.; Zhang, Q. *Synth. Commun*. **2013**, *43*, 3141.

(15) Baba, D.; Fuchigami, T. *Tetrahedron Lett.* **2003**, *44*, 3133.

(16) Maji, B.; Baidya, M.; Ammer, J.; Kobayashi, S.; Mayer, P.; Ofial, A. R.; Mayr, H. *Eur. J. Org. Chem.* **2013**, *16*, 3369.

(17) Morofuji, T.; Shimizu, A.; Yoshida, J. *Angew. Chem., Int. Ed.* **2012**, *51*, 7259.

(18) Shiozawa, T.; Tada, A.; Nukaya, H.; Watanabe, T.; Takahashi, Y.; Asanoma, M.; Ohe, T.; Sawanishi, H.; Katsuhara, T.; Sugimura, T.; Wakabayashi, K.; Terao, O. *Chem. Res. Toxicol.* **2000**, *13*, 535.