

Electrooxidative C–H Functionalization of Aromatic Compounds Based on Rational Design

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Preface

The studies presented in this thesis have been carried out under the direction of Professor Jun-ichi Yoshida at the Department of Synthetic Chemistry and Biological Chemistry of Kyoto University during 2010-2015. The studies are concerned with development of new electrochemical reactions.

The author would like to express his sincerest gratitude to Professor Jun-ichi Yoshida for his kind guidance and valuable discussions throughout this work. The author appreciates the circumstance to investigate in the field of the chemistry. The author is greatly indebted to Dr. Akihiro Shimizu for his constant advice and valuable discussions during the course of this work. The author deeply appreciates to Dr. Aiichiro Nagaki and Dr. Heejin Kim for their kind guidance and encouragement. The author is also thankful to Associate Professor Toshiki Nokami of Tottori University and Dr. Keisuke Asano for their helpful advice.

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General Introduction

I. Rational Design of Organic Reactions

In organic synthesis, we build up small molecules into desired target molecules step-by-step using suitable reactions. Achievements in organic synthesis in the last several decades are beyond all expectations. In fact, organic synthesis plays a major role to develop new medicinal compounds, agrochemicals, and functional materials. Despite such extraordinary achievements, organic synthesis is still far from ideal synthesis because it is time and labor-consuming and significant amounts of wastes are usually produced to synthesize complex organic molecules. Therefore, development of new organic reactions which make organic synthesis much more efficient is highly desired.

To design highly efficient organic reactions, the following three points should be considered (Figure 1). At first, a desired reaction pathway to give a desired product is rational and efficient. To achieve such a desired pathway, the use of highly reactive catalysis and/or reagents is often needed. Second, undesired reaction pathways to give byproducts should be avoided or such side reactions should be suppressed. Third, desired products should be stable under the reaction conditions. If overreactions occur, a desired product cannot be obtained in a high yield and in high purity. These points should be the key to the success of developing new organic reactions that have been believed to be difficult or impossible.

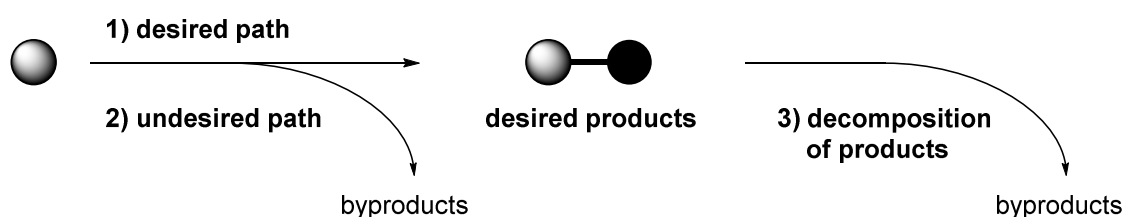


Figure 1. Design Points of Organic Reactions

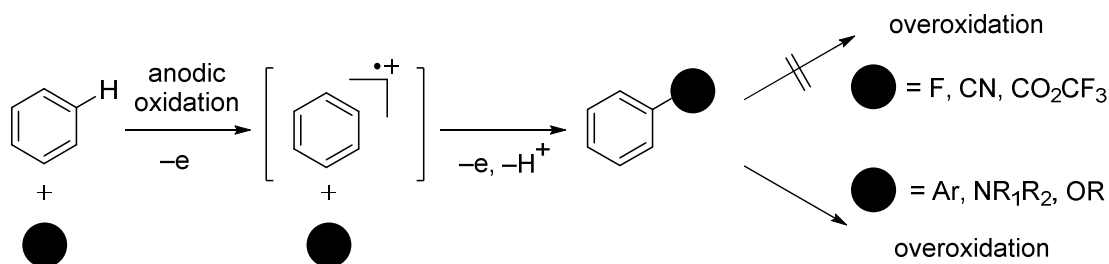
This thesis proposes a rational design for electrooxidative C–H functionalization of organic compounds, which avoids the overoxidation that is usually problematic in conventional electrooxidative methods.

II. Electroorganic Synthesis

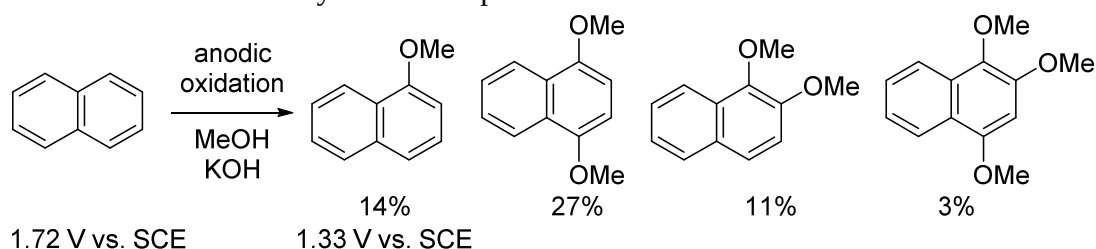
Electrochemical organic synthesis is a long-established methodology since Kolbe electrolysis was reported in 1848.¹ Electrolysis of organic compounds can generate highly reactive species such as carbocations, carbanions, radical ions, and free radicals under mild conditions via single electron transfer.² Notably, chemical oxidants or chemical reductants, which inevitably produce stoichiometric amounts of byproducts, are not required. Taking such an advantage, electroorganic reactions have been applied to synthesis of various complex organic molecules,³ and some electroorganic reactions have been used for industrial production.⁴

Electrochemical oxidation is, in particular, attractive because it enables straightforward functionalization of carbon–hydrogen (C–H) bonds of organic molecules. For example, C_{sp^3} –H bonds⁵ as well as aromatic C_{sp^2} –H bonds (Scheme 1)⁶ can be functionalized by anodic oxidation. Single electron transfer from an aromatic compound gives the corresponding open-shell radical cation. The radical cation reacts with a nucleophile such as fluoride ion, cyanide ion, and trifluoroacetic acid to give the corresponding functionalized product. Usually, overoxidation does not occur in these cases because the products are less reactive toward the electrochemical oxidation because of a strong electron-withdrawing effect of the substituent that is introduced by the transformation.

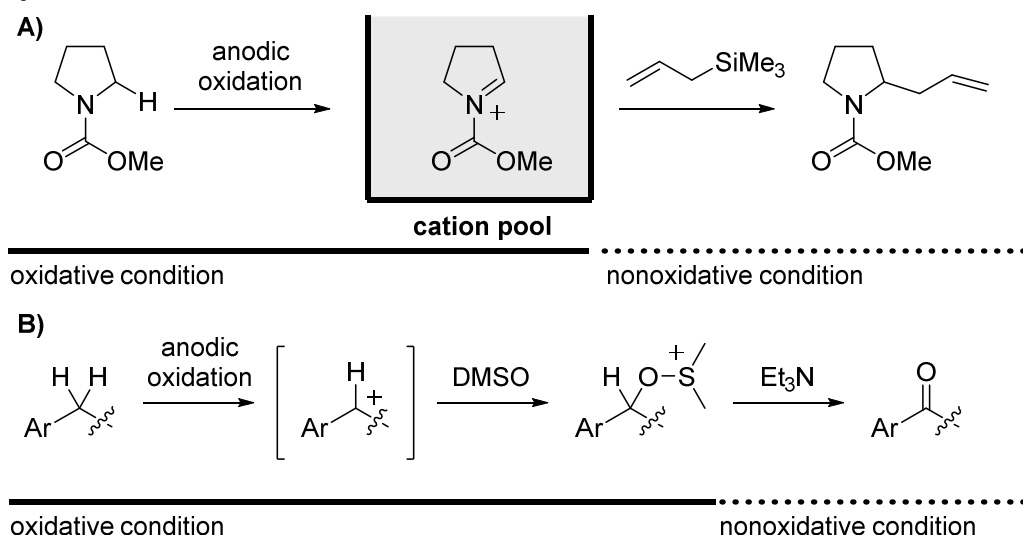
Scheme 1. Electrooxidative Transformation of Aromatic C_{sp^2} –H Bond



However, when the substituent introduced to the aromatic ring is electron-donating, the oxidation potential of the product is lower than that of the starting material, and therefore the transformation suffers from further oxidation of the product, which is called overoxidation.⁷ Anodic methoxylation of naphthalene reported by Fritz in 1976 is such a case (Scheme 2).^{7a} Electrochemical oxidation of naphthalene in the presence of methoxide gives polymethoxynaphthalene. Because an oxidation potential of methoxynaphthalene is lower than that of naphthalene,⁸ overoxidation is unavoidable. For the same reason, electrooxidative introduction of other electron-donating groups such as electron rich aryl groups, or amino groups into aromatic rings still remains challenging.

Scheme 2. Anodic Methoxylation of Naphthalene

In 1999, Yoshida and coworkers reported the generation and accumulation of *N*-acyliminium ions by low temperature electrochemical oxidation, and this method is called the cation pool method (Scheme 3A).⁹ After the electrolysis, the accumulated cation can be used for the reactions with various nucleophiles under nonoxidative conditions. The method was successfully applied to alkoxy-carbenium ions,^{9b} diarylcarbenium ions,^{9c} and heteroatom cations.^{9d,9e} They also reported integrated reactions involving conversion of electrochemically generated cationic species to another cationic species using the chemical method (Scheme 3B).¹⁰ However, these methods are limited to use closed-shell cationic intermediates having a formal charge on a sp^3 carbon atom because closed shell cationic species having a formal charge on a sp^2 carbon atom are too unstable to generate. Therefore, the method cannot be applied to C_{sp^2} -H bond functionalization.

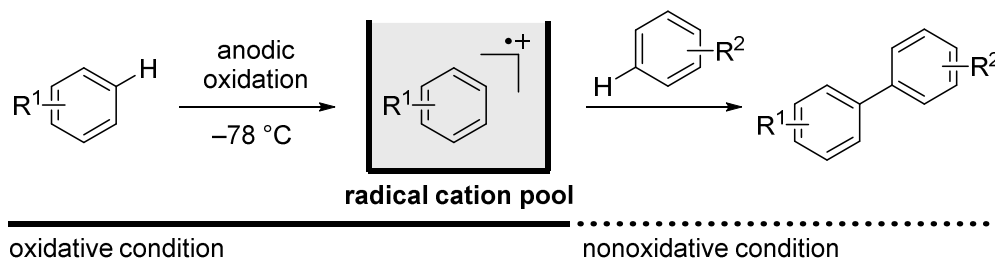
Scheme 3. (A) Cation Pool Method. (B) Integrated Electrochemical–Chemical Reaction via Alkoxy-sulfonium Ions.

III. Contents of This Thesis

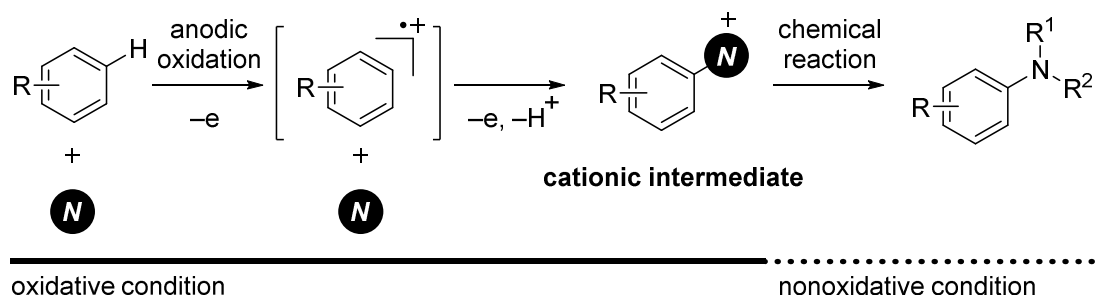
This thesis described a new reaction design inheriting the essence of the cation pool method and the reaction integration, which solves the overoxidation problem in electrooxidative C_{sp2}-H bond functionalization. Based on the rational designs, electrooxidative C-H arylation and C-H amination of aromatic compounds have been achieved.

In chapter 1, metal- and chemical-oxidant-free C-H/C-H cross-coupling¹¹ of aromatic compounds using electrochemical oxidation is described. In general, such transformations suffer from overoxidation because oxidation potentials of biaryl products are lower than that of starting materials. The present approach is outlined in scheme 4. The key design of the method is generation and accumulation of radical cations of aromatic compounds by low temperature electrolysis. Because another aromatic compound can be added after the electrolysis under nonoxidative conditions, overoxidation is intrinsically avoided. The method was named the radical cation pool method.

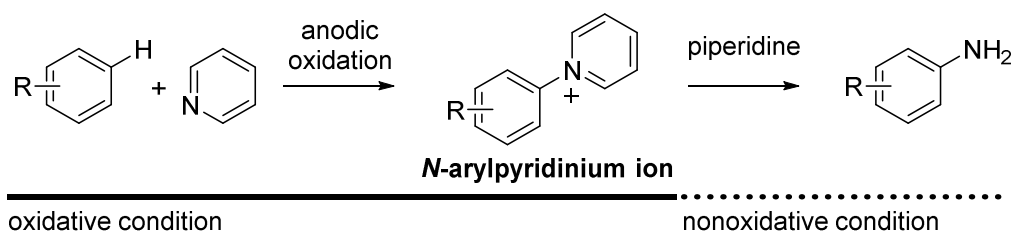
Scheme 4. C-H/C-H Cross-Coupling of Aromatic Compounds Using Radical Cation Pools



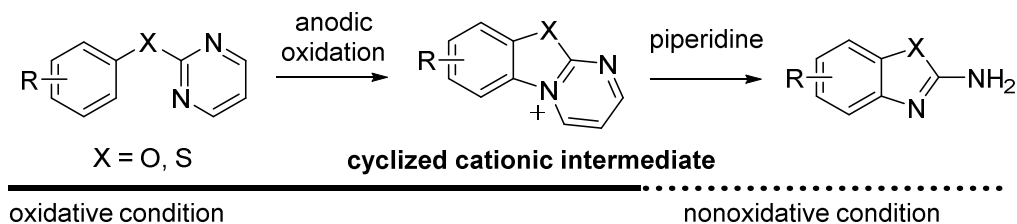
From chapter 2 to chapter 5, C-H amination reactions using electrochemical oxidation are described. In general, installation of nitrogen functionalities into aromatic rings by the electrooxidative method is challenging because oxidation potentials of aromatic amines are usually lower than those of starting materials, and this situation inevitably leads to overoxidation. To circumvent the overoxidation problem, the transformations involving conversion of radical cation of aromatic compounds to closed-shell cationic intermediate was designed as outlined in scheme 5. Electrochemical oxidation of an aromatic substrate in the presence of an appropriate nitrogen source gives a cationic intermediate. Overoxidation is suppressed because of strong electron-withdrawing effect of a positive charge. After the electrolysis, the cationic intermediates are converted to desired neutral aromatic amines under nonoxidative conditions. Based on this rational design, overoxidation is intrinsically avoided because aromatic amines as final products are not exposed to oxidative conditions.

Scheme 5. Electrooxidative C–H Amination of Aromatic Compounds via Cationic Intermediate

In chapter 2, a method for synthesizing aromatic primary amines is described. Electrochemical oxidation of aromatic compounds in the presence of pyridine followed by the treatment with piperidine gives corresponding aromatic primary amines (Scheme 6). The key design of the reactions is intermediacy of electrooxidatively inactive *N*-arylpyridinium ions. Overoxidation is suppressed because of strong electron-withdrawing effect of a positive charge on the pyridinium nitrogen. Synthetic utility of the present method is demonstrated by C–H amination of aromatic compounds bearing a nitro group to give a key intermediate for the synthesis of VLA-4 antagonist.¹² The transformation proves the rationality of the reaction design described in scheme 5.

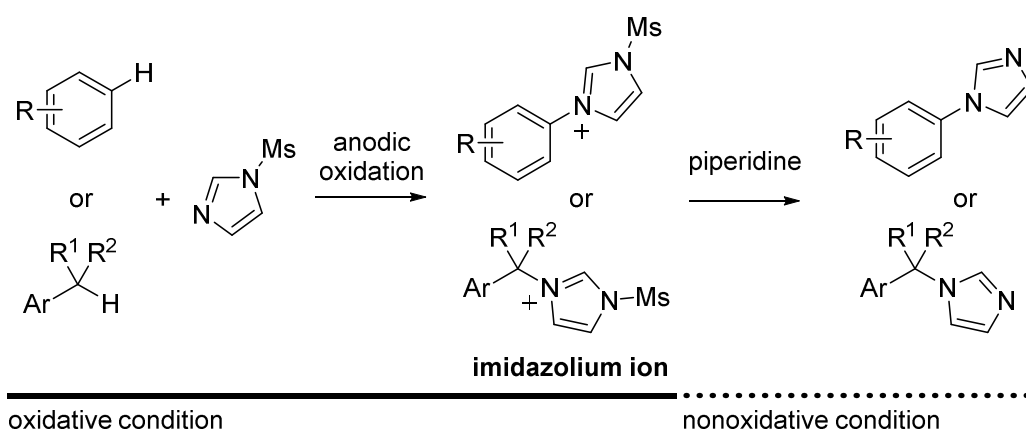
Scheme 6. Synthesis of Aromatic Primary Amines via *N*-Arylpyridinium Ions

In chapter 3, an intramolecular version of the amination is described (scheme 7). Electrochemical oxidation of 2-pyrimidyloxybenzenes and 2-pyrimidylthiobenzenes, which can be easily prepared from phenols and thiophenols, respectively, followed by the treatment of the resulting pyrimidinium ions gives 2-aminobenzoxazoles and 2-aminobenzothiazoles, respectively. The method serves as metal- and chemical-oxidant-free routes to the benzoxazoles and benzothiazoles having a variety of functionality. The transformation indicates the power of the reaction design in the synthesis of heterocyclic compounds.

Scheme 7. Intramolecular C–H Amination via Cyclized Cationic Intermediates

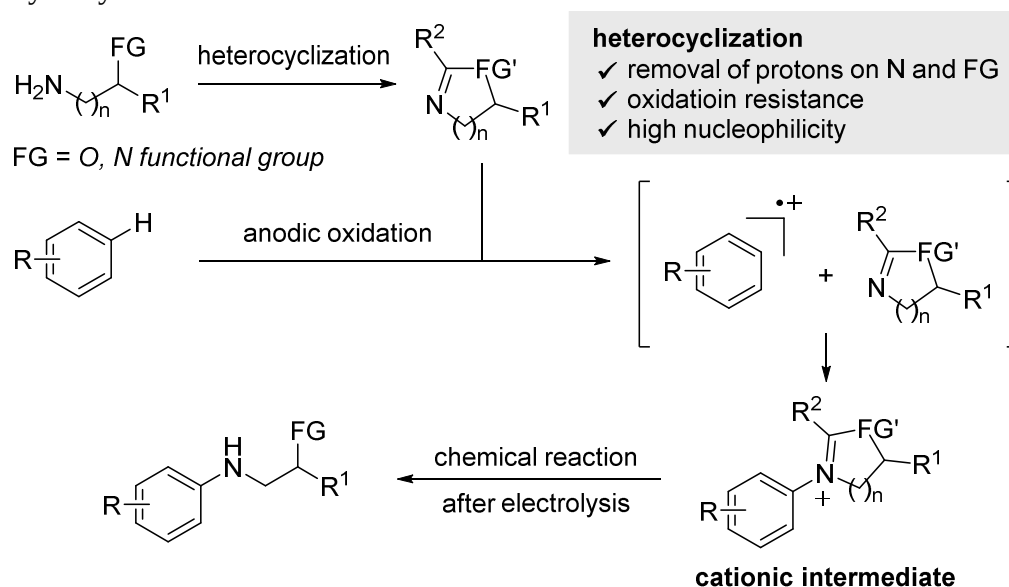
Chapters 4 and 5 describe the application of the present reaction design to the electrooxidative C–H aminations by modification of nitrogen sources are prior to electrooxidative generation of cationic intermediates.

Chapter 4, describes electrooxidative coupling of imidazoles with aromatic or benzylic compounds based on this approach (scheme 8). An appropriate protecting group is introduced to imidazoles in advance. Electrochemical oxidation of aromatic or benzylic compounds in the presence of the protected imidazoles gives electrooxidatively inactive imidazolium ions. After electrolysis, the imidazolium ions are converted to the desired C–N coupling products by deprotection under nonoxidative condition. To demonstrate the power of the method, a P450 17 inhibitor¹³ and an antifungal agent¹⁴ having *N*-substituted imidazole structures were synthesized. The successful transformations achieved by modification of nucleophiles prior to electrochemical oxidation open the possibility of developing new electrochemical transformations that are impossible by the conventional ways.

Scheme 8. Electrooxidative C–N Coupling of Imidazoles with Aromatic or Benzylic Compounds

Chapter 5 describes another example, which enables electrooxidative coupling of aromatic compounds with primary alkylamines bearing a functional group such as a hydroxyl group and an amino group. The key to the success of the transformation is initial heterocyclization of a functional primary alkylamines (scheme 9). The following points should be stressed: (1) The formation of the heterocycles removes protons in the amino and the functional groups, leading to the formation of cationic intermediates. (2) The oxidation potential of the heterocycles is higher than those of the corresponding alkylamines because of the sp^2 -hybridization of nitrogen atoms, enabling selective oxidation of aromatics. (3) The heterocycles have sufficient nucleophilicity¹⁵ toward the radical cations of aromatic compounds. (4) The resulting cationic intermediates, which are stable enough to be accumulated in solution, are not oxidized because of strong electron-withdrawing effect of a positive charge. Electrochemical oxidation of aromatic compounds in the presence of the heterocycles followed by the chemical reaction gives the desired coupling products under nonoxidative condition. A key intermediate for synthesis of a mutagen isolated from blue cotton-absorbed materials in the Nikko River¹⁶ was successfully synthesized using the present method.

Scheme 9. Heterocyclization Approach for Electrooxidative Coupling of Functional Primary Alkylamines with Aromatics



The author believes that the rational designs and successful transformations based on the designs described in this thesis would inspire chemists who are interested in developing new methods for C–H functionalization of aromatic compounds via single electron transfer.¹⁷

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General Introduction

Chapter 1

Metal- and Chemical-Oxidant-Free C–H/C–H Cross-Coupling of Aromatic Compounds: The Use of “Radical Cation Pools”

Abstract

A method for oxidative C–H/C–H cross-coupling has been developed using “radical-cation pools”. Aromatic compounds react with aryl radical cations, which are generated and accumulated by low-temperature electrolysis. This method avoids both the nonselective oxidation of substrates and oxidation of products and effects the C–H/C–H cross-coupling of aromatic compounds without metal complexes and chemical oxidants.

Introduction

The direct oxidative C–H/C–H cross-coupling, also known as the dehydrogenative cross-coupling,¹ of unactivated aromatic compounds has fascinated many chemists because it does not require prefunctionalization of starting aromatic compounds and it serves as a straightforward, atom-,² and step-economical³ method for connecting two aromatic rings by a single C–C bond.^{4,5} In 2007, a metal-catalyzed C–C cross-coupling reaction involving two C–H activations and employing a stoichiometric amount of oxidant was achieved^{4a-d} and, since then, the method has been studied extensively.^{4e-n} In 2008, a metal-free biaryl compound synthesis that uses a stoichiometric amount of an organoiodine(III) oxidant was developed.⁵ A new synthetic method that enables metal- and chemical-oxidant-free C–H/C–H cross-coupling of two aromatic compounds is needed. Electrochemical oxidation^{6,7} serves as an efficient method that does not use metal catalysts and chemical oxidants for activating aromatic compounds. In fact, the subjection of a mixture of two unactivated aromatic compounds to electrochemical oxidation can give the cross-coupling products, although yields are usually low.⁸ In 2012, Waldvogel and co-workers reported a selective electrochemical phenol–arene cross-coupling reaction using boron-doped diamond electrodes.⁹ This method, however, cannot be applied to aromatic compounds that do not have a hydroxy group because the phenoxyl radical intermediate plays a crucial role.

In general, the oxidative C–H/C–H cross-coupling of two aromatic compounds suffers from the formation of homo-coupling products derived from the nonselective oxidation of the starting materials (Figure 1a). Based on statistics, the yield of the cross-coupling product will be, at most, moderate because of the formation of products derived from homo-coupling. Overoxidation is also unavoidable because the biaryl products have lower oxidation potentials than those of the corresponding starting materials owing to the extended π conjugation of the biaryl products (see below). Therefore, the development of methods for direct anodic cross-coupling is very challenging.

To avoid nonselective oxidation of starting materials and the oxidation of products, a method using “radical-cation pools” has been developed (Scheme 1b). Thus, an aromatic compound is allowed to react with a radical cation of another aromatic compound, a species, which is generated and accumulated by low-temperature electrolysis. In 1999, Yoshida and coworkers developed the cation-pool method, which involves generation and accumulation of an unstable organic cation in the absence of a nucleophile by low-temperature electrochemical oxidation and a subsequent reaction of the cation with a nucleophile under nonelectrolytic conditions. The method has been successfully applied to *N*-acyliminium ions,¹⁰ alkoxy-carbenium ions,¹¹ and diaryl-carbenium ions.¹² The present radical-cation-pool method has been developed by analogy with the cation-pool method. This new method

serves as a powerful and selective method for synthesizing unsymmetrical biaryl compounds from unactivated electron-rich aromatic compounds in a straightforward and efficient way.

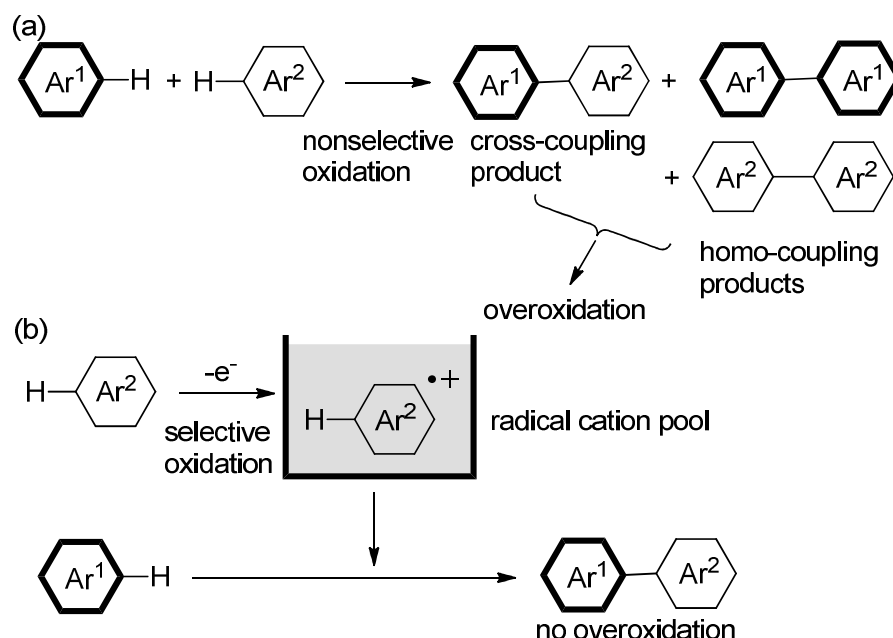
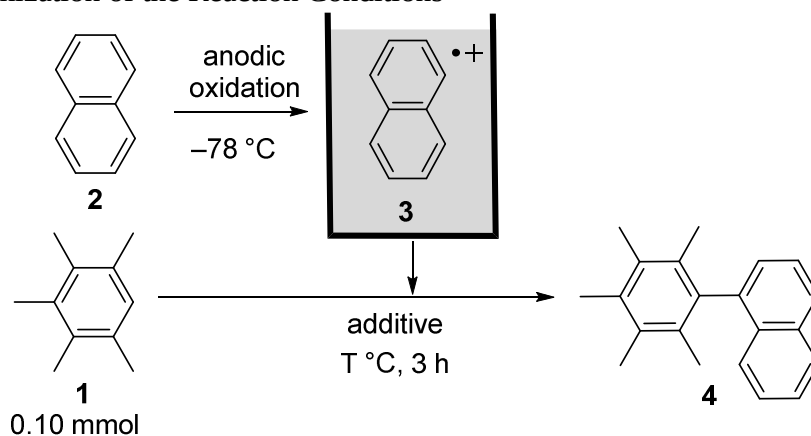


Figure 1. Oxidative C-H/C-H cross-coupling of aromatic compounds. (a) A conventional approach. (b) An approach based on the “radical cation pool” method

Results and Discussions

First, pentamethylbenzene (**1**) was chosen to use as a substrate because of simplicity of product selectivity (see Table 1). As a coupling partner, naphthalene (**2**) was chosen to use because oxidation of **2** to give the corresponding radical cation **3** is known in the literature.^{5a,8a,b,13} The electrochemical oxidation of **2** (0.44 mmol) was carried out in a 0.1 M solution of $\text{Bu}_4\text{NB}(\text{C}_6\text{F}_5)_4$ in CH_2Cl_2 in a H-type divided cell equipped with a graphite felt anode and a platinum plate cathode at $-78\text{ }^\circ\text{C}$ in the absence of **1**. After 0.45 *F* of electricity was consumed, **1** (0.10 mmol) was added. The reaction mixture was stirred at $-78\text{ }^\circ\text{C}$ for 3 h. The desired cross-coupling product **4** was obtained in 33% yield. (Table 1, entry 2). Four moles of **2** is necessary to produce one mole of **4** because **3** is accumulated as a complex with **2** (the radical cation of the naphthalene dimer)^{13a} and **4** is produced by the reaction of **1** and **3** followed by one-electron oxidation, wherein the radical-cation naphthalene dimer is the oxidant.

Table 1. Optimization of the Reaction Conditions

entry	T ($^{\circ}\text{C}$)	additive	4 (%)	recovery ^a of 1 (%)	entry	T ($^{\circ}\text{C}$)	additive	4 (%)	recovery ^a of 1 (%)
1	-40	—	11	40	5 ^c	-90	Et_2O	66	25
2	-78	—	33	55	6 ^d	-90	DME	73	23
3	-90	—	27	52	7 ^{d,e}	-90	DME	91	—
4 ^b	-90	THF	46	32					

^a Yields were determined by GC analysis using hexadecane as an internal standard. ^b Tetrahydrofuran (THF) (0.5 mL) was added. ^c Diethyl ether (0.5 mL) was added. ^d 1,2-Dimethoxyethane (DME) (0.5 mL) was added.

^e The reactions were carried out using **2** (0.66 mmol).

To optimize the reaction conditions the reactions were carried out at a variety of temperatures for the second step. When the second step was carried out at $-40\text{ }^{\circ}\text{C}$ (Table 1, entry 1) the yield of **4** was lower than when the step was carried out at $-78\text{ }^{\circ}\text{C}$ (Table 1, entry 2) presumably because the decomposition of **3** was competing with the cross-coupling reaction. The reaction at $-90\text{ }^{\circ}\text{C}$ (Table 1, entry 3) also gave a lower yield, presumably because of precipitation of **3** at this temperature. To solve this solubility problem, the effect of additives that may enhance the solubility of **3** at low temperatures was examined (Table 1, entries 4–6), and we found that 1,2-dimethoxyethane (DME) was quite effective (Table 1, entry 6). Moreover, the use of 0.45 *F* of electricity and 0.66 mmol of **2** improved the yield of **4** to 91% (Table 1, entry 7). It should be noted that the present method does not suffer from oxidation of the products, although the oxidation potential of **4** (1.48 V versus SCE in a 0.1 M solution of $\text{Bu}_4\text{NB}(\text{C}_6\text{F}_5)_4$ in CH_2Cl_2) is lower than those of **1** (1.57 V) and **2** (1.60 V).

The regioselectivity of the reaction is notable, because only the 1-substituted naphthalene derivative **4** was obtained. The corresponding 2-substituted product was not detected. This is consistent with the high regioselectivity reported for the reaction of naphthalene radical cations with other nucleophiles such as CN^- and CH_3CO_2^- .^{13c} Spin density analysis using the DFT calculation also suggests that reaction at the 1-position is favored (Figure 1a).

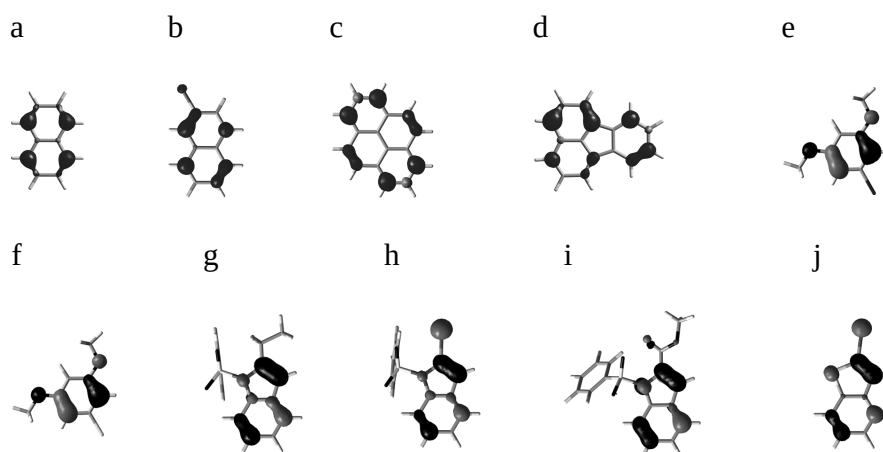
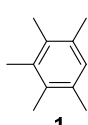
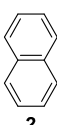
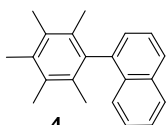
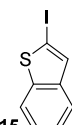
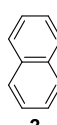
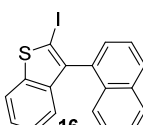
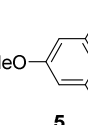
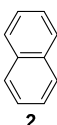
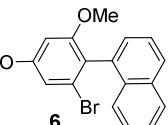
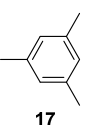
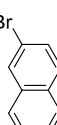
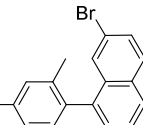
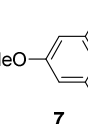
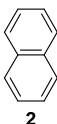
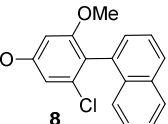
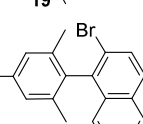
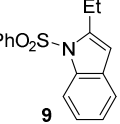
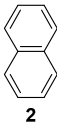
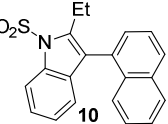
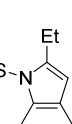
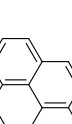
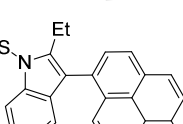
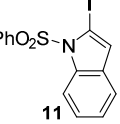
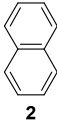
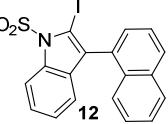
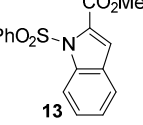
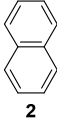
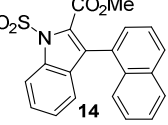
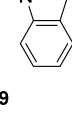
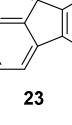
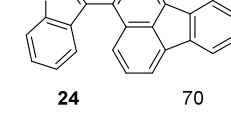


Figure 2. Spin densities of radical cations and HOMO of nucleophilic aromatic coupling partners obtained by DFT calculations (B3LYP/6-31G*). a-d, Spin densities of radical cations of **2**, **18**, **21**, and **23**. e-j, HOMO of **5**, **7**, **9**, **11**, **13**, and **15** (The 3-21G* basis set was used for iodo-containing compounds **11** and **15**).

Under the optimized reaction conditions, the reaction of several aromatic compounds were examined (Table 2). The reaction of radical cation **3** with pentamethylbenzene (**1**) gave the cross-coupling product **4** in 87% yield upon isolation (Table 2, entry 1). Electron-rich benzenes such as **5** and **7** reacted with **3** to give the corresponding cross-coupling products in good yields (Table 2, entries 2 and 3). The regioselectivity observed for **5** and **7** was excellent, in that other isomers were not detected. The HOMO coefficients obtained by DFT calculations are consistent with the observed regioselectivity (Figure 1e and f). Heteroaromatic compounds, such as indoles **9** and **11**, also gave the corresponding cross-coupling products in good yields (Table 2, entries 4 and 5), although the reactivity of electron-deficient indole **13** was low (Table 2, entry 6). The energy of the HOMO of **13** was lower than that of other substrates; this finding is consistent with the lower reactivity of **13** (see the Experimental Section). Benzothiophene **15** was also effective in this reaction (Table 2, entry 7). The regioselectivity of these reactions was also consistent with the HOMO coefficients obtained by DFT calculations (Figure 1 g-j). Notably, iodine-containing compounds **12** and **16** were obtained in very good yields. Usually the oxidative coupling of iodine-containing compounds under electrophilic

conditions leads to proto-deiodination¹⁴ and only molybdenum pentachloride is capable of mediating an oxidative coupling of iodoarenes without loss of the iodine substituent.¹⁵

Table 2. Direct oxidative cross-coupling of two unactivated arenes based on the “radical cation pool” method.^a

entry	Ar ¹ H	Ar ² H	product (yield (%)) ^b	entry	Ar ¹ H	Ar ² H	product (yield (%)) ^b
1			 87	7 ^f			 84
2 ^c			 73	8 ^g			 84 (19/20 = 1.7/1)
3			 67				
4			 92	9 ^{d,h,i}			 71
5			 86				
6 ^{d,e}			 36	10 ^{d,h,i}			 70

^aGeneral reaction conditions: The radical cation pool was generated with 0.66 mmol of Ar¹H using 0.45 F of electricity in Bu₄NB(C₆F₅)₄/CH₂Cl₂ at -78 °C. Then, 0.10 mmol of Ar²H and DME (0.5 mL) were added at -90 °C and the mixture was stirred at -90 °C for 3 h. ^bIsolated yields based on Ar²H. ^c5.5 mmol of Ar¹H was used. ^d8.8 mmol of Ar¹H was used. ^eAdditional stirring at -30 °C for 5 h. ^fAdditional stirring at -20 °C for 2 h. ^g0.1 mL of DME was used. ^hBu₄NPF₆ was used instead of Bu₄NB(C₆F₅)₄. ⁱ0.05 mmol of Ar²H was used and the mixture was stirred at -40 °C for 3 h and then -15 °C for 1.5 h.

The present method could also be applied to other radical cations. The reaction of 2-bromonaphthalene (**18**) is interesting: the radical-cation pool derived from **18** was generated in an effective manner by anodic oxidation and the subsequent coupling reaction took place preferentially on the benzene ring not bearing the bromine atom to give **19**. The product derived from C–C bond formation at the position ortho to the bromine atom (**20**)

was also obtained as a minor product. The regioselectivity is consistent with the spin density values obtained by DFT calculations (Figure 1b). The anodic oxidation of pyrene (**21**), and fluoranthene (**23**) gave the corresponding radical-cation pools, which reacted with **9** to give the corresponding cross-coupling products in good yields with high regioselectivity, a result, which is consistent with the DFT calculations (Figure 1c and d). It should be noted that the cheaper electrolyte, Bu_4NPF_6 , could be used in these reactions.

Notably, the regioselectivity of the cross-coupling is generally very high and is predictable based on the spin density of the radical cation and the HOMO coefficients of the nucleophilic aromatic partner obtained by DFT calculations. The high regioselectivity of this method contrasts with the lower regioselectivity of homolytic aromatic substitutions that are used for biaryl compound synthesis.¹⁶ This difference in regioselectivity is probably due to the different reactivity of the reactive intermediates: in homolytic aromatic substitutions, a highly reactive s radical (aryl radical) reacts with the arene, whereas in the approach herein, a less reactive p radical (aryl radical cation) reacts with the arene. Notably, halogen-substituted aromatic compounds are effective as both substrates (Table 2, entries 2, 3, 5, and 7) and precursors of a radical cation (Table 2, entry 8) and the halogen functionality in the cross-coupling products can be used for further transformations, such as halogen/metal exchange and transition-metal catalyzed coupling reactions. Therefore, this new method will form the basis of a wide range of synthetic strategies for making organic compounds containing aromatic rings.

Conclusions

In conclusion, an efficient method for the C–H/C–H cross-coupling of two unactivated aromatic compounds using “radical-cation pools” has been developed. Because this method consists of two sequential steps, namely the generation and accumulation of a radical cation of an aromatic compound under oxidative conditions and then the coupling of the radical cation with another aromatic substrate under nonoxidative conditions, nonselective oxidation of the starting materials and oxidation of the products are avoided. Thus, the method serves as a selective technique for effecting a C–H/C–H cross-coupling of aromatic compounds. The absence of metal complexes and chemical oxidants in the reaction conditions is also advantageous. Exploration of the full range of reactivity of various aromatic compounds and radical-cation pools, and applications to the synthesis of biaryl and heterobiaryl compounds with interesting functions and biological activity is currently in progress.

Experimental Section

General: ^1H and ^{13}C NMR spectra were recorded in CDCl_3 or CD_2Cl_2 on Varian MERCURY plus-400 (^1H 400 MHz, ^{13}C 100 MHz), or JEOL ECA-600P spectrometer (^1H 600 MHz, ^{13}C 150 MHz). Mass spectra were obtained on JEOL JMS SX-102A mass spectrometer. IR spectra were measured with a Shimadzu IRAffinity (FTIR). Rotating-disk electrode (RDE) voltammetry was carried out using BAS 600C and BAS RRDE-3 rotating disk electrodes. Measurements were carried out in 0.1 M $\text{Bu}_4\text{NB}(\text{C}_6\text{F}_5)_4/\text{CH}_2\text{Cl}_2$ using a glassy carbon disk working electrode, a platinum wire counter electrode, and an SCE reference electrode with sweep rate of 10 mVs^{-1} at 3000 rpm. Merck precoated silica gel F₂₅₄ plates (thickness 0.25 mm) was used for thin-layer chromatography (TLC) analysis. Flash chromatography was carried out on a silica gel (Kanto Chem. Co., Silica Gel N, spherical, neutral, 40-100 μm). Preparative gel permeation chromatography (GPC) was carried out on Japan Analytical Industry LC-918 equipped with JAIGEL-1H and 2H using CHCl_3 as an eluent. All reactions were carried out under argon atmosphere unless otherwise noted. Compounds **9**,¹⁷ **11**,¹⁸ **13**,¹⁹ and **15**²⁰ were prepared according to the reported procedures. Compounds **4**,^{5a} **19**,^{5a} and **S2**²² were identified by comparison with their ^1H and ^{13}C NMR spectra reported in the literature. Bu_4NBF_4 was purchased from TCI and dried at $50^\circ\text{C}/1 \text{ mmHg}$ overnight. $\text{Bu}_4\text{NB}(\text{C}_6\text{F}_5)_4$ was prepared according to the reported procedure²³. Dichloromethane was washed with water, distilled from P_2O_5 , redistilled from dried K_2CO_3 to remove a trace amount of acid, and stored over molecular sieves 4A. Unless otherwise noted, all materials were obtained from commercial suppliers and used without further purification. DFT calculations were performed with the Gaussian 09 program.²⁴ All geometry optimizations were carried out at the RB3LYP or UB3LYP level of density functional theory with the 6-31G(d) or 3-21G(d) basis set.

Reaction of naphthalene (**2**) and **1**, **7**, **9** or **11**

The anodic oxidation was carried out using an H-type divided cell (4G glass filter) equipped with a carbon felt anode (Nippon Carbon JF-20-P7, ca. 160 mg, dried at $300^\circ\text{C}/1 \text{ mmHg}$ for 4 h before use) and a platinum plate cathode (10 mm $\times$ 10 mm). In the anodic chamber was placed a solution of naphthalene (**2**) (84.6 mg, 0.66 mmol) in 0.1 M $\text{Bu}_4\text{NB}(\text{C}_6\text{F}_5)_4/\text{CH}_2\text{Cl}_2$ (10.0 mL). In the cathodic chamber were placed trifluoromethanesulfonic acid (150 μL) and 0.1 M $\text{Bu}_4\text{NBF}_4/\text{CH}_2\text{Cl}_2$ (10.0 mL). The constant current electrolysis (8.0 mA) was carried out at -78°C with magnetic stirring for 60 min. Pentamethylbenzene (**1**) (14.8 mg, 0.10 mmol) and 1,2-dimethoxyethane (0.5 mL) were added to the anodic chamber at -90°C . The resulting mixture was stirred at -90°C

for 3 h. Then, Et₃N (0.2 mL) was added and the resulting mixture was warmed to room temperature. After removal of the solvent under reduced pressure, the residue was quickly filtered through a short column (2 × 4 cm) of silica gel to remove electrolyte using hexane/EtOAc 1:1 as an eluent. The solvent was removed from the filtrate under reduced pressure, and the crude product was purified with flash chromatography to obtain the cross-coupling product **4**^{5a} (23.8 mg, 87%) as white solid.

1-(2-Chloro-4,6-dimethoxyphenyl)naphthalene (8). Reaction of **2** and 1-chloro-3,5-dimethoxybenzene (**7**) (0.10 mmol, 17.3 mg) followed by preparative GPC gave the cross-coupling product **8** (20.1 mg, 67%) as white solid. mp: 166–167 °C; ¹H NMR (400 MHz, CDCl₃): δ 3.62 (s, 3H), 3.89 (s, 3H), 6.53 (d, *J* = 2.0 Hz, 1H), 6.72 (d, *J* = 2.4 Hz, 1H), 7.33–7.57 (m, 5H), 7.89 (m, 2H); ¹³C NMR (150 MHz, CDCl₃): δ 55.9, 56.2, 97.9, 105.9, 121.1, 125.6, 125.8, 125.9, 126.2, 128.2, 128.4, 128.5, 132.6, 133.7, 133.8, 135.9, 159.6, 160.5; HRMS (ESI): [M+H]⁺ calcd. for C₁₈H₁₆ClO₂, 299.0833; found, 299.0827.

2-Ethyl-3-(1-naphthyl)-1-(phenylsulfonyl)-1H-indole (10). Reaction of **2** and 2-ethyl-1-(phenylsulfonyl)-1H-indole (**9**) (0.10 mmol, 28.5 mg) followed by flash chromatography gave the cross-coupling product **10** (38.0 mg, 92%) as light yellow solid. mp: 135–136 °C; ¹H NMR (400 MHz, CDCl₃): δ 1.28 (t, *J* = 7.2 Hz, 3H), 2.74 (dq, *J* = 14.4, 7.2 Hz, 1H), 2.96 (dq, *J* = 14.4, 7.2 Hz, 1H), 6.93 (d, *J* = 8.0 Hz, 1H), 7.13 (t, *J* = 8.0 Hz, 1H), 7.18–7.60 (m, 9H), 7.79 (m, 2H), 7.91 (d, *J* = 8.0 Hz, 2H), 8.31 (d, *J* = 8.4 Hz, 1H); ¹³C NMR (150 MHz, CDCl₃): δ 15.8, 20.9, 115.5, 119.8, 122.1, 124.0, 125.5, 125.7, 125.9, 126.0, 126.2, 128.2, 128.3, 129.1, 130.5, 131.9, 132.4, 133.6, 133.7, 136.8, 138.6, 141.2; LRMS (ESI) (*m/z*): 411 [M]⁺, HRMS (ESI) [M+H]⁺ calcd. for C₂₆H₂₂NO₂S, 412.1345; found, 412.1366.

2-Iodo-3-(1-naphthyl)-1-(phenylsulfonyl)-1H-indole (12). Reaction of **2** and 2-iodo-1-(phenylsulfonyl)-1H-indole (**11**) (0.10 mmol, 38.3 mg) followed by flash chromatography gave the cross-coupling product **12** (43.9 mg, 86%) as light yellow solid. mp: 155–156 °C; ¹H NMR (400 MHz, CDCl₃): δ 6.97 (d, *J* = 8.0 Hz, 1H), 7.12–7.16 (m, 2H), 7.26–7.37 (m, 3H), 7.46–7.63 (m, 5H), 7.91–7.99 (m, 4H), 8.44 (d, *J* = 8.0 Hz, 1H); ¹³C NMR (150 MHz, CDCl₃): δ 81.4, 116.0, 119.9, 124.1, 125.3, 125.4, 125.5, 126.0, 126.2, 127.3, 128.4, 128.8, 128.9, 129.1, 131.3, 131.6, 131.9, 133.7, 133.7, 134.1, 138.1, 139.2; HRMS (ESI): [M+Na]⁺ calcd. for C₂₄H₁₆INO₂SNa, 531.9839; found, 531.9839.

Reaction of naphthalene (2) and 5

The anodic oxidation was carried out using an H-type divided cell (4G glass filter) equipped with a carbon felt anode (Nippon Carbon JF-20-P7, ca. 160 mg, dried at 300 °C/1 mmHg for 4 h before use) and a platinum plate cathode (10 mm × 10 mm). In the anodic chamber was placed a solution of naphthalene (**2**) (70.5 mg, 0.55 mmol) in 0.1 M Bu₄NB(C₆F₅)₄/CH₂Cl₂ (10.0 mL). In the cathodic chamber were placed trifluoromethanesulfonic acid (150 µL) and 0.1 M Bu₄NBF₄/CH₂Cl₂ (10.0 mL). The constant current electrolysis (8.0 mA) was carried out at −78 °C with magnetic stirring for 50 min. 1-Bromo-3,5-dimethoxybenzene (**5**) (21.7 mg, 0.10 mmol) and 1,2-dimethoxyethane (0.5 mL) were added to the anodic chamber at −90 °C. The resulting mixture was stirred at −90 °C for 3 h. Then, Et₃N (0.2 mL) was added and the resulting mixture was warmed to room temperature. After removal of the solvent under reduced pressure, the residue was quickly filtered through a short column (2 × 4 cm) of silica gel to remove electrolyte using Et₂O as an eluent. The solvent was removed from the filtrate under reduced pressure, and the crude product was purified with preparative GPC to obtain the cross-coupling product **6** (25.1 mg, 73%) as white solid.

1-(2-Bromo-4,6-dimethoxyphenyl)naphthalene (6). mp: 155–156 °C; ¹H NMR (400 MHz, CDCl₃): δ 3.61 (s, 3H), 3.89 (s, 3H), 6.58 (d, *J* = 2.4 Hz, 1H), 6.91 (d, *J* = 2.4 Hz, 1H), 7.32–7.57 (m, 5H), 7.89 (m, 2H); ¹³C NMR (150 MHz, CDCl₃): δ 55.9, 56.2, 98.5, 109.0, 123.2, 125.6, 125.8, 125.9, 126.0, 126.1, 128.2, 128.3, 128.5, 132.5, 133.7, 135.8, 159.5, 160.7; HRMS (ESI): [M+H]⁺ calcd. for C₁₈H₁₆BrO₂, 343.0328; found, 343.0323.

Reaction of naphthalene (2) and 13

The anodic oxidation was carried out using an H-type divided cell (4G glass filter) equipped with a carbon felt anode (Nippon Carbon JF-20-P7, ca. 160 mg, dried at 300 °C/1 mmHg for 4 h before use) and a platinum plate cathode (10 mm × 10 mm). In the anodic chamber were placed a solution of naphthalene (**2**) (112.8 mg, 0.88 mmol) in 0.1 M Bu₄NB(C₆F₅)₄/CH₂Cl₂ (10.0 mL). In the cathodic chamber were placed trifluoromethanesulfonic acid (150 µL) and 0.1 M Bu₄NBF₄/CH₂Cl₂ (10.0 mL). The constant current electrolysis (8.0 mA) was carried out at −78 °C with magnetic stirring for 80 min. Then methyl 1-(phenylsulfonyl)-1*H*-indole-2-carboxylate (**13**) (31.5 mg, 0.10 mmol) and 1,2-dimethoxyethane (0.5 mL) were added to the anodic chamber at −90 °C. The resulting mixture was stirred at −90 °C for 3 h and warmed to −30 °C for 5 h. Then, Et₃N (0.2 mL) was added and the resulting mixture was warmed to room temperature. The

solvent was removed from the resulting mixture under reduced pressure, and the crude product was purified with preparative GPC to obtain the cross-coupling product **14** (16.0 mg, 36%) as white solid.

Methyl 3-(1-naphthyl)-1-(phenylsulfonyl)-1H-indole-2-carboxylate (14). mp: 65–67 °C; ¹H NMR (400 MHz, CDCl₃): δ 3.68 (s, 3H), 7.05 (d, *J* = 8.0 Hz, 1H), 7.17 (t, *J* = 8.0 Hz, 1H), 7.30–7.64 (m, 9H), 7.91 (dd, *J* = 8.4, 4.8 Hz, 2H), 8.06 (d, *J* = 8.8 Hz, 2H), 8.16 (d, *J* = 8.8 Hz, 1H); ¹³C NMR (150 MHz, CDCl₃): δ 52.8, 115.3, 121.9, 124.4, 125.2, 125.8, 126.0, 126.2, 126.9, 127.2, 127.4, 128.0, 128.3, 128.5, 128.9, 129.0, 129.3, 130.5, 132.0, 133.6, 134.0, 136.3, 137.4, 162.6; IR (neat): 1732 cm⁻¹; HRMS (ESI): [M+H]⁺ calcd. for C₂₆H₂₀NO₄S, 442.1108; found, 442.1094.

Reaction of naphthalene (2) and 2-iodobenzo[*b*]thiophene (15)

The anodic oxidation was carried out using an H-type divided cell (4G glass filter) equipped with a carbon felt anode (Nippon Carbon JF-20-P7, ca. 160 mg, dried at 300 °C/1 mmHg for 4 h before use) and a platinum plate cathode (10 mm × 10 mm). In the anodic chamber were placed a solution of naphthalene (**2**) (84.6 mg, 0.66 mmol) in 0.1 M Bu₄NB(C₆F₅)₄/CH₂Cl₂ (10.0 mL). In the cathodic chamber were placed trifluoromethanesulfonic acid (150 μL) and 0.1 M Bu₄NBF₄/CH₂Cl₂ (10.0 mL). The constant current electrolysis (8.0 mA) was carried out at -78 °C with magnetic stirring for 60 min. Then 2-iodobenzo[*b*]thiophene (**15**) (26.0 mg, 0.10 mmol) and 1,2-dimethoxyethane (0.5 mL) were added to the anodic chamber at -90 °C. The resulting mixture was stirred at -90 °C for 3 h and warmed to -20 °C for 2 h. Then, Et₃N (0.2 mL) was added and the resulting mixture was warmed to room temperature. The solvent was removed from the resulting mixture under reduced pressure, and the crude product was purified with preparative GPC to obtain the cross-coupling product **16** (32.5 mg, 84%) as white solid.

2-Iodo-3-(1-naphthyl)benzo[*b*]thiophene (16). mp: 116–118 °C; ¹H NMR (400 MHz, CDCl₃): δ 7.14–7.20 (m, 2H), 7.30–7.54 (m, 5H), 7.63 (dd, *J* = 4.2, 3.5 Hz, 1H), 7.86 (dt, *J* = 8.0, 1.0 Hz, 1H), 7.99 (dd, *J* = 7.1, 4.0 Hz, 2H); ¹³C NMR (150 MHz, CDCl₃): δ 82.8, 121.5, 123.3, 124.6, 125.5, 125.9, 126.1, 126.3, 128.4, 128.6, 128.8, 131.9, 133.7, 133.8, 137.6, 142.1, 143.7; LRMS (ESI) (*m/z*): 386 [M]⁺; HRMS (EI): [M]⁺ calcd. for C₁₈H₁₁IS, 385.9626; found, 385.9629.

Cross-coupling of 2-bromonaphthalene (18) and mesitylene (17)

The anodic oxidation was carried out using an H-type divided cell (4G glass filter) equipped with a carbon felt anode (Nippon Carbon JF-20-P7, ca. 160 mg, dried at 300 °C/1 mmHg for 4 h before use) and a platinum plate cathode (10 mm × 10 mm). In the anodic chamber were placed a solution of 2-bromonaphthalene (**18**) (136.7 mg, 0.66 mmol) in 0.1 M Bu₄NB(C₆F₅)₄/CH₂Cl₂ (10.0 mL). In the cathodic chamber were placed trifluoromethanesulfonic acid (150 µL) and 0.1 M Bu₄NBF₄/CH₂Cl₂ (10.0 mL). The constant current electrolysis (8.0 mA) was carried out at -78 °C with magnetic stirring for 60 min. Then mesitylene (**17**) (12.0 mg, 0.10 mmol) and 1,2-dimethoxyethane (0.1 mL) were added to the anodic chamber at -90 °C. The resulting mixture was stirred at -90 °C for 3 h. Then, Et₃N (0.2 mL) was added and the resulting mixture was warmed to room temperature. The solvent was removed from the resulting mixture under reduced pressure, and the crude product was purified with preparative GPC to obtain the cross-coupling products **19**^[5] (17.0 mg, 53%) and **20** (10.0 mg, 31%) as white solids.

2-Bromo-1-mesitylnaphthalene (20). mp: 86–87 °C; ¹H NMR (400 MHz, CDCl₃): δ 1.83 (s, 6H), 2.40 (s, 3H), 7.03 (s, 2H), 7.26 (d, *J* = 8.4 Hz, 1H), 7.35 (t, *J* = 8.4 Hz, 1H), 7.48 (t, *J* = 8.4 Hz, 1H), 7.73 (s, 2H), 7.86 (d, *J* = 8.8 Hz, 1H); ¹H NMR (400 MHz, CD₂Cl₂): δ 1.80 (s, 6H), 2.38 (s, 3H), 7.02 (s, 2H), 7.21 (d, *J* = 8.4 Hz, 1H), 7.35 (t, *J* = 8.4 Hz, 1H), 7.49 (t, *J* = 8.4 Hz, 1H), 7.73 (d, *J* = 9.2 Hz, 1H), 7.76 (d, *J* = 8.4 Hz, 1H), 7.88 (d, *J* = 8.8 Hz, 1H); ¹³C NMR (150 MHz, CDCl₃): δ 19.8, 21.3, 122.0, 125.6, 126.1, 127.0, 128.1, 128.2, 128.7, 129.9, 132.4, 133.1, 135.6, 136.3, 137.4, 138.6; HRMS (ESI): [M]⁺ calcd. for C₁₉H₁₇Br, 324.0508; found, 324.0501.

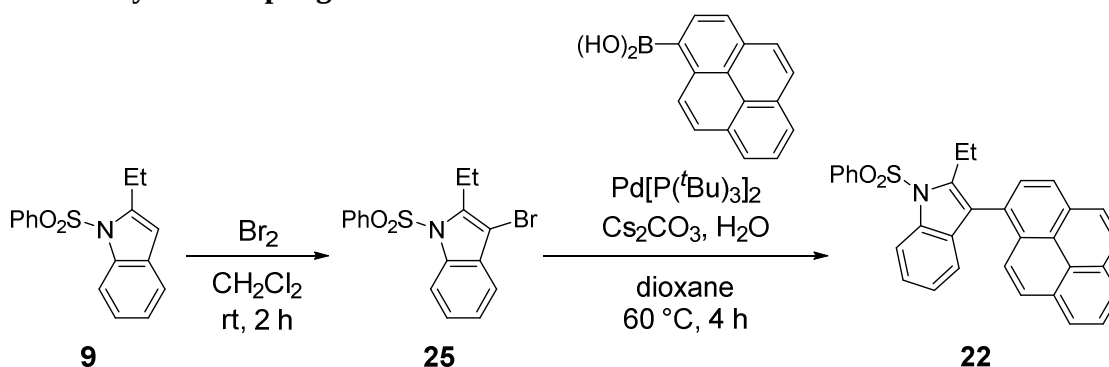
Cross-coupling of pyrene (21) and 2-ethyl-1-(phenylsulfonyl)-1H-indole (9)

The anodic oxidation was carried out using an H-type divided cell (4G glass filter) equipped with a carbon felt anode (Nippon Carbon JF-20-P7, ca. 160 mg, dried at 300 °C/1 mmHg for 4 h before use) and a platinum plate cathode (10 mm × 10 mm). In the anodic chamber were placed a solution of pyrene (**21**) (178 mg, 0.88 mmol) in 0.1 M Bu₄NPF₆/CH₂Cl₂ (10.0 mL). In the cathodic chamber were placed trifluoromethanesulfonic acid (150 µL) and 0.1 M Bu₄NPF₆/CH₂Cl₂ (10.0 mL). The constant current electrolysis (8.0 mA) was carried out at -78 °C with magnetic stirring for 80 min. Then 2-ethyl-1-(phenylsulfonyl)-1H-indole (**9**) (14.3 mg, 0.05 mmol) and 1,2-dimethoxyethane (0.5 mL) were added to the anodic chamber, and the resulting mixture was stirred at -40 °C for 3 h and warmed to -15 °C for 1.5 h. Then, Et₃N (0.2 mL) was added and the resulting

mixture was warmed to room temperature. After removal of the solvent under reduced pressure, the residue was quickly filtered through a short column (2 × 4 cm) of silica gel to remove electrolyte using as CH₂Cl₂ an eluent. The solvent was removed from the filtrate under reduced pressure, and the crude product was purified with preparative GPC to obtain the cross-coupling product **22** (17.2 mg, 71%) as light yellow solid. The structure of the product was confirmed by the following synthesis.

2-Ethyl-1-(phenylsulfonyl)-3-(pyren-1-yl)-1H-indole (22). mp: 159–160 °C; ¹H NMR (400 MHz, CDCl₃): δ 1.19 (t, *J* = 7.2 Hz, 3H), 2.80 (m, 1H), 2.99 (m, 1H), 6.95 (d, *J* = 8.0 Hz, 1H), 7.14 (t, *J* = 7.4 Hz, 1H), 7.35 (t, *J* = 7.8 Hz, 1H), 7.42–7.66 (m, 4H), 7.82–7.90 (m, 4H), 7.98–8.05 (m, 1H), 8.10–8.18 (m, 3H), 8.23 (t, *J* = 7.6 Hz, 2H), 8.34 (d, *J* = 8.4 Hz, 1H); ¹³C NMR (150 MHz, CDCl₃): δ 15.6, 20.9, 115.5, 119.8, 122.5, 124.1, 124.6, 124.6, 124.8, 124.9, 125.2, 125.3, 126.1, 126.3, 127.3, 127.6, 127.7, 127.9, 128.4, 129.2, 130.0, 130.9, 131.1, 131.2, 132.1, 133.7, 136.8, 138.7, 141.4; LRMS (EI) (*m/z*) 485 [M]⁺; HRMS (EI): [M]⁺ calcd. for C₃₂H₂₃NO₂S, 485.1450; found, 485.1415.

Preparation of 2-ethyl-1-(phenylsulfonyl)-3-(pyren-1-yl)-1H-indole (22) by Suzuki-Miyaura coupling



To a 50 mL Schlenk flask were added 2-ethyl-1-(phenylsulfonyl)-1H-indole (**9**) (142.7 mg, 0.5 mmol) and CH₂Cl₂ (5 mL). A solution of bromine (87.9 mg, 0.55 mmol) in CH₂Cl₂ (1 mL) was slowly added. After 2 h, solvent was removed under reduced pressure to obtain **3-bromo-2-ethyl-1-(phenylsulfonyl)-1H-indole (25)** (180 mg, 99%).

To a 50 mL round-bottom flask were added 3-bromo-2-ethyl-1-(phenylsulfonyl)-1H-indole (**25**) (36.4 mg, 0.10 mmol), 1-pyreneboronic acid (36.9 mg, 0.15 mmol), cesium carbonate (81.5 mg, 0.25 mmol), Pd[P(^{*t*}Bu)₃]₂ (5.1 mg, 0.01 mmol), water (18 mg, 1.0 mmol), and dioxane (5 mL). Then, the reaction mixture was stirred at 60 °C for 4 h. After removal of the solvent under reduced

pressure, the residue was quickly filtered through a short column (4 × 6 cm) of silica gel using CH₂Cl₂ as an eluent. The solvent was removed from the filtrate under reduced pressure, and the crude product was purified with preparative GPC to obtain **2-ethyl-1-(phenylsulfonyl)-3-(pyren-1-yl)-1H-indole (22)** (34.1 mg, 70%) as light yellow solid. The ¹H NMR spectrum was identical to that for the compound obtained by the “radical cation pool” method.

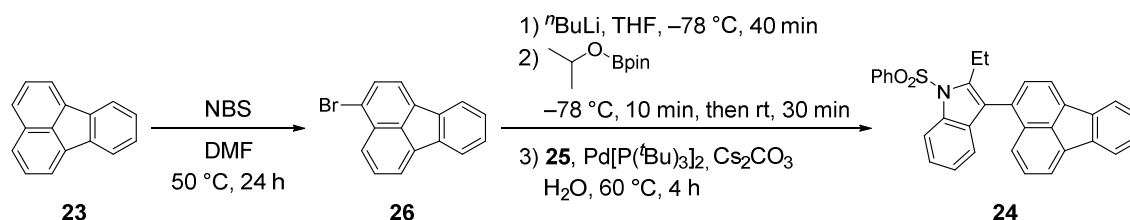
3-Bromo-2-ethyl-1-(phenylsulfonyl)-1H-indole (25). mp: 106–107 °C; ¹H NMR (400 MHz, CDCl₃): δ 1.30 (t, *J* = 7.4 Hz, 3H), 3.12 (q, *J* = 7.4 Hz, 2H), 7.30–7.58 (m, 6H), 7.73 (d, *J* = 8.4 Hz, 2H), 8.19 (d, *J* = 7.2 Hz, 1H); ¹³C NMR (150 MHz, CDCl₃): δ 14.2, 21.1, 101.4, 115.0, 119.3, 124.2, 125.3, 126.3, 129.2, 129.3, 133.9, 135.9, 138.6, 140.0; LRMS (EI) (*m/z*) 363 [M]⁺; HRMS (EI): [M]⁺ calcd. for C₁₆H₁₄NO₂SBr, 362.9929; found, 362.9919.

Cross-coupling of fluoranthene (23) and 2-ethyl-1-(phenylsulfonyl)-1H-indole (9)

The anodic oxidation was carried out using an H-type divided cell (4G glass filter) equipped with a carbon felt anode (Nippon Carbon JF-20-P7, ca. 160 mg, dried at 300 °C/1 mmHg for 4 h before use) and a platinum plate cathode (10 mm × 10 mm). In the anodic chamber were placed a solution of fluoranthene (**23**) (178 mg, 0.88 mmol) in 0.1 M Bu₄NPF₆/CH₂Cl₂ (10.0 mL). In the cathodic chamber were placed trifluoromethanesulfonic acid (150 μL) and 0.1 M Bu₄NPF₆/CH₂Cl₂ (10.0 mL). The constant current electrolysis (8.0 mA) was carried out at −78 °C with magnetic stirring for 80 min. Then 2-ethyl-1-(phenylsulfonyl)-1H-indole (**9**) (14.3 mg, 0.05 mmol) and 1,2-dimethoxyethane (0.5 mL) were added to the anodic chamber, and the resulting mixture was stirred at −40 °C for 3 h and warmed to −15 °C for 1.5 h. Then, Et₃N (0.2 mL) was added and the resulting mixture was warmed to room temperature. After removal of the solvent under reduced pressure, the residue was quickly filtered through a short column (2 × 4 cm) of silica gel to remove electrolyte using CH₂Cl₂ as an eluent. The solvent was removed from the filtrate under reduced pressure, and the crude product was purified with preparative GPC to obtain the cross-coupling product **24** (17.1 mg, 70%) as light yellow solid. The structure of the product was confirmed by the following synthesis.

2-Ethyl-3-(fluoranthen-3-yl)-1-(phenylsulfonyl)-1H-indole (24). mp: 161–162 °C; ^1H NMR (400 MHz, CDCl_3): δ 1.23 (t, J = 7.2 Hz, 3H), 2.84 (m, 1H), 3.04 (m, 1H), 7.06 (d, J = 7.2 Hz, 1H), 7.14–7.18 (m, 2H), 7.34 (t, J = 7.8 Hz, 1H), 7.39–7.62 (m, 7H), 7.81 (d, J = 8.8 Hz, 2H), 7.88–7.96 (m, 3H), 8.00 (d, J = 7.2 Hz, 1H), 8.31 (d, J = 8.0 Hz, 1H); ^{13}C NMR (150 MHz, CDCl_3): δ 15.9, 20.9, 115.4, 119.8, 120.0, 120.2, 121.1, 121.6, 124.0, 124.6, 125.1, 126.3, 127.7, 127.7, 128.0, 129.2, 129.5, 130.0, 130.7, 132.0, 132.7, 133.7, 136.7, 137.0, 137.2, 138.7, 139.1, 139.5, 141.4; LRMS (EI) (m/z): 485 [M] $^+$; HRMS (EI): [$\text{M}+\text{H}$] $^+$ calcd. for $\text{C}_{32}\text{H}_{24}\text{NO}_2\text{S}$: 486.1522; found, 486.1514.

Preparation of 2-ethyl-1-(phenylsulfonyl)-3-(fluoranthen-1-yl)-1H-indole (24) by Suzuki-Miyaura coupling



To a 100 mL round-bottom flask were added fluoranthene (**23**) (6.2 g, 30.7 mmol), *N*-bromosuccinimide (9.0 g, 50.6 mmol), and DMF (25 mL). The mixture was stirred at 50 °C for 24 h. To the reaction mixture, water (50 mL) was added, and crystals formed were separated by filtration. A part of the separated crystals (300 mg) were purified with preparative GPC to obtain **3-bromofluoranthene (26)** (40 mg) as light yellow solid.

To a 50 mL Schlenk flask were added 3-bromofluoranthene (**26**) (14.1 mg, 0.05 mmol) and THF (1 mL). The mixture was cooled to –78 °C. $n\text{-BuLi}$ in hexane (1.62 M, 37 μL) was added, and the reaction mixture was stirred at –78 °C for 40 min. Then 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (10.1 mg, 0.06 mmol) was added. The reaction mixture was stirred at –78 °C for 10 min, and then at room temperature for 30 min. To the mixture, 3-bromo-2-ethyl-1-(phenylsulfonyl)-1H-indole (**25**) (0.06 mmol, 21.9 mg), cesium carbonate (32.6 mg, 0.10 mmol), $\text{Pd}[\text{P}(\text{t-Bu})_3]_2$ (5.1 mg, 0.01 mmol), water (3.6 mg, 0.2 mmol), and dioxane (2 mL) were added, and the reaction mixture was stirred at 60 °C for 4 h. The solvent was removed under reduced pressure, and the crude product was purified with preparative GPC to obtain **2-ethyl-1-(phenylsulfonyl)-3-(fluoranthen-1-yl)-1H-indole (24)** (9.0 mg, 37%) as light yellow solid. The ^1H NMR spectrum was identical to that for the compound obtained by the “radical cation pool” method.

The highest occupied molecular orbital (HOMO) energies of nucleophilic aromatic partners

HOMO energies (eV) of **5**, **7**, **9**, **11**, **13**, and **15** calculated at the RB3LYP/6-31G(d) level.

	5	7	9	11	13	15
HOMO (eV)	-5.982	-5.988	-5.730	-5.912	-6.101	-6.074

Cartesian coordinates (Å) of the optimized structures

Cartesian coordinates (Å) of the optimized structure for the radical cation of naphthalene (**2**) (D_{2h} symmetry) calculated at the UB3LYP/6-31G(d) level.

Atom	X	Y	Z	Atom	X	Y	Z
C	0.000000	0.716377	0.000000	C	-1.236176	-1.402353	0.000000
C	0.000000	-0.716377	0.000000	H	1.243374	-2.488976	0.000000
C	1.236176	-1.402353	0.000000	H	3.389914	-1.242832	0.000000
C	2.452416	-0.696227	0.000000	H	3.389914	1.242832	0.000000
C	2.452416	0.696227	0.000000	H	1.243374	2.488976	0.000000
C	1.236176	1.402353	0.000000	H	-1.243374	2.488976	0.000000
C	-1.236176	1.402353	0.000000	H	-3.389914	1.242832	0.000000
C	-2.452416	0.696227	0.000000	H	-3.389914	-1.242832	0.000000
C	-2.452416	-0.696227	0.000000	H	-1.243374	-2.488976	0.000000

Cartesian coordinates (Å) of the optimized structure for the radical cation of 2-bromonaphthalene (**18**) (C_s symmetry) calculated at the UB3LYP/6-31G(d) level.

Atom	X	Y	Z	Atom	X	Y	Z
C	1.440280	0.561482	0.000000	C	0.863896	-1.832240	0.000000
C	1.857368	-0.810454	0.000000	H	3.559413	-2.137518	0.000000
C	3.229978	-1.102220	0.000000	H	5.241854	-0.317757	0.000000
C	4.185742	-0.067010	0.000000	H	4.526762	2.062429	0.000000
C	3.784969	1.270655	0.000000	H	2.108090	2.628385	0.000000
C	2.425867	1.589457	0.000000	H	-1.235554	-2.314087	0.000000
C	0.068822	0.859719	0.000000	H	1.176956	-2.872752	0.000000
C	-0.888472	-0.183610	0.000000	H	-0.269040	1.891403	0.000000
C	-0.490031	-1.527096	0.000000	Br	-2.701412	0.265789	0.000000

Cartesian coordinates (Å) of the optimized structure for the radical cation of pyrene (**21**) (D_{2h} symmetry) calculated at the UB3LYP/6-31G(d) level.

Atom	X	Y	Z	Atom	X	Y	Z
C	2.450626	-0.692561	0.000000	C	-1.206647	-2.843828	0.000000
C	2.450626	0.692561	0.000000	C	0.000000	-3.540019	0.000000
C	1.233919	1.421053	0.000000	C	1.206647	-2.843828	0.000000
C	0.000000	0.708358	0.000000	H	3.392501	-1.233524	0.000000

C	0.000000	-0.708358	0.000000	H	3.392501	1.233524	0.000000
C	1.233919	-1.421053	0.000000	H	-3.392501	1.233524	0.000000
C	-1.233919	1.421053	0.000000	H	-3.392501	-1.233524	0.000000
C	-2.450626	0.692561	0.000000	H	2.147347	3.387586	0.000000
C	-2.450626	-0.692561	0.000000	H	0.000000	4.624832	0.000000
C	-1.233919	-1.421053	0.000000	H	-2.147347	3.387586	0.000000
C	1.206647	2.843828	0.000000	H	-2.147347	-3.387586	0.000000
C	0.000000	3.540019	0.000000	H	0.000000	-4.624832	0.000000
C	-1.206647	2.843828	0.000000	H	2.147347	-3.387586	0.000000

Cartesian coordinates (Å) of the optimized structure for the radical cation of fluoranthene (**23**) (C_s symmetry) calculated at the UB3LYP/6-31G(d) level.

Atom	X	Y	Z	Atom	X	Y	Z
C	-1.458600	-2.460868	0.000000	C	2.424593	0.683623	0.000000
C	-0.743408	-3.693546	0.000000	C	2.485855	2.079608	0.000000
C	0.644591	-3.720796	0.000000	C	1.327172	2.889933	0.000000
C	1.376757	-2.518666	0.000000	H	-2.544571	-2.471757	0.000000
C	0.683059	-1.302942	0.000000	H	-1.301830	-4.624427	0.000000
C	-0.748579	-1.279681	0.000000	H	1.169656	-4.670048	0.000000
C	1.157058	0.068464	0.000000	H	2.462710	-2.542317	0.000000
C	0.000000	0.901492	0.000000	H	-1.262327	4.056769	0.000000
C	-1.178329	0.138407	0.000000	H	-3.350156	2.746486	0.000000
C	0.036606	2.303972	0.000000	H	-3.346639	0.279960	0.000000
C	-1.218036	2.971654	0.000000	H	3.340422	0.100658	0.000000
C	-2.398511	2.224607	0.000000	H	3.456751	2.564828	0.000000
C	-2.400418	0.812874	0.000000	H	1.437117	3.971032	0.000000

Cartesian coordinates (Å) of the optimized structure for 1-bromo-3,5-dimethoxybenzene (**5**) (C_s symmetry) calculated at the RB3LYP/6-31G(d) level.

Atom	X	Y	Z	Atom	X	Y	Z
C	-1.283645	0.301504	0.000000	H	-0.411559	-3.014168	0.000000
C	0.000000	0.815418	0.000000	H	-4.052087	-3.052133	0.000000
C	1.142789	0.010037	0.000000	H	-2.548703	-3.412227	0.894889
C	0.960867	-1.375146	0.000000	H	-2.548703	-3.412227	-0.894889
C	-0.327395	-1.935044	0.000000	H	3.954614	-2.675448	0.000000
C	-1.440452	-1.097027	0.000000	H	3.522786	-1.191366	-0.894937
C	-2.967186	-2.933647	0.000000	H	3.522786	-1.191366	0.894937
C	3.314197	-1.791723	0.000000	O	-2.730599	-1.533694	0.000000
H	-2.158725	0.938926	0.000000	O	1.980547	-2.279881	0.000000
H	2.124050	0.463395	0.000000	Br	0.234311	2.716828	0.000000

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Cartesian coordinates (Å) of the optimized structure for 1-chloro-3,5-dimethoxybenzene (**7**) (C_s symmetry) calculated at the RB3LYP/6-31G(d) level.

Atom	X	Y	Z	Atom	X	Y	Z
C	0.083755	-1.509058	0.000000	H	2.137261	1.237029	0.000000
C	-1.118276	-0.824164	0.000000	H	4.430706	-1.590635	0.000000
C	-1.197674	0.572555	0.000000	H	3.777446	-0.189511	0.894832
C	0.000000	1.291393	0.000000	H	3.777446	-0.189511	-0.894832
C	1.240028	0.631558	0.000000	H	-0.844411	4.444372	0.000000
C	1.275485	-0.761239	0.000000	H	-1.737594	3.183164	-0.895025
C	3.663064	-0.814901	0.000000	H	-1.737594	3.183164	0.895025
C	-1.137840	3.393184	0.000000	O	2.419649	-1.500286	0.000000
H	0.128294	-2.590993	0.000000	O	0.073922	2.652710	0.000000
H	-2.163861	1.057977	0.000000	Cl	-2.621618	-1.743554	0.000000

Cartesian coordinates (Å) of the optimized structure for 2-ethyl-1-(phenylsulfonyl)-1*H*-indole (**9**) (C_1 symmetry) calculated at the RB3LYP/6-31G(d) level.

Atom	X	Y	Z	Atom	X	Y	Z
C	4.028873	-1.510713	-0.787039	H	1.556649	-2.121488	1.504984
C	3.650922	-0.251600	-1.237183	H	3.586187	-3.157170	0.536737
C	2.490488	0.337106	-0.714233	H	2.188871	2.369006	-1.626729
C	1.733627	-0.351124	0.264325	H	-1.252416	2.473950	-0.312824
C	2.118341	-1.611433	0.734255	H	-0.310045	3.144810	0.989985
C	3.268293	-2.178695	0.187412	H	-3.274877	0.972313	0.519738
C	1.842852	1.597317	-0.953474	H	-4.837681	0.158455	-1.251673
C	0.734901	1.687477	-0.165648	H	-4.268271	-1.874465	-2.560089
C	-0.243844	2.822604	-0.054630	H	-2.157652	-3.101508	-2.103209
C	-1.856912	-0.605840	0.169110	H	-0.607835	-2.295108	-0.336370
C	-3.041306	0.092628	-0.069892	H	-0.623967	4.808627	-0.828506
C	-3.910099	-0.372574	-1.058577	H	1.098311	4.426375	-0.685231
C	-3.589550	-1.516497	-1.791031	H	0.141657	3.731665	-2.006665
C	-2.401771	-2.208293	-1.535696	N	0.652853	0.497817	0.618298
C	-1.527502	-1.759922	-0.547728	O	-0.335584	-1.165610	2.267495
C	0.118589	4.013338	-0.948260	O	-1.346576	1.160795	2.070585
H	4.924235	-1.980939	-1.184294	S	-0.750800	-0.023624	1.458983
H	4.241542	0.274595	-1.982568				

Cartesian coordinates (Å) of the optimized structure for 2-iodo-1-(phenylsulfonyl)-1*H*-indole (**11**) (C_1 symmetry) calculated at the RB3LYP/3-21G(d) level.

Atom	X	Y	Z	Atom	X	Y	Z
C	-4.622656	-0.856393	-0.799310	H	-3.721339	-2.431595	-1.966374
C	-3.563866	-1.637068	-1.246550	H	-2.993634	1.185479	1.418063

C	-2.279070	-1.382467	-0.746843	H	-5.254753	0.747433	0.497266
C	-2.077872	-0.343288	0.200749	H	-0.815966	-2.845807	-1.639677
C	-3.146545	0.430700	0.663740	H	-1.339413	2.967982	0.074670
C	-4.411972	0.162762	0.147676	H	-0.610166	4.589622	-1.665485
C	-1.002352	-2.007244	-0.990798	H	1.742305	4.581909	-2.454150
C	-0.061776	-1.373033	-0.233436	H	3.370555	2.969784	-1.502187
C	0.600493	2.044080	0.216372	H	2.627792	1.340056	0.237075
C	-0.321319	2.963189	-0.292371	N	-0.687625	-0.326276	0.517554
C	0.095309	3.873889	-1.261389	O	-0.984304	1.494774	2.237013
C	1.422385	3.869932	-1.702593	O	1.260859	0.282542	2.049935
C	2.339653	2.960896	-1.169955	S	0.080358	0.886539	1.444936
C	1.932178	2.042699	-0.201918	I	1.972026	-1.937321	-0.157797
H	-5.623070	-1.038015	-1.173658				

Cartesian coordinates (Å) of the optimized structure for methyl 1-(phenylsulfonyl)-1*H*-indole-2-carboxylate (**13**) (C_1 symmetry) calculated at the RB3LYP/6-31G(d) level.

Atom	X	Y	Z	Atom	X	Y	Z
C	2.768163	-3.614187	-0.704615	H	-0.374082	-2.900913	0.462598
C	3.293418	-2.337310	-0.832056	H	1.060759	-4.815012	-0.151847
C	2.487773	-1.237933	-0.490629	H	3.598348	0.693156	-0.839458
C	1.161205	-1.447895	-0.036939	H	-2.921076	-1.814009	1.114114
C	0.631074	-2.735285	0.098415	H	-4.957535	-1.908860	-0.325896
C	1.451110	-3.805269	-0.242864	H	-5.347796	-0.142931	-2.028669
C	2.708803	0.176069	-0.508122	H	-3.720323	1.713985	-2.295474
C	1.558250	0.795954	-0.102590	H	-1.681626	1.804138	-0.858511
C	-2.198937	-0.009479	0.187270	H	3.287642	4.771771	0.050235
C	-3.104589	-1.058399	0.358662	H	1.542329	4.786055	0.472289
C	-4.242449	-1.100482	-0.447916	H	2.038182	4.587920	-1.226772
C	-4.460489	-0.105805	-1.402607	N	0.576630	-0.184256	0.181100
C	-3.545220	0.939615	-1.554196	O	-0.815554	-1.119999	2.137602
C	-2.404351	1.001311	-0.755415	O	-0.606446	1.394894	1.821821
C	1.290486	2.244713	-0.224146	O	0.242721	2.756996	-0.566895
C	2.304214	4.367000	-0.189401	O	2.416781	2.948156	0.014044
H	3.374506	-4.477767	-0.962435	S	-0.770878	0.056134	1.271394
H	4.307522	-2.181967	-1.189879				

Cartesian coordinates (Å) of the optimized structure for 2-iodobenzo[*b*]thiophene (**15**) (C_s symmetry) calculated at the RB3LYP/3-21G(d) level.

Atom	X	Y	Z	Atom	X	Y	Z
C	1.746570	-3.958689	0.000000	H	2.523074	-4.714326	0.000000
C	2.092613	-2.613823	0.000000	H	3.133236	-2.310336	0.000000
C	1.079890	-1.637681	0.000000	H	-1.662765	-3.716776	0.000000
C	-0.279717	-2.053400	0.000000	H	0.146167	-5.408566	0.000000
C	-0.624295	-3.407773	0.000000	H	2.154646	0.321176	0.000000

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C	0.395960	-4.354230	0.000000	S	-1.366620	-0.674548	0.000000
C	1.207241	-0.197942	0.000000	I	-0.342226	2.516751	0.000000
C	0.000000	0.429170	0.000000				

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Chapter 2

Electrochemical C–H Amination: Synthesis of Aromatic Primary Amines via *N*-Arylpyridinium Ions

Abstract

A new method for C–H amination of aromatic compounds based on electrochemical oxidation has been developed. Anodic treatment of aromatic compounds in the presence of pyridine followed by the reaction of the resulting *N*-arylpyridinium ions with an alkylamine gave corresponding aromatic primary amines. This new transformation serves as a powerful method for synthesizing aromatic primary amines from aromatic compounds without using metal catalysts and harsh chemical reagents. High chemoselectivity of the present method is demonstrated by C–H amination of aromatic compounds bearing a nitro group to give a key intermediate for the synthesis of VLA-4 antagonist.

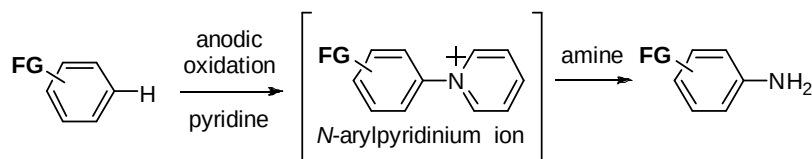
Introduction

Functionalized aromatic primary amines are relevant intermediates in the synthesis of organic functional materials such as dyes and pigments, and biological active medicinal and agrochemical compounds.¹ Therefore, a variety of protocols for synthesizing aromatic primary amines from corresponding aromatic compounds were developed. Among them, the most popular protocol is nitration of aromatic compounds followed by reduction of the nitro compounds.² Although various methods for reduction of nitroarenes have been developed, chemoselectivity is still a major concern in addition to safety issues of nitration.³ Transition-metal-catalyzed amination serves as an alternative method, but it requires preintroduction of a halogen atom⁴ or a metal⁵ into aromatic compounds. Recently, transition-metal catalyzed direct amination of C–H bonds of aromatic compounds has been developed.⁶ Although these methods are useful, development of a new method, which does not use metal compounds nor harsh chemical reagents, is desired to provide an efficient and chemoselective synthetic route to aromatic primary amines.

Electrochemical oxidation^{7,8} serves as a powerful method for functionalize C–H bonds of aromatic compounds by the intermediacy of radical cations.⁹ As described in chapter 1, an effective method for the metal- and chemical-oxidant-free C–H/C–H cross-coupling of two aromatic compounds has been developed using the “radical-cation-pool” method.¹⁰

On the basis of these backgrounds, it is reasonable to consider that the sequential transformations consisting of electrochemical oxidation of aromatic compounds in the presence of an appropriate nitrogen source followed by chemical reaction would serve as a powerful method for direct conversion of C–H to C–NH₂ in aromatic compounds.

Pyridine was chosen to use as nitrogen source for the following reasons: (1) high oxidation potential of pyridine enables selective oxidation of aromatic compounds in the presence of pyridine, (2) extremely high nucleophilicity of pyridine¹¹ leads to nucleophilic attack of pyridine to radical cation of aromatic compounds to give *N*-arylpyridinium ions,¹² and (3) overoxidation is suppressed because of strong electron-withdrawing effect of a positive charge on the pyridinium nitrogen, avoiding introduction of multiple NH₂ groups, (4) the *N*-arylpyridinium ion can be converted to NH₂ group by the attack of a suitable nucleophile,^{13,14} although the process has not been utilized so far from a synthetic point of view. This chapter describes electrochemical oxidation of aromatic compounds in the presence of pyridine and a subsequent chemical reaction of the resulting *N*-arylpyridinium ions gave aromatic primary amines (Scheme 1). Because the method does not require the use of metal compounds, reducing reagents, and strong acids, it exhibits remarkable functional group compatibility.

Scheme 1. Electrochemical C–H Amination**Results and Discussions**

Anisole (**1**) was chosen to use as a substrate because oxidation potential of **1** is lower than that of pyridine (**2**). The electrochemical oxidation of **1** was carried out in a 0.3 M solution of Bu_4NBF_4 in $\text{CH}_3\text{CN/pyridine}$ (100/5) in an H-type divided cell equipped with an anode consisting of fine fibers made from carbon felt and a platinum plate cathode at 25 °C. After 3.0 *F* of electricity was consumed, the reaction mixture was treated with piperidine at 80 °C for 12 h to give 4-methoxyaniline in 69% yield (Table 1, entry 1).

The reaction seems to proceed by the initial one-electron oxidation of an aromatic compound to produce the radical cation. The subsequent attack of pyridine followed by one-electron oxidation and elimination of a proton gives the *N*-arylpyridinium ion. In fact, the regioselectivity of the reaction is consistent with the lowest unoccupied molecular orbital (LUMO) of the radical cation of anisole (**1**) obtained by DFT calculations (Figure 1a). The amino group is introduced to the carbon bearing hydrogen with the largest coefficient of the LUMO of the radical cation of **1**. Because the LUMO of neutral **1** has no coefficient at the 4-position, a mechanism involving initial formation of the zwitter ion by the nucleophilic attack of pyridine to **1** followed by one-electron oxidation is excluded (Figure 1b). The reaction of the *N*-arylpyridinium ion with piperidine proceeds by the addition of piperidine to 2-position of *N*-arylpyridinium ion followed by ring opening and reaction of imine (Figure 2).



Figure 1. The lowest unoccupied molecular orbitals of (a) radical cation of **1** and (b) **1** obtained by DFT calculations (B3LYP/6-31G*).

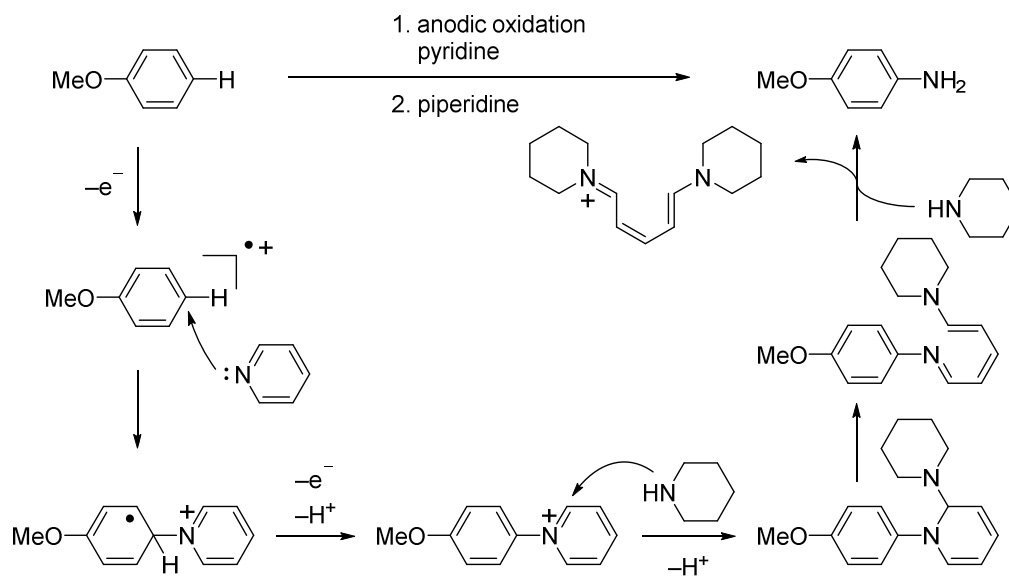


Figure 2. Proposed reaction mechanism of C-H amination of aromatic compounds via N-arylpiperidinium ion.

π -Extended aromatic compounds such as biphenyl, naphthalene, and diphenylether gave corresponding primary amines in good yields (Table 1, entries 2–4). Functional group compatibility of the present transformation is remarkable. Iodoanisoles gave the corresponding iodine-substituted aniline derivatives in very good yields (Table 1, entries 5–7). These results are notable because iodo-substituents are often not compatible with the oxidation of aromatic compounds¹⁵ and the reduction of nitro groups to amino groups.¹⁶ 2-Methylanisole is also a suitable substrate and benzylic C-H was not affected (entry 8). Anisoles with an electron-withdrawing group such as ester, amide, and ketone functionalities also gave the corresponding aniline derivatives in good yields (entries 9–11). It should be emphasized that the present transformation is compatible with nitro groups. For example, anisoles bearing a nitro group gave corresponding aniline derivatives in excellent yields without affecting the nitro group (entries 12 and 13). This contrasts sharply with the conventional nitration/reduction process.

Furthermore, regioselectivities of the amination of these π -extended aromatic compounds and functionalized anisoles are predictable based on the DFT calculations (Figure 3).

Table 1. Synthesis of Functionalized Aromatic Primary Amines by Electrochemical C–H Amination^a

entry	substrate	product [yield, ^b (electricity)]	entry	substrate	product [yield, ^b (electricity)]
1		 69% (3.0 F)	8		 74% (3.0 F)
2		 71% (3.5 F)	9		 92% (20/21=70/30) (3.0 F)
3		 99% (3.0 F)	10		 97% (3.5 F)
4		 92% (8/9=57/43) (3.5 F)	11 ^c		 66% (7.0 F)
5		 81% (3.0 F)	12		 95% (27/28=70/30) (3.5 F)
6		 97% (13/14=66/34) (3.0 F)	13		 quant (3.5 F)
7		 84% (3.5 F)			

^a The reactions were carried out on a 0.20 mmol scale. ^b Isolated yields are given. ^c LiClO₄ was used as a supporting electrolyte.

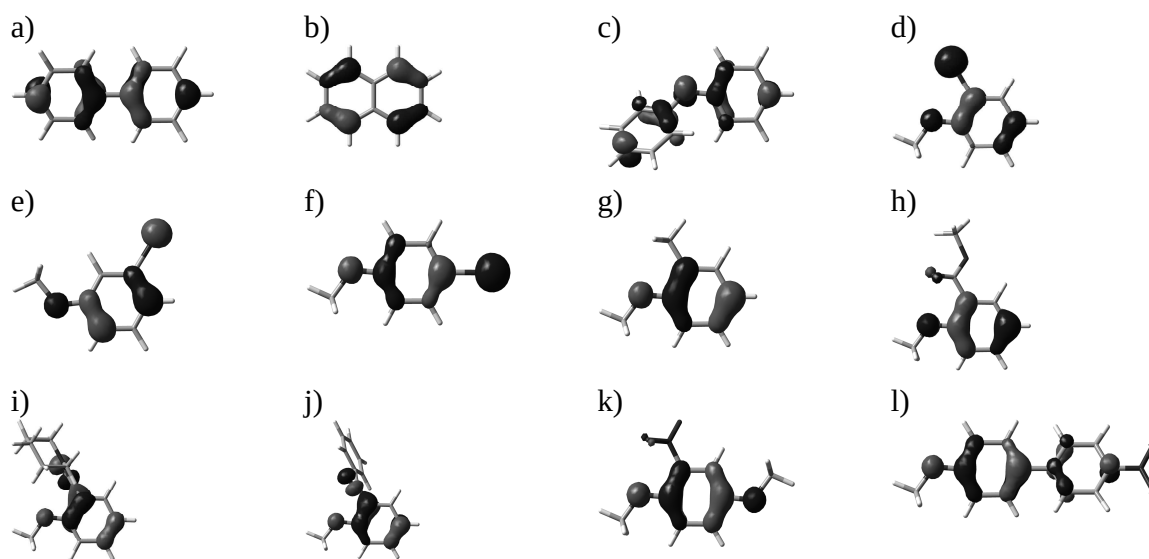


Figure 3. The lowest unoccupied molecular orbitals of radical cation of (a) **3**, (b) **5**, (c) **7**, (d) **10**, (e) **12**, (f) **15**, (g) **17**, (h) **19**, (i) **22**, (j) **24**, (k) **26**, (l) **29** obtained by DFT calculations (UB3LYP/6-31G^{*}).

To demonstrate the utility of the electrochemical C–H amination, a key intermediate for the synthesis of VLA-4 antagonist **31**¹⁷ was synthesized (Figure 4). Starting material **32** was prepared from commercially available **33** in one step (quantitative yield). The electrochemical oxidation of **32** in the presence of pyridine followed by treatment with piperidine gave **31** in 89% isolated yield. In the previous work reported in the literature, synthesis of **31** requires protection and deprotection steps of the amino group because the amino group should be introduced prior to the introduction of the nitro group. However, the present method enabled the direct amination in the presence of the nitro group avoiding the protection and deprotection of the amino group, demonstrating the power of the present method from view points of redox economy,¹⁸ step economy,¹⁹ and protecting-group-free synthesis.²⁰

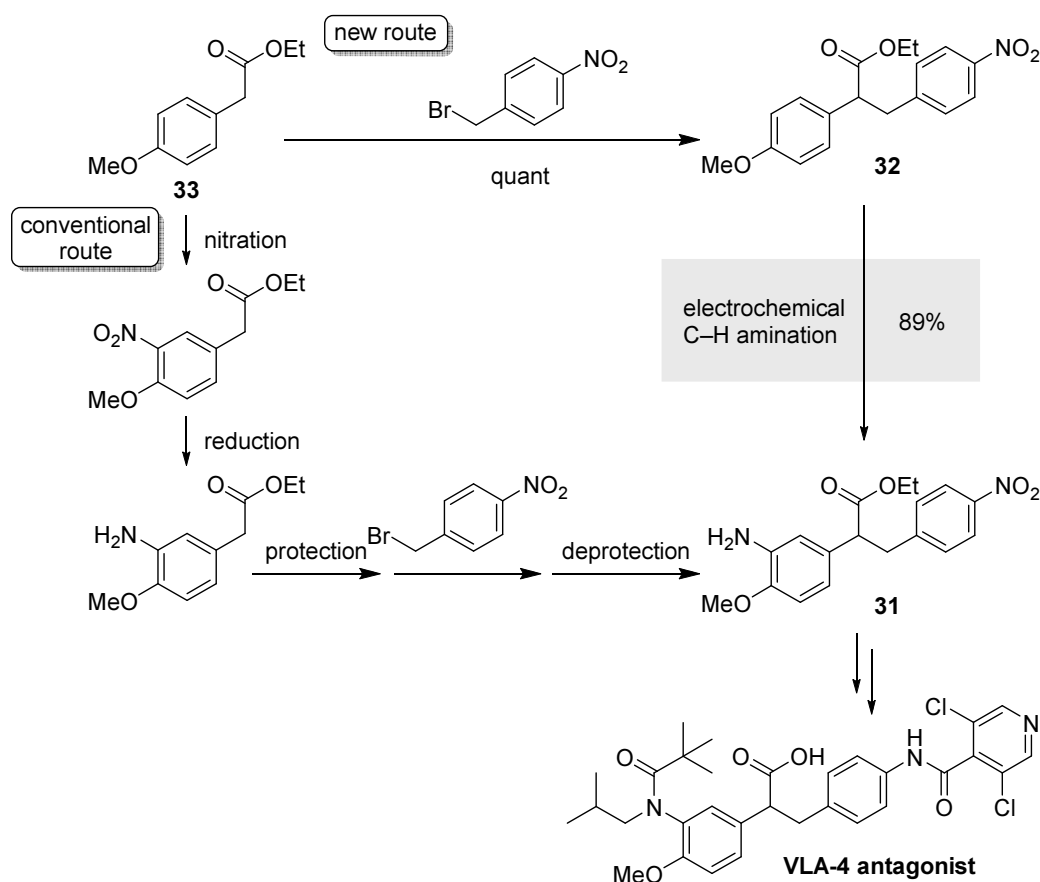


Figure 4. Synthesis of a key intermediate for the synthesis of VLA-4 Antagonist **31**.

Conclusion

In conclusion, an efficient method for the C–H bond amination of aromatic compounds was developed by integration of the electrochemical and chemical reactions.²¹ The present method provides chemoselective metal-free routes to the aromatic primary amines having a variety of functionalities including iodide and a nitro groups.

Experimental Section

General: ¹H and ¹³C NMR spectra were recorded in CDCl₃ on Varian MERCURY plus-400 (¹H 400 MHz, ¹³C 100 MHz), or JEOL ECA-600P spectrometer (¹H 600 MHz, ¹³C 150 MHz). Mass spectra were obtained on JEOL JMS SX-102A mass spectrometer. IR spectra were measured with a Shimadzu IRAffinity (FTIR). Merck precoated silica gel F₂₅₄ plates (thickness 0.25 mm) was used for thin-layer chromatography (TLC) analysis. Flash chromatography was carried out on a silica gel (Kanto Chem. Co., Silica Gel N, spherical,

neutral, 40-100 μm). Preparative gel permeation chromatography (GPC) was carried out on Japan Analytical Industry LC-918 equipped with JAIGEL-1H and 2H using CHCl_3 as an eluent. All reactions were carried out under argon atmosphere unless otherwise noted. Compounds **22**²² and **24**²³ were prepared according to the reported procedures. Compounds **2**,²⁴ **4**,²⁵ **6**,²⁶ **8**,²⁷ **9**,²⁸ **13**,²⁹ **14**,³⁰ **18**,³¹ **20**,³² **21**,³³ **27**,³⁴ and **28**³⁵ were identified by comparison with their ^1H and ^{13}C NMR spectra reported in the literature. Bu_4NBF_4 was purchased from TCI and dried at 50 $^\circ\text{C}$ /1 mmHg overnight. Unless otherwise noted, all materials were obtained from commercial suppliers and used without further purification. DFT calculations were performed with the Gaussian 09 program.³⁶ All geometry optimizations were carried out at the RB3LYP or UB3LYP level of density functional theory with the 6-31G(d) or 3-21G(d) basis set.

General Procedure of the C–H Amination of Aromatic Compounds

The anodic oxidation was carried out using an H-type divided cell (4G glass filter) equipped with an anode consisting of fine fibers made from carbon felt (Nippon Carbon JF-20-P7, ca. 160 mg, dried at 300 $^\circ\text{C}$ /1 mmHg for 4 h before use) and a platinum plate cathode (10 mm $\times$ 10 mm). In the anodic chamber was placed a solution of aromatic compound (0.20 mmol) and pyridine (0.5 mL) in 0.3 M $\text{Bu}_4\text{NBF}_4/\text{CH}_3\text{CN}$ (10.0 mL). In the cathodic chamber were placed trifluoromethanesulfonic acid (200 μL) and 0.3 M $\text{Bu}_4\text{NBF}_4/\text{CH}_3\text{CN}$ (10.0 mL). The constant current electrolysis (8.0 mA) was carried out at 25 $^\circ\text{C}$ with magnetic stirring. After $X F$ ($3.0 < X < 7.0$) of electricity was consumed, the reaction mixture was transferred to a round-bottom flask and was evaporated. Then, piperidine (200 μL , 2.0 mmol) and CH_3CN (10 mL) were added to the reaction mixture. The resulting mixture was stirred at 80 $^\circ\text{C}$ for 12 h. After removal of the solvent under reduced pressure, the crude product was purified with flash chromatography or preparative GPC to obtain the aromatic aniline.

4-methoxyaniline (2).²⁴ Electrochemical oxidation (8 mA, 3.0 F) of anisole (**1**) and subsequent treatment with piperidine gave the title compound (16.9 mg, 69%) as pale brown solid.

4-phenylaniline (4).²⁵ Electrochemical oxidation (8 mA, 3.5 F) of biphenyl (**3**) and subsequent treatment with piperidine gave the title compound (24.3 mg, 72%) as white solid.

1-aminonaphthalene (6).²⁶ Electrochemical oxidation (8 mA, 3.0 F) of naphthalene (**5**)

and subsequent treatment with piperidine gave the title compound (28.4 mg, 99%) as pale brown solid.

4-phenoxyaniline (8)²⁷ and 2-phenoxyaniline (9).²⁸ Electrochemical oxidation (8 mA, 3.0 *F*) of diphenyl ether (7) and subsequent treatment with piperidine gave **8** (19.6 mg, 53%) and **9** (14.7 mg, 40%) as pale brown solids.

3-iodo-4-methoxyaniline (11). Electrochemical oxidation (8 mA, 3.0 *F*) of 2-iodoanisole (**10**) and subsequent treatment with piperidine gave the title compound (40.4 mg, 81%) as pale brown solid. ¹H NMR (400 MHz, CDCl₃): δ 3.80 (s, 3H), 6.66 (m, 2H), 7.16 (d, *J* = 2.0 Hz, 1H); ¹³C NMR (150 MHz, CDCl₃): δ 57.0, 86.7, 112.3, 116.1, 126.2, 141.3, 151.6; HRMS (ESI): calcd. for [M+H]⁺ C₇H₉INO, 249.9723; found, 249.9721.

2-iodo-4-methoxyaniline (13)²⁹ and 4-iodo-2-methoxyaniline (14).³⁰ Electrochemical oxidation (8 mA, 3.5 *F*) of 3-iodoanisole (**12**) and subsequent treatment with piperidine gave **13** (31.4 mg, 63%) and **14** (17.0 mg, 34%) as pale brown solids.

5-iodo-2-methoxyaniline (16). Electrochemical oxidation (8 mA, 3.5 *F*) of 4-iodoanisole (**15**) and subsequent treatment with piperidine gave the title compound (41.7 mg, 84%) as pale brown solid. ¹H NMR (400 MHz, CDCl₃): δ 3.70–3.84 (m, 5H), 6.52 (d, *J* = 8.0 Hz, 1H), 6.98–7.05 (m, 2H); ¹³C NMR (150 MHz, CDCl₃): δ 55.6, 83.2, 112.3, 123.6, 127.7, 136.9, 147.5; HRMS (ESI): calcd. for C₇H₈INO, 248.9651; found, 248.9655.

4-methoxy-3-methylaniline (18).³¹ Electrochemical oxidation (8 mA, 3.0 *F*) of 2-methylanisole (**17**) and subsequent treatment with piperidine gave the title compound (20.4 mg, 74%) as white solid.

4-methoxy-3-methoxycarbonylaniline (20)³² and 2-methoxy-3-methoxycarbonylaniline (21).³³ Electrochemical oxidation (8 mA, 4.5 *F*) of 2-methoxycarbonylanisole (**19**) and subsequent treatment with piperidine gave **20** (23.3 mg, 64%) and **21** (10.2 mg, 28%) as pale brown solids.

4-methoxy-3-(piperidin-1-ylcarbonyl)aniline (23). Electrochemical oxidation (8 mA, 3.5 *F*) of 2-(piperidin-1-ylcarbonyl)anisole (**22**) and subsequent treatment with piperidine gave the title compound (45.5 mg, 97%) as pale brown solid. The product was determined by a NOE analysis. mp: 42–44 °C; ¹H NMR (400 MHz, CDCl₃): δ 1.30–1.80 (m, 6H),

3.10–3.30 (m, 2H), 3.58–3.80 (m, 5H), 6.59 (d, $J = 2.8$ Hz, 1H), 6.67 (dd, $J = 8.4, 2.8$ Hz, 1H), 6.72 (d, $J = 8.8$ Hz, 1H); ^{13}C NMR (150 MHz, CDCl_3): δ 24.6, 25.6, 26.4, 42.5, 47.9, 56.2, 112.6, 114.9, 116.5, 127.2, 140.1, 148.4, 167.6; HRMS (ESI): calcd. for $[\text{M}+\text{H}]^+$ $\text{C}_{13}\text{H}_{19}\text{N}_2\text{O}_2$, 235.1441; found, 235.1437.

3-benzoyl-4-methoxyaniline (25). In the anodic chamber was placed a solution of **2-benzoylanisole (24)** (42.4 mg, 0.20 mmol) and pyridine (0.5 mL) in 0.3 M $\text{LiClO}_4/\text{CH}_3\text{CN}$ (10.0 mL). In the cathodic chamber were placed trifluoromethanesulfonic acid (200 μL) and 0.3 M $\text{LiClO}_4/\text{CH}_3\text{CN}$ (10.0 mL). The constant current electrolysis (8.0 mA) was carried out at 25 °C with magnetic stirring. After 7.0 F of electricity was consumed, the reaction mixture was transferred to a round-bottom flask and was evaporated. Then, piperidine (200 μL , 2.0 mmol) and CH_3CN (10 mL) were added to the reaction mixture. The resulting mixture was stirred at 80 °C for 12 h. After removal of the solvent under reduced pressure, the crude product was purified with flash chromatography to obtain **25** (30.0 mg, 66%) as brown oil. The product was determined by a NOE analysis. ^1H NMR (400 MHz, CDCl_3): δ 3.46–3.60 (bs, 2H), 3.63 (s, 3H), 6.70 (d, $J = 2.8$ Hz, 1H), 6.76–6.85 (m, 2H), 7.42 (t, $J = 7.6$ Hz, 2H), 7.54 (t, $J = 7.4$ Hz, 1H), 7.82 (dd, $J = 8.0, 1.6$ Hz, 2H); ^{13}C NMR (150 MHz, CDCl_3): δ 56.3, 113.3, 116.3, 118.4, 128.1, 129.5, 129.8, 132.9, 137.7, 139.9, 150.4, 196.5; HRMS (ESI): calcd. for $[\text{M}+\text{H}]^+$ $\text{C}_{14}\text{H}_{14}\text{NO}_2$, 228.1019; found, 228.1016.

2,5-dimethoxy-4-nitroaniline (27)³⁴ and **3,6-dimethoxy-2-nitroaniline (28)**.³⁵ Electrochemical oxidation (8 mA, 3.5 F) of 1,4-dimethoxy-2-nitrobenzene (**26**) and subsequent treatment with piperidine gave **27** (26.0 mg, 66%) and **28** (12.0 mg, 30%) as brown solids.

3-amino-4-methoxy-4'-nitro-1,1'-biphenyl (30). Electrochemical oxidation (8 mA, 3.5 F) of 4-methoxy-4'-nitro-1,1'-biphenyl (**29**) and subsequent treatment with piperidine gave the title compound (51.0 mg, quant) as red solid. The product was determined by a NOE analysis. mp: 150–152 °C; ^1H NMR (400 MHz, CDCl_3): δ 3.92 (s, 3H), 3.92–4.00 (bs, 2H), 6.88 (d, $J = 8.0$ Hz, 1H), 6.98–7.03 (m, 2H), 7.67 (d, $J = 9.2$ Hz, 2H), 8.25 (d, $J = 8.8$ Hz, 2H); ^{13}C NMR (150 MHz, CDCl_3): δ 55.6, 110.6, 113.4, 117.7, 124.0, 127.1, 131.6, 136.8, 146.4, 147.7, 148.2; HRMS (ESI): calcd. for $[\text{M}+\text{H}]^+$ $\text{C}_{13}\text{H}_{13}\text{N}_2\text{O}_3$, 245.0921; found, 245.0913.

Synthesis of a Key Intermediate for the Synthesis of VLA-4 Antagonist

To a 100 mL round-bottom flask were added diisopropylamine (1.01 g, 10 mmol) and THF (30 mL). The mixture was cooled to $-78\text{ }^{\circ}\text{C}$. To the mixture, $n\text{BuLi}$ in hexane (1.65 M, 6.06 mL) was added, and the reaction mixture was stirred at $-78\text{ }^{\circ}\text{C}$ for 10 min and then at $25\text{ }^{\circ}\text{C}$ for 10 min. The mixture was cooled to $-78\text{ }^{\circ}\text{C}$. To the mixture, ethyl 2-(4-methoxyphenyl)acetate (1.94 g, 10 mmol) was added, and the mixture was stirred at $-78\text{ }^{\circ}\text{C}$ for 1 hour. To the mixture, 1-(bromomethyl)-4-nitrobenzene (2.16 g, 10 mmol) in THF (5 mL) was added, and the mixture was stirred at $25\text{ }^{\circ}\text{C}$ for 12 h. After removal of the solvent under reduced pressure, the residue was purified with flash chromatography to obtain **ethyl 2-(4-methoxyphenyl)-3-(4-nitrophenyl)propanoate (32)** (3.30 g, quant) as white solid.

The anodic oxidation was carried out using an H-type divided cell (4G glass filter) equipped with an anode consisting of fine fibers made from carbon felt (Nippon Carbon JF-20-P7, ca. 160 mg, dried at $300\text{ }^{\circ}\text{C}/1\text{ mmHg}$ for 4 h before use) and a platinum plate cathode (10 mm $\times$ 10 mm). In the anodic chamber was placed a solution of ethyl 2-(4-methoxyphenyl)-3-(4-nitrophenyl)propanoate (**32**) (0.20 mmol) and pyridine (0.5 mL) in 0.3 M $\text{Bu}_4\text{NBF}_4/\text{CH}_3\text{CN}$ (10.0 mL). In the cathodic chamber were placed trifluoromethanesulfonic acid (200 μL) and 0.3 M $\text{Bu}_4\text{NBF}_4/\text{CH}_3\text{CN}$ (10.0 mL). The constant current electrolysis (8.0 mA) was carried out at $25\text{ }^{\circ}\text{C}$ with magnetic stirring. After 3.5 F of electricity was consumed, the reaction mixture was transferred to a round-bottom flask and was evaporated. Then, piperidine (200 μL , 2.0 mmol) and CH_3CN (10 mL) were added to the reaction mixture. The resulting mixture was stirred at $80\text{ }^{\circ}\text{C}$ for 12 h. After removal of the solvent under reduced pressure, the crude product was purified with flash chromatography to obtain **ethyl 2-(3-amino-4-methoxyphenyl)-3-(4-nitrophenyl)propanoate (31)** (61.2 mg, 89%) as pale yellow oil.

ethyl 2-(4-methoxyphenyl)-3-(4-nitrophenyl)propanoate (32). mp: $52\text{--}54\text{ }^{\circ}\text{C}$; ^1H NMR (400 MHz, CDCl_3): δ 1.13 (t, $J = 8.0\text{ Hz}$, 3H), 3.09 (dd, $J = 14.4, 8.0\text{ Hz}$, 1H), 3.46 (dd, $J = 14.0, 8.4\text{ Hz}$, 1H), 3.70–3.80 (m, 4H), 4.00–4.18 (m, 2H), 6.84 (d, $J = 6.4\text{ Hz}$, 2H), 7.18 (d, $J = 6.6\text{ Hz}$, 2H), 7.25 (d, $J = 8.4\text{ Hz}$, 2H), 8.08 (d, $J = 8.4\text{ Hz}$, 2H); ^{13}C NMR (150 MHz, CDCl_3): δ 14.0, 39.6, 52.2, 55.2, 61.0, 114.1, 123.5, 128.9, 129.8, 129.9, 146.7, 146.9, 159.0, 173.0; HRMS (ESI): $[\text{M}-\text{H}]^+$ calcd. for $\text{C}_{18}\text{H}_{18}\text{N}_1\text{O}_5$, 328.1190; found, 328.1190.

ethyl 2-(3-amino-4-methoxyphenyl)-3-(4-nitrophenyl)propanoate (31) The product was determined by a NOE analysis. ^1H NMR (400 MHz, CDCl_3): δ 1.14 (t, $J = 7.0\text{ Hz}$, 3H), 3.08 (dd, $J = 14.0, 7.2\text{ Hz}$, 1H), 3.46 (dd, $J = 13.6, 8.4\text{ Hz}$, 1H), 3.62–3.73 (m, 3H), 3.82 (s, 3H), 3.98–4.14 (m, 2H), 6.57 (dd, $J = 8.0, 2.0\text{ Hz}$, 1H), 6.66–6.71 (m, 2H), 7.27 (d, $J = 8.8$

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Hz, 2H), 8.08 (d, $J = 8.8$ Hz, 2H) ; ^{13}C NMR (150 MHz, CDCl_3): δ 14.0, 39.5, 52.3, 55.4, 60.9, 110.18, 113.9, 117.8, 123.4, 129.8, 130.3, 136.3, 146.5, 146.7, 147.1, 173.1; HRMS (ESI): $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{18}\text{H}_{21}\text{N}_2\text{O}_5$, 345.1445; found, 345.1440.

DFT Calculations

Cartesian coordinates ($\text{\AA}$) of the optimized structure for the radical cation of anisole (**1**) (C_s symmetry) calculated at the UB3LYP/6-31G(d) level.

Atom	X	Y	Z	Atom	X	Y	Z
C	-0.986268	-0.520055	0.000000	H	-1.286178	-2.633515	0.000000
C	-0.560968	-1.826197	0.000000	H	1.140180	-3.175988	0.000000
C	0.828530	-2.135827	0.000000	H	2.857846	-1.367175	0.000000
C	1.803441	-1.112076	0.000000	H	2.110378	1.028622	0.000000
C	1.406213	0.203108	0.000000	H	-2.146004	1.985907	0.903204
C	0.000000	0.518027	0.000000	H	-2.146004	1.985907	-0.903204
C	-1.628927	2.317896	0.000000	H	-1.509856	3.399050	0.000000
H	-2.042594	-0.278726	0.000000	O	-0.268736	1.798334	0.000000

Cartesian coordinates ($\text{\AA}$) of the optimized structure for anisole (**1**) (C_s symmetry) calculated at the RB3LYP/6-31G(d) level.

Atom	X	Y	Z	Atom	X	Y	Z
C	-0.929916	-0.516672	0.000000	H	-1.204824	-2.646540	0.000000
C	-0.476049	-1.839921	0.000000	H	1.228543	-3.161000	0.000000
C	0.885984	-2.130334	0.000000	H	2.874643	-1.287273	0.000000
C	1.808109	-1.077512	0.000000	H	2.074717	1.071638	0.000000
C	1.373454	0.242818	0.000000	H	-2.213244	1.834701	0.894442
C	0.000000	0.529602	0.000000	H	-2.213244	1.834701	-0.894442
C	-1.698309	2.210449	0.000000	H	-1.727427	3.301746	0.000000
H	-1.995435	-0.316813	0.000000	O	-0.325421	1.857282	0.000000

Cartesian coordinates ($\text{\AA}$) of the optimized structure for the radical cation of biphenyl (**3**) (D_2 symmetry) calculated at the UB3LYP/6-31G(d) level.

Atom	X	Y	Z	Atom	X	Y	Z
C	-0.207134	1.209159	-1.462349	C	-0.207134	-1.209159	1.462349
C	-0.217063	1.202789	-2.841445	H	-0.405022	2.136803	-0.939138
C	0.000000	0.000000	-3.541700	H	-0.396730	2.122516	-3.388390
C	0.217063	-1.202789	-2.841445	H	0.000000	0.000000	-4.627669
C	0.207134	-1.209159	-1.462349	H	0.396730	-2.122516	-3.388390
C	0.000000	0.000000	-0.721853	H	0.405022	-2.136803	-0.939138
C	0.000000	0.000000	0.721853	H	0.405022	2.136803	0.939138
C	0.207134	1.209159	1.462349	H	0.396730	2.122516	3.388390
C	0.217063	1.202789	2.841445	H	0.000000	0.000000	4.627669
C	0.000000	0.000000	3.541700	H	-0.396730	-2.122516	3.388390

C	-0.217063	-1.202789	2.841445	H	-0.405022	-2.136803	0.939138
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Cartesian coordinates (Å) of the optimized structure for the radical cation of naphthalene **(5)** (D_2 symmetry) calculated at the UB3LYP/6-31G(d) level.

Atom	X	Y	Z	Atom	X	Y	Z
C	0.000000	0.716377	0.000000	C	-1.236176	-1.402353	0.000000
C	0.000000	-0.716377	0.000000	H	1.243374	-2.488976	0.000000
C	1.236176	-1.402353	0.000000	H	3.389914	-1.242832	0.000000
C	2.452416	-0.696227	0.000000	H	3.389914	1.242832	0.000000
C	2.452416	0.696227	0.000000	H	1.243374	2.488976	0.000000
C	1.236176	1.402353	0.000000	H	-1.243374	2.488976	0.000000
C	-1.236176	1.402353	0.000000	H	-3.389914	1.242832	0.000000
C	-2.452416	0.696227	0.000000	H	-3.389914	-1.242832	0.000000
C	-2.452416	-0.696227	0.000000	H	-1.243374	-2.488976	0.000000

Cartesian coordinates (Å) of the optimized structure for the radical cation of diphenyl ether **(7)** (C_2 symmetry) calculated at the UB3LYP/6-31G(d) level.

Atom	X	Y	Z	Atom	X	Y	Z
C	0.000000	3.585347	0.686190	H	0.284277	4.456595	1.266866
C	0.170188	2.318163	1.214503	H	0.587652	2.155472	2.202383
C	-0.181365	1.198687	0.427464	H	-1.106812	0.475282	-1.403940
C	-0.757233	1.342089	-0.855213	H	-1.399675	2.757874	-2.326845
C	-0.935170	2.621358	-1.355720	H	-0.696577	4.739395	-1.003499
C	-0.548244	3.742880	-0.599521	H	-0.587652	-2.155472	2.202383
C	0.181365	-1.198687	0.427464	H	-0.284277	-4.456595	1.266866
C	-0.170188	-2.318163	1.214503	H	0.696577	-4.739395	-1.003499
C	0.000000	-3.585347	0.686190	H	1.399675	-2.757874	-2.326845
C	0.548244	-3.742880	-0.599521	H	1.106812	-0.475282	-1.403940
C	0.935170	-2.621358	-1.355720	O	0.000000	0.000000	1.039708
C	0.757233	-1.342089	-0.855213				

Cartesian coordinates (Å) of the optimized structure for the radical cation of 2-iodoanisole **(10)** (C_s symmetry) calculated at the UB3LYP/3-21G(d) level.

Atom	X	Y	Z	Atom	X	Y	Z
C	-2.872644	0.147704	0.000000	H	-4.288220	-1.447612	0.000000
C	-3.239187	-1.178925	0.000000	H	-2.568054	-3.246606	0.000000
C	-2.255364	-2.210174	0.000000	H	-0.158123	-2.676815	0.000000
C	-0.905117	-1.894417	0.000000	H	-1.258076	3.784621	0.000000
C	-0.504828	-0.552510	0.000000	H	-2.555911	2.930476	-0.903150
C	-1.503043	0.499657	0.000000	H	-2.555911	2.930476	0.903150
C	-1.941643	2.939445	0.000000	O	-1.037958	1.749298	0.000000
H	-3.628266	0.920650	0.000000	I	1.513787	-0.029042	0.000000

Cartesian coordinates (Å) of the optimized structure for the radical cation of 3-iodoanisole

(12) (C_s symmetry) calculated at the UB3LYP/3-21G(d) level.

Atom	X	Y	Z	Atom	X	Y	Z
C	2.710766	1.128914	0.000000	H	2.057581	3.170415	0.000000
C	1.758156	2.130587	0.000000	H	-0.355908	2.569824	0.000000
C	0.399506	1.795469	0.000000	H	0.634452	-1.630311	0.000000
C	0.000000	0.417616	0.000000	H	4.119227	-3.008009	0.000000
C	0.943323	-0.595188	0.000000	H	2.570518	-2.886506	0.902894
C	2.309025	-0.253433	0.000000	H	2.570518	-2.886506	-0.902894
C	3.113299	-2.595966	0.000000	O	3.327950	-1.119695	0.000000
H	3.772053	1.338775	0.000000	I	-2.064085	0.002300	0.000000

Cartesian coordinates (Å) of the optimized structure for the radical cation of 4-iodoanisole
(15) (C_s symmetry) calculated at the UB3LYP/3-21G(d) level.

Atom	X	Y	Z	Atom	X	Y	Z
C	-0.847198	-0.903105	0.000000	H	-0.955713	-3.028462	0.000000
C	-0.303857	-2.166035	0.000000	H	3.025030	-1.336763	0.000000
C	1.109289	-2.327959	0.000000	H	2.053673	0.955354	0.000000
C	1.955524	-1.175472	0.000000	H	1.809586	-5.548155	0.000000
C	1.412381	0.084152	0.000000	H	0.406069	-4.885318	0.903161
C	0.000000	0.240245	0.000000	H	0.406069	-4.885318	-0.903161
C	1.015453	-4.805898	0.000000	O	1.743726	-3.501470	0.000000
H	-1.921375	-0.775060	0.000000	I	-0.845711	2.147923	0.000000

Cartesian coordinates (Å) of the optimized structure for the radical cation of 2-methylanisole (17) (C_s symmetry) calculated at the UB3LYP/6-31G(d) level.

Atom	X	Y	Z	Atom	X	Y	Z
C	1.421559	0.349600	0.000000	H	1.630107	-3.045025	0.000000
C	1.986986	-0.900148	0.000000	H	-0.839109	-2.863289	0.000000
C	1.161746	-2.065433	0.000000	H	-2.841929	-1.532181	0.000000
C	-0.233068	-1.963043	0.000000	H	-2.677097	0.006906	0.877787
C	-0.858830	-0.722981	0.000000	H	-2.677097	0.006906	-0.877787
C	0.000000	0.457412	0.000000	H	-0.771554	3.617720	0.000000
C	-2.343914	-0.560974	0.000000	H	0.638292	2.975574	0.902531
C	0.029847	2.882045	0.000000	H	0.638292	2.975574	-0.902531
H	2.040396	1.238688	0.000000	O	-0.649106	1.596352	0.000000
H	3.066589	-1.010553	0.000000				

Cartesian coordinates (Å) of the optimized structure for the radical cation of methyl 2-methoxybenzoate (C_1 symmetry) calculated at the UB3LYP/6-31G(d) level.

Atom	X	Y	Z	Atom	X	Y	Z
C	-2.379273	-0.279790	-0.027410	H	-1.329928	-3.509186	0.091680
C	-2.449962	-1.649515	0.022286	H	0.904845	-2.414732	0.112848
C	-1.260400	-2.425941	0.066977	H	4.399200	-0.714240	-0.787051

C	0.006167	-1.809682	0.077653	H	3.841496	0.993433	-0.715969
C	0.122181	-0.433399	0.046179	H	4.052682	0.065956	0.796194
C	-1.096201	0.358552	-0.025786	H	-1.570324	3.562422	-0.259524
C	1.467084	0.237457	0.175317	H	-2.627217	2.387400	-1.110313
C	3.776461	0.004696	-0.258209	H	-2.660851	2.504428	0.692546
C	-2.045990	2.585730	-0.206696	O	1.621991	1.285866	0.758761
H	-3.280781	0.318896	-0.076632	O	2.421043	-0.506035	-0.383424
H	-3.415133	-2.145588	0.019283	O	-0.937333	1.647990	-0.123454

Cartesian coordinates (Å) of the optimized structure for the radical cation of 2-methoxycarbonylanisole (**22**) (C_1 symmetry) calculated at the UB3LYP/6-31G(d) level.

Atom	X	Y	Z	Atom	X	Y	Z
C	3.103862	0.676625	-0.385098	H	-1.990118	-1.622855	-1.602576
C	3.754420	-0.504970	-0.687717	H	-0.539064	-0.617260	-1.706585
C	3.110419	-1.764333	-0.550396	H	1.896928	3.269244	-0.645227
C	1.808751	-1.833902	-0.089320	H	2.436466	3.066953	1.061459
C	1.105193	-0.650689	0.192639	H	0.785009	3.656582	0.704658
C	1.772018	0.623165	0.072132	H	-1.880841	1.438999	-1.406169
C	-0.240858	-0.695520	0.839312	H	-2.560795	0.498548	-2.737722
C	-1.535583	-0.683613	-1.262215	H	-4.352080	1.359511	-1.161644
C	1.590979	3.005710	0.371070	H	-4.342865	-0.396129	-1.266270
C	-2.414859	0.511511	-1.651934	H	-3.100977	1.293346	0.983076
C	-3.763357	0.469537	-0.916439	H	-4.519537	0.255190	1.117692
C	-3.559530	0.371373	0.603150	H	-2.412412	-0.835776	2.030487
C	-2.664431	-0.818230	0.968525	H	-3.154961	-1.766507	0.715537
H	3.617858	1.624988	-0.481176	N	-1.398372	-0.761676	0.202851
H	4.783788	-0.471685	-1.031447	O	-0.060950	-0.698234	2.076807
H	3.646935	-2.670786	-0.810495	O	1.030800	1.673350	0.392836
H	1.314326	-2.791547	0.037046				

Cartesian coordinates (Å) of the optimized structure for the radical cation of 2-benzoylanisole (**24**) (C_1 symmetry) calculated at the UB3LYP/6-31G(d) level.

Atom	X	Y	Z	Atom	X	Y	Z
C	1.672433	0.016099	0.295882	H	0.931695	-1.058519	-1.436402
C	1.805880	-0.650698	-0.936626	H	3.172274	-1.296773	-2.466544
C	3.062972	-0.783849	-1.516361	H	5.165802	-0.359978	-1.325183
C	4.185082	-0.254043	-0.870663	H	4.935667	0.818384	0.847080
C	4.057620	0.411946	0.355298	H	2.686193	1.060579	1.891445
C	2.807047	0.550238	0.941124	H	-3.960892	0.556530	-0.916380
C	0.369138	0.175687	0.919410	H	-4.416084	-1.839099	-0.556510
C	-0.909502	-0.438495	0.397871	H	-2.669641	-3.342169	0.378766
C	-1.927270	0.433279	-0.149608	H	-0.453202	-2.438978	1.042130
C	-3.194449	-0.090147	-0.507133	H	-1.904792	3.613372	-0.822055
C	-3.444773	-1.428643	-0.298626	H	-2.772815	2.422109	-1.841811
C	-2.452280	-2.286147	0.254201	H	-3.344804	2.773486	-0.168055

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C	-1.207533	-1.784963	0.616688	O	0.130036	0.778748	1.964225
C	-2.474744	2.686528	-0.823886	O	-1.563427	1.690040	-0.300712

Cartesian coordinates (Å) of the optimized structure for the radical cation of 1,4-dimethoxy-2-nitrobenzene (**26**) (C_1 symmetry) calculated at the UB3LYP/6-31G(d) level.

Atom	X	Y	Z	Atom	X	Y	Z
C	-0.317932	0.564224	-0.007350	H	4.943648	0.000894	0.052685
C	1.049956	0.583530	-0.003881	H	3.768804	0.977653	-0.883881
C	1.758473	-0.650045	0.031324	H	3.750045	1.016961	0.920879
C	1.038900	-1.887848	0.044192	H	-3.086095	-2.340435	0.767839
C	-0.329083	-1.896635	0.010048	H	-4.225406	-1.358211	-0.205486
C	-1.060461	-0.670091	-0.021966	H	-2.986200	-2.352615	-1.036290
C	3.934460	0.406671	0.033185	N	-1.017952	1.870489	0.030640
C	-3.215704	-1.758869	-0.148027	O	-2.006777	1.936576	0.745391
H	1.560230	1.538479	-0.034678	O	-0.511280	2.772245	-0.624336
H	1.611302	-2.809147	0.070047	O	3.067101	-0.758635	0.049679
H	-0.863087	-2.839089	0.000011	O	-2.361449	-0.584377	-0.107079

Cartesian coordinates (Å) of the optimized structure for the radical cation of 4-methoxy-4'-nitro-1,1'-biphenyl (**29**) (C_1 symmetry) calculated at the UB3LYP/6-31G(d) level.

Atom	X	Y	Z	Atom	X	Y	Z
C	3.053573	1.398070	-0.298087	H	3.719165	-1.913337	0.429227
C	3.817829	0.217962	-0.043370	H	1.289712	-1.988623	0.442363
C	3.153434	-1.013905	0.218078	H	1.127379	2.246367	-0.506023
C	1.781153	-1.050612	0.212520	H	-0.749162	2.178181	0.422104
C	0.990648	0.119872	-0.030395	H	-3.219561	2.060076	0.428418
C	1.686291	1.345775	-0.281554	H	-3.063869	-2.145489	-0.414451
C	-0.459295	0.061652	-0.017297	H	-0.592612	-2.071736	-0.453654
C	-1.235092	1.232212	0.213728	H	7.025689	-0.293309	0.076663
C	-2.617991	1.180052	0.235901	H	5.878736	-1.124588	1.171699
C	-3.245249	-0.046909	0.008150	H	5.885269	-1.500818	-0.592077
C	-2.528834	-1.221395	-0.232320	N	-4.727269	-0.105051	0.022370
C	-1.145896	-1.165806	-0.235278	O	5.123320	0.377007	-0.073269
C	6.031338	-0.726260	0.165260	O	-5.238885	-1.208232	-0.133095
H	3.589363	2.317222	-0.509764	O	-5.320769	0.954620	0.188475

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Chapter 2

Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, Ö. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, and D. J. Fox, Gaussian, Inc., Wallingford CT, **2009**.

Chapter 3

Electrochemical Intramolecular C–H Amination: Synthesis of Benzoxazoles and Benzothiazoles

Abstract

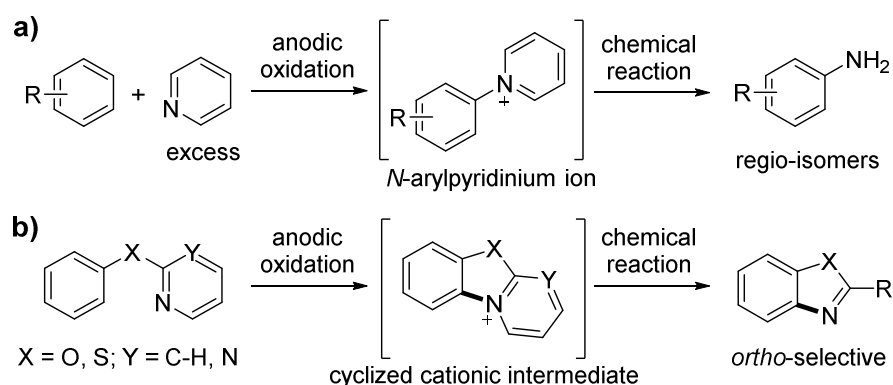
A new method for metal-free intramolecular C–H amination has been developed. Electrochemical oxidation of 2-pyrimidylloxybenzenes and 2-pyrimidylthiobenzenes, which can be easily prepared from phenols and thiophenols, respectively followed by the treatment of the resulting pyrimidinium ions with piperidine gives 2-aminobenzoxazoles and 2-aminobenzothiazoles, respectively.

Introduction

C–H amination¹ serves as powerful methods for synthesizing nitrogen-containing organic compounds, and a variety of transformations have been developed based on transition-metals,² hypervalent iodines,³ radical species.⁴ Electrochemical oxidation^{5,6} serves as a straightforward method for functionalizing C–H bond of aromatic compounds without using metal or chemical oxidant.⁷ Despite the usefulness of the method, it often suffers from overoxidation when the oxidation potential of the product is lower than that of the starting material,⁸ and this is often the case. Therefore, C–H amination of aromatic compounds by conventional electrochemical oxidation is usually difficult to achieve selectively. To solve the problem, the electrochemical intermolecular C–H amination of aromatic compounds via *N*-arylpyridinium ions was developed as described in chapter 2 (Scheme 1a).⁹

The key to the success of the method is the intermediacy of the electrooxidatively inactive cationic intermediates which avoid overoxidation. However, there is another problem, *i.e.* regioselectivity. Sometimes a mixture of regioisomers are produced. To solve this problem an intramolecularization approach¹⁰ is promising (Scheme 1b). In addition, resulting cyclized cationic intermediate could be converted to nitrogen containing heteroaromatics. This chapter describes that the intramolecular electrochemical C–H amination offers an intriguing way of making benzoxazoles and benzothiazoles from phenols and thiophenols, respectively.¹¹

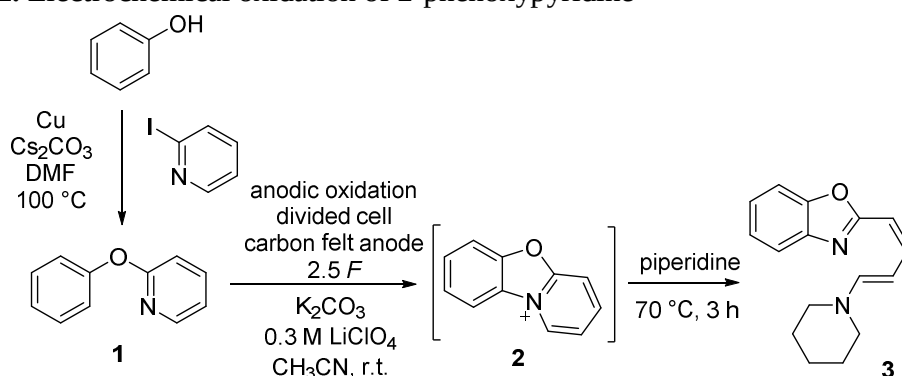
Scheme 1. Electrochemical C–H amination. (a) Intermolecular approach. (b) Intramolecular approach



Results and Discussions

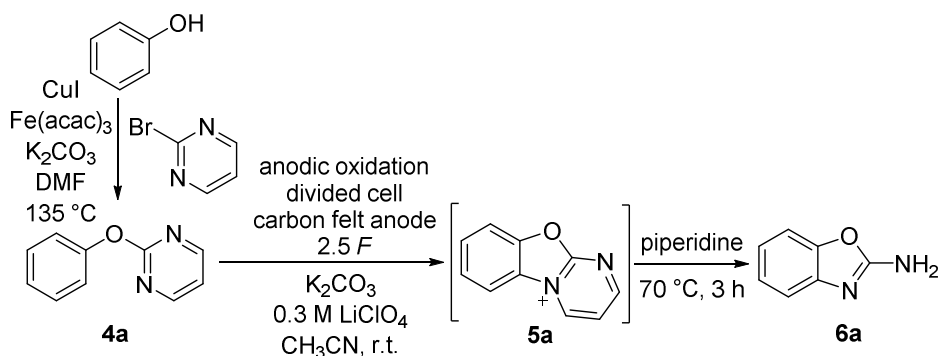
At first, electrochemical oxidation of 2-phenoxy pyridine (**1**), which can be easily prepared from phenol and a halopyridine in one step¹² was examined (Scheme 2). The anodic oxidation led to the formation of cyclized pyridinium ion **2**, which was characterized by NMR. Although treatment of **2** with piperidine gave the 2-substituted benzoxazole **3** in 60% yield, the synthetic utility of **3** seemed to be limited.

Scheme 2. Electrochemical oxidation of 2-phenoxy pyridine



To explore a more useful transformation, a transformation using a pyrimidine ring instead of a pyridine ring was designed as shown in Scheme 3. The starting 2-pyrimidyloxybenzene (**4a**) was prepared from phenol and 2-bromopyrimidine in one step.¹² The anodic oxidation of **4a** gave the cyclized pyrimidinium ion **5a**, which was characterized by NMR (Figure 1). Treatment of **5a** with piperidine gave 2-aminobenzoxazole (**6a**), which constitutes a key scaffold in therapeutically important molecules^{13,14} in 85% yield. The present transformation can be performed on 2.0 mmol scale (Table 1, entry 1).

Scheme 3. Electrochemical oxidation of 2-pyrimidyloxybenzene



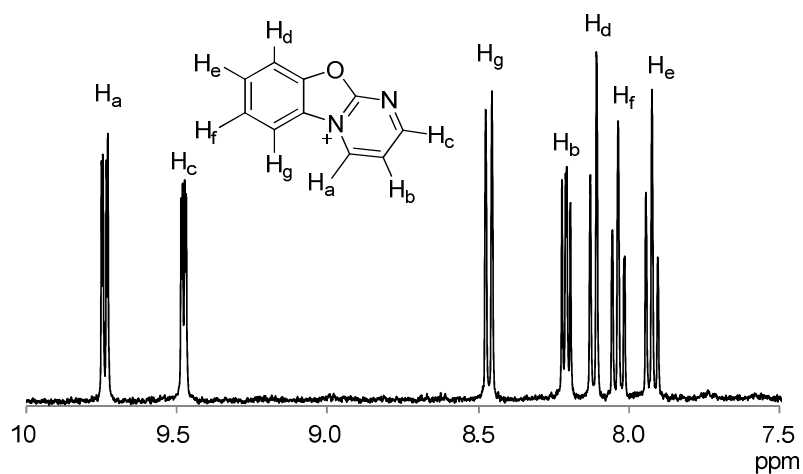
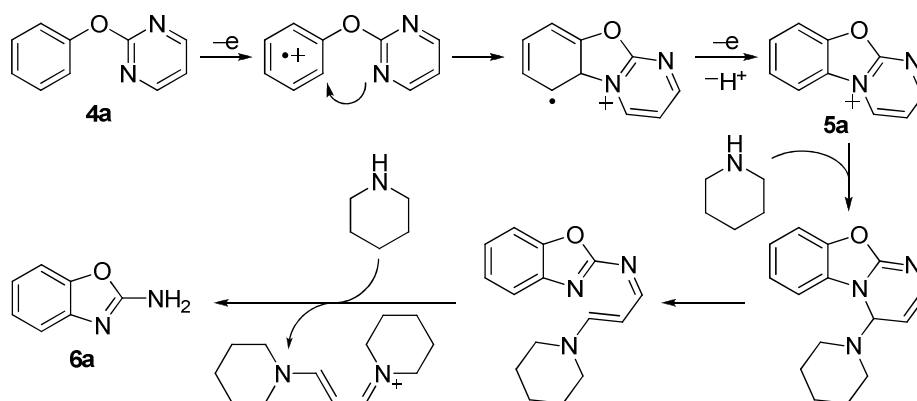


Figure 1. ^1H NMR spectrum of **5a**.

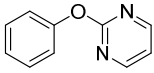
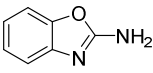
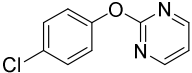
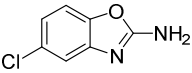
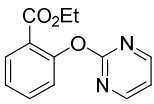
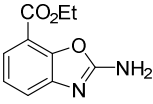
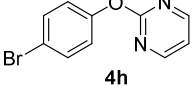
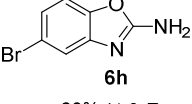
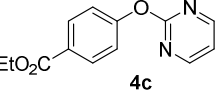
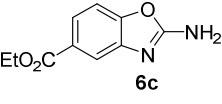
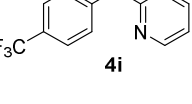
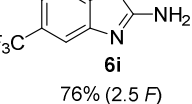
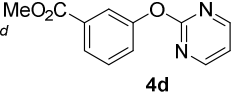
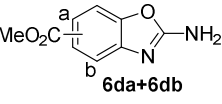
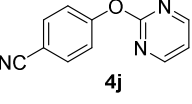
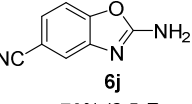
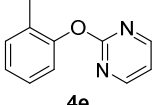
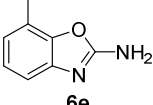
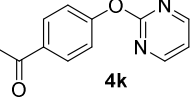
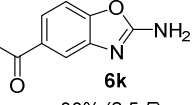
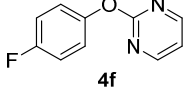
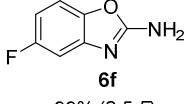
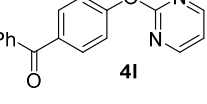
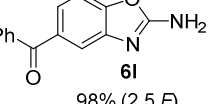
The following reaction mechanism seems to be reasonable (Scheme 4). One electron oxidation of **4a** gives the corresponding radical cation. The subsequent intramolecular attack of the nitrogen atom of the pyrimidine ring followed by one-electron oxidation and extrusion of a proton gives cyclized cationic intermediate **5a**. In the next step, the attack of piperidine to the carbon next to the positively charged nitrogen atom of **5a** followed by the ring opening and the attack of another molecule of piperidine on the resulting imine gives 2-aminobenzoxazole (**6a**). Because the oxidation potential of **6a** (0.88 V vs Ag/AgNO₃) is much lower than that of **4a** (1.57 V vs Ag/AgNO₃), intermediacy of the cationic species **5**, which is electrooxidatively inactive under the conditions, would be critical for the success of the reaction.



Scheme 4. A mechanism of electrochemical intramolecular C–H amination and the subsequent chemical reaction with piperidine.

As shown in Table 1, the present method is applicable to various substituted 2-pyrimidylxybenzenes to give the corresponding 2-aminobenzoxazoles in good yields. *o*- and *p*-Ethoxycarbonyl-substituted phenol derivatives **4b** and **4c** gave the corresponding 2-aminobenzoxazoles **6b** and **6c**, respectively (entries 2 and 3). The reaction of *m*-methoxycarbonyl-substituted phenol derivative **4d** gave a mixture of two regioisomers **6da** and **6db** (entry 4). The benzylic C–H group was not affected as shown in entry 5. The transformation is compatible with various functional groups such as halogen, trifluoromethyl, cyano, and ketone carbonyl groups (entries 5–12).

Table 1. Synthesis of 2-aminobenzoxazoles by electrochemical intramolecular C–H amination.^a

entry	starting material	product [yield ^b (electricity)]	entry	starting material	product [yield ^b (electricity)]
1		 85% (2.5 F) 92% ^b (2.5 F)	7 ^d		 82% (2.5 F)
2		 74% (2.5 F)	8 ^d		 68% (4.0 F)
3		 89% (2.5 F)	9 ^d		 76% (2.5 F)
4 ^d		 80% (a/b=1/1.0) (3.0 F)	10		 78% (2.5 F)
5 ^{d,e}		 48% (2.5 F)	11		 88% (2.5 F)
6		 99% (2.5 F)	12		 98% (2.5 F)

^a Compound **4** (0.2 mmol) was oxidized electrochemically in the presence of 0.6 mmol of K₂CO₃ in a 0.3 M solution of LiClO₄ in CH₃CN in an H-type divided cell under constant current conditions at room temperature unless otherwise stated, and the resulting solution was treated with piperidine (2.0 mmol) at 70 °C. ^b Isolated yields. ^c The transformation was performed on 2.0 mmol scale. ^d 1.0 M solution of LiClO₄ was used. ^e The electrolysis was carried out at 50 °C.

Next, the reaction of 2-pyrimidylthiobenzenes **7**, which were prepared from thiophenols and a halopyrimidine or from aryl halides and 2-pyrimidinethiol in one step,¹⁵ was examined. Electrochemical oxidation of **7** and the subsequent chemical reaction with piperidine gave 2-aminobenzothiazoles **8**, which also serve as an intriguing motif in medicinal chemistry.¹⁶ The results are summarized in Table 2. Notably, 2-aminobenzothiazoles are often used as precursors of 2-aminothiophenols, which are important intermediates for synthesis of bioactive molecules.¹⁷

Table 2. Synthesis of 2-aminobenzothiazoles by electrochemical intramolecular C–H amination.^a

entry	starting material	product [yield ^b (electricity)]	entry	starting material	product [yield ^b (electricity)]
1 ^{c,d}		 73% (2.5 F)	4 ^{c,d}		 84% (2.5 F)
2		 68% (4.0 F)	5 ^c		 75% (2.5 F)
3		 72% (2.5 F)	6		 80% (2.5 F)

^a Compound **7** (0.2 mmol) was oxidized electrochemically in the presence of 0.6 mmol of K₂CO₃ in a 0.3 M solution of LiClO₄ in CH₃CN in an H-type divided cell under constant current conditions at room temperature unless otherwise stated, and the resulting solution was treated with piperidines (2.0 mmol) at 70 °C. ^b Isolated yields. ^c 1.0 M solution of LiClO₄ was used. ^d The electrolysis was carried out at 50 °C.

The most popular protocols for synthesizing benzoxazoles and benzothiazoles involve the condensation of 2-aminophenol and 2-aminothiophenol, respectively, with either a carboxylic acid or aldehyde followed by intramolecular cyclization.¹⁸ Although protocols based on cyclization using C–H functionalization have also been developed,¹⁹ most of them involve intramolecular C–O or C–S coupling, and therefore aniline derivatives are required as starting materials.

In contrast, only a few examples that employ intramolecular C–H amination (C–N coupling) of substrates derived from phenols for constructing benzoxazoles have been reported. In 2011, Punniyamurthy and coworkers reported copper catalyzed intramolecular C–H amination of bisaryloxime ether to give 2-arylbenzoxazoles.¹¹ Although the method is useful for synthesizing 2-arylbenzoxazoles, multistep preparation of starting bisaryloxime ethers is required. In addition, the method cannot be applied to the synthesis of benzothiazoles. To the best of our knowledge, no example employs intramolecular C–H amination of thiophenol derivatives for constructing benzothiazoles. The present electrochemical transformation serves as a simple and powerful route to benzoxazoles and benzothiazoles via intramolecular C–H amination.

Conclusion

In conclusion, a powerful method for intramolecular C–H amination of aromatic compounds using the electrochemical method was developed. The present method provides metal- and chemical-oxidant-free routes to the benzoxazoles and benzothiazoles having a variety of functionality.

Experimental Section

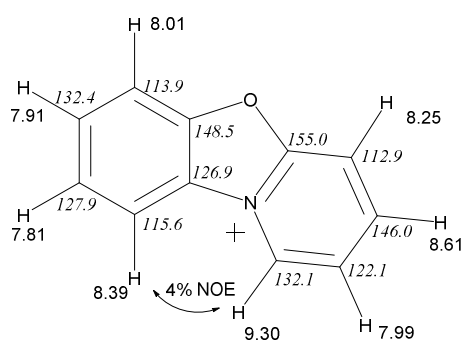
General: ¹H and ¹³C NMR spectra were recorded in CDCl₃ on Varian MERCURY plus-400 (¹H 400 MHz, ¹³C 100 MHz), or JEOL ECA-600P spectrometer (¹H 600 MHz, ¹³C 150 MHz). Mass spectra were obtained on JEOL JMS SX-102A mass spectrometer. IR spectra were measured with a Shimadzu IRAffinity (FTIR). Merck precoated silica gel F₂₅₄ plates (thickness 0.25 mm) was used for thin-layer chromatography (TLC) analysis. Flash chromatography was carried out on a silica gel (Kanto Chem. Co., Silica Gel N, spherical, neutral, 40-100 μm). Preparative gel permeation chromatography (GPC) was carried out on Japan Analytical Industry LC-918 equipped with JAIGEL-1H and 2H using CHCl₃ as an eluent. All reactions were carried out under argon atmosphere unless otherwise noted. Unless otherwise noted, all materials were obtained from commercial suppliers and used without further purification.

Electrochemical intramolecular C-H amination of 2-pyridyloxybenzene (1).

2-Pyridyloxybenzene (**1**) was prepared according to the reported procedure.²⁰

NMR analysis of the cationic intermediate 2.

The anodic oxidation was carried out using an H-type divided cell (4G glass filter) equipped with a carbon felt anode (Nippon Carbon JF-20-P7, ca. 160 mg, dried at 300 °C/1 mmHg for 4 h before use) and a platinum plate cathode (20 mm × 20 mm). In the anodic chamber was placed a solution of 2-pyrimidylxybenzene (**1**) (0.20 mmol) and K₂CO₃ (0.6 mmol) in 0.3 M LiClO₄/CH₃CN (10.0 mL). In the cathodic chamber were placed trifluoromethanesulfonic acid (150 μL) and 0.3 M LiClO₄/CH₃CN (10.0 mL). The constant current electrolysis (8.0 mA) was carried out at room temperature with magnetic stirring. After the electrolysis (2.5 F), the reaction mixture was transferred to a round-bottom flask. After removal of the solvent under reduced pressure, the intermediate **2** was observed by NMR analysis using CD₃CN as solvent.



¹H NMR (400 MHz, CD₃CN): δ 7.81 (ddd, *J* = 1.2, 7.6, 8.4 Hz, 1H), 7.91 (ddd, *J* = 1.2, 7.6, 8.8 Hz, 1H), 7.99 (ddd, *J* = 0.8, 6.4, 7.6 Hz, 1H), 8.01 (ddd, *J* = 0.8, 1.2, 8.8 Hz, 1H), 8.25 (ddd, *J* = 0.8, 0.8, 9.2 Hz, 1H), 8.39 (ddd, *J* = 0.8, 1.2, 8.4 Hz, 1H), 8.61 (ddd, *J* = 1.2, 7.6, 9.2 Hz, 1H), 9.30 (ddd, *J* = 0.8, 1.2, 6.4 Hz, 1H); ¹³C NMR (150 MHz, CD₃CN): δ 112.9, 113.9, 115.6, 121.1, 126.9, 127.9, 132.1, 132.4, 146.0, 148.5, 155.0.

The ¹H NMR and ¹³C NMR signals were assigned to the each protons and carbons, respectively by COSY, NOE, HMQC, and HMBC analyses.

Electrochemical oxidation of 2-pyridyloxybenzene (1**) followed by treatment with piperidine.**

The anodic oxidation was carried out using an H-type divided cell (4G glass filter) equipped with a carbon felt anode (Nippon Carbon JF-20-P7, ca. 160 mg, dried at 300 °C/1 mmHg for 4 h before use) and a platinum plate cathode (20 mm × 20 mm). In the anodic chamber was placed a solution of 2-phenoxybenzene (**1**) (0.20 mmol) and K₂CO₃ (0.6 mmol) in LiClO₄/CH₃CN (0.3 M, 10.0 mL). In the cathodic chamber were placed trifluoromethanesulfonic acid (150 μL) and LiClO₄/CH₃CN (0.3 M, 10.0 mL). The constant current electrolysis (8.0 mA) was carried out at room temperature with magnetic stirring. After the electrolysis (2.5 F), piperidine (200 μL) was added to the reaction mixture. The

reaction mixture was transferred to a round-bottom flask and stirred at 70 °C for 3 h. After removal of the solvent under reduced pressure, H₂O (20 mL) and ethyl acetate (10 mL) were added to the mixture. The mixture was extracted with ethyl acetate/hexane (2/1, 20 mL x 3), and the combined extracts were washed with water (20 mL) and brine (20 mL), and was dried over Na₂SO₄. After removal of the solvent under reduced pressure, the crude product was purified with flash chromatography to obtain the 2-substituted benzoxazole **3** (30.3 mg, 60%) as yellow solid.

1-Piperidino-4-(2-benzoxazolyl)buta-1,3-diene (3). ¹H NMR (400 MHz, CDCl₃): δ 1.58-1.63 (m, 6H), 3.10-3.20 (m, 4H), 5.37 (dd, *J* = 11.6, 12.8 Hz, 1H), 6.02 (d, *J* = 14.8 Hz, 1H), 6.59 (d, *J* = 12.8 Hz, 1H), 7.15-7.25 (m, 2H) 7.38-7.55 (m, 2H), 7.56 (d, *J* = 8.0 Hz, 1H); ¹³C NMR (150 MHz, CDCl₃): δ 24.1, 25.3, 49.6, 97.5, 103.0, 109.4, 118.3, 123.2, 123.8, 142.7, 142.8, 148.8, 150.2, 165.5; HRMS (APCI): calcd. for [M+H]⁺ C₁₆H₁₉N₂O, 255.1492; found, 255.1490.

Preparation of 4.

To the 50 mL flask, phenol derivative (1 equiv), 2-bromopyrimidine (1.5 equiv), CuI (15 mol%), Fe(acac)₃ (30 mol%), K₂CO₃ (2.5 equiv), and DMF (0.5 M) were added. The mixture was stirred at 135 °C for 24 h. After removal of the solvent under reduced pressure, the crude product was purified with flash chromatography to obtain **4**.

2-Pyrimidinylloxybenzene (4a). Reaction of phenol (15 mmol) with 2-bromopyrimidine gave the title compound (1.83 g, 88%) as white solid, which was identified by comparison with their NMR spectra reported in the literature.^{12a}

2-Ethoxycarbonyl(2-pyrimidinylloxy)benzene (4b). Reaction of ethyl 2-hydroxybenzoate (2 mmol) with 2-bromopyrimidine gave the title compound (215 mg, 44%) as white solid. ¹H NMR (400 MHz, DMSO-d₆): δ 0.95 (t, *J* = 7.2 Hz, 3H), 4.01 (q, *J* = 7.1 Hz, 2H), 7.23 (t, *J* = 4.6 Hz, 1H), 7.33 (d, *J* = 8.0 Hz, 1H), 7.42 (t, *J* = 8.0 Hz, 1H), 7.67-7.72 (m, 1H), 7.92-7.95 (m, 1H), 8.60 (d, *J* = 4.8 Hz, 2H); ¹³C NMR (100 MHz, DMSO-d₆): δ 13.5, 60.5, 116.5, 123.9, 124.0, 125.7, 131.3, 134.2, 151.5, 159.7, 164.3, 164.8; HRMS (ESI): calcd. for [M+H]⁺ C₁₃H₁₃N₂O₃, 245.0921; found, 245.0918.

4-Ethoxycarbonyl(2-pyrimidinylloxy)benzene (4c). Reaction of ethyl 4-hydroxybenzoate (2 mmol) with 2-bromopyrimidine gave the title compound (188 mg, 38%) as white solid. ¹H NMR (400 MHz, DMSO-d₆): δ 1.31 (t, *J* = 7.2 Hz, 3H), 4.31 (q, *J* = 7.1 Hz, 2H),

7.29-7.35 (m, 3H), 8.01 (dd, $J = 2.0$ Hz 6.8 Hz, 2H), 8.66 (d, $J = 4.8$ Hz, 2H); ^{13}C NMR (100 MHz, DMSO- d_6): δ 14.1, 60.7, 117.4, 121.7, 126.6, 130.9, 156.6, 160.1, 164.1, 165.0; HRMS (ESI): calcd. for $[\text{M}+\text{H}]^+$ $\text{C}_{13}\text{H}_{13}\text{N}_2\text{O}_3$, 245.0921; found, 245.0918.

3-Methoxycarbonyl(2-pyrimidinylloxy)benzene (4d). Reaction of methyl 3-hydroxybenzoate (4 mmol) with 2-bromopyrimidine gave the title compound (151 mg, 16%) as white solid. ^1H NMR (400 MHz, DMSO- d_6): δ 3.86 (s, 3H), 7.29 (t, $J = 4.8$ Hz, 1H), 7.51-7.54 (m, 1H), 7.61 (t, $J = 7.8$ Hz, 1H), 7.71-7.73 (m, 1H), 7.86 (d, $J = 7.6$ Hz, 1H), 8.65 (d, $J = 4.8$ Hz, 2H); ^{13}C NMR (100 MHz, DMSO- d_6): δ 52.3, 117.2, 122.2, 125.9, 126.7, 130.2, 131.2, 152.8, 160.1, 164.4, 165.4; HRMS (ESI): calcd. for $[\text{M}+\text{H}]^+$ $\text{C}_{12}\text{H}_{11}\text{N}_2\text{O}_3$, 231.0764; found, 231.0761.

2-Methyl(2-pyrimidinylloxy)benzene (4e). Reaction of 2-methylphenol (10 mmol) with 2-bromopyrimidine gave the title compound (1.63 g, 88%) as white solid, which was identified by comparison with their NMR spectra reported in the literature.²¹

4-Fluoro(2-pyrimidinylloxy)benzene (4f). Reaction of 4-fluorophenol (2 mmol) with 2-bromopyrimidine gave the title compound (340 mg, 89%) as white solid. ^1H NMR (400 MHz, DMSO- d_6): δ 7.24-7.28 (m, 5H), 8.64 (d, $J = 4.8$ Hz, 2H); ^{13}C NMR (100 MHz, DMSO- d_6): δ 116.1 (d, $J = 23$ Hz), 116.9, 123.4 (d, $J = 8.3$ Hz), 148.8, 159.2 (d, $J = 240$ Hz), 160.0, 164.7; HRMS (ACPI): calcd. for $[\text{M}+\text{H}]^+$ $\text{C}_{10}\text{H}_8\text{FN}_2\text{O}$, 191.0615; found, 191.0610.

4-Chloro(2-pyrimidinylloxy)benzene (4g). Reaction of 4-chlorophenol (2 mmol) with 2-bromopyrimidine gave the title compound (400 mg, 97%) as white solid. ^1H NMR (400 MHz, DMSO- d_6): δ 7.24-7.30 (m, 3H), 7.47-7.51 (m, 2H), 8.65 (d, $J = 4.4$ Hz, 2H); ^{13}C NMR (100 MHz, DMSO- d_6): δ 117.0, 123.6, 129.2, 129.5, 151.5, 160.0, 164.4; HRMS (ESI): calcd. for $[\text{M}+\text{H}]^+$ $\text{C}_{10}\text{H}_8\text{ClN}_2\text{O}$, 207.0320; found, 207.0317.

4-Trifluoromethyl(2-pyrimidinylloxy)benzene (4i). Reaction of 4-trifluoromethylphenol (2 mmol) with 2-bromopyrimidine gave the title compound (321 mg, 67%) as white solid. ^1H NMR (400 MHz, DMSO- d_6): δ 7.32 (t, $J = 4.8$ Hz, 1H), 7.45 (d, $J = 8.8$ Hz, 2H), 7.82 (d, $J = 8.8$ Hz, 2H), 8.68 (d, $J = 4.8$ Hz, 2H); ^{13}C NMR (100 MHz, DMSO- d_6): δ 117.4, 122.5, 124 (q, $J = 270$ Hz), 125.7 (q, $J = 32$ Hz), 127.0, (q, $J = 3.7$ Hz), 155.7, 160.1, 164.1; HRMS (ACPI): calcd. for $[\text{M}+\text{H}]^+$ $\text{C}_{11}\text{H}_8\text{F}_3\text{N}_2\text{O}$, 241.0583; found, 241.0578.

4-Cyano(2-pyrimidinylloxy)benzene (4j). Reaction of 4-cyanophenol (4 mmol) with 2-bromopyrimidine gave the title compound (340 mg, 57%) as white solid, which was identified by comparison with their NMR spectra reported in the literature.²²

4-Acetyl(2-pyrimidinylloxy)benzene (4k). Reaction of 4-hydroxybenzophenone (2 mmol) with 2-bromopyrimidine gave the title compound (229 mg, 52%) as white solid. ¹H NMR (400 MHz, DMSO-d₆): δ 2.58 (s, 3H), 7.30-7.35 (m, 3H), 8.02 (d, *J* = 8.8 Hz, 2H), 8.66 (d, *J* = 4.8 Hz, 2H); ¹³C NMR (100 MHz, DMSO-d₆): δ 26.7, 117.4, 121.6, 130.1, 133.8, 156.5, 160.1, 164.2, 196.7; HRMS (ESI): calcd. for [M+H]⁺ C₁₂H₁₁N₂O₂, 215.0815; found, 218.0813.

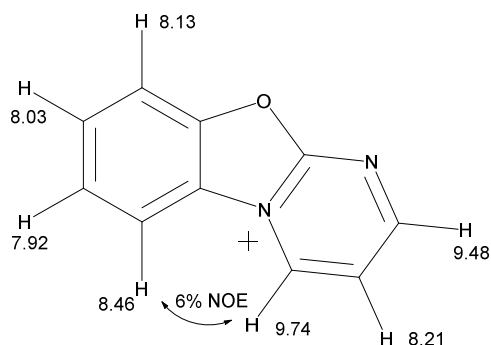
4-Benzoyl(2-pyrimidylloxy)benzene (4l). Reaction of 4-hydroxybenzophenone (2 mmol) with 2-bromopyrimidine gave the title compound (327 mg, 59%) as white solid. ¹H NMR (400 MHz, DMSO-d₆): δ 7.33 (t, *J* = 4.8 Hz, 1H), 7.39 (d, *J* = 8.4 Hz, 2H), 7.58 (t, *J* = 7.8 Hz, 2H), 7.69 (t, *J* = 7.8 Hz, 1H), 7.76 (d, *J* = 8.4 Hz, 2H), 7.83 (d, *J* = 8.4 Hz, 2H), 8.70 (d, *J* = 4.8 Hz, 2H); ¹³C NMR (100 MHz, DMSO-d₆): δ 117.4, 121.6, 128.5, 129.4, 131.6, 132.5, 133.7, 137.0, 156.2, 160.2, 164.2, 194.6; HRMS (ESI): calcd. for [M+H]⁺ C₁₇H₁₃N₂O₂, 277.0972; found, 277.0969.

4-Bromo(2-pyrimidinylloxy)benzene (4h). To the 50 mL flask, 4-bromophenol (3 mmol), 2-chloropyrimidine (10 mmol), K₂CO₃ (20 mmol), and DMF (5 mL) were added. The mixture was stirred at 135 °C for 24 h. After removal of the solvent under reduced pressure, the crude product was purified with flash chromatography to obtain the title compound (347 mg, 46%) as white solid. ¹H NMR (400 MHz, DMSO-d₆): δ 7.19 (d, *J* = 8.8 Hz, 2H), 7.28 (t, *J* = 4.8 Hz, 1H), 7.62 (d, *J* = 8.8 Hz, 2H), 8.65 (d, *J* = 4.8 Hz, 2H); ¹³C NMR (100 MHz, DMSO-d₆): δ 117.1, 117.3, 124.0, 132.4, 152.0, 160.0, 164.3; HRMS (ESI): calcd. for [M+H]⁺ C₁₀H₈BrN₂O, 250.9815; found, 250.9811.

NMR analysis of the cationic intermediate 5a.

The anodic oxidation was carried out using an H-type divided cell (4G glass filter) equipped with a carbon felt anode (Nippon Carbon JF-20-P7, ca. 160 mg, dried at 300 °C/1 mmHg for 4 h before use) and a platinum plate cathode (20 mm × 20 mm). In the anodic chamber was placed a solution of 2-pyrimidinylloxybenzene (**4a**) (0.20 mmol) and K₂CO₃ (0.6 mmol) in 0.3 M LiClO₄/CH₃CN (10.0 mL). In the cathodic chamber were placed trifluoromethanesulfonic acid (150 μL) and 0.3 M LiClO₄/CH₃CN (10.0 mL). The constant

current electrolysis (8.0 mA) was carried out at room temperature with magnetic stirring. After the electrolysis (2.5 *F*), the reaction mixture was transferred to a round-bottom flask. After removal of the solvent under reduced pressure, the intermediate **5a** was observed by NMR analysis using CD₃CN as solvent.



¹H NMR (400 MHz, CD₃CN): δ 7.92 (t, *J* = 8.4 Hz, 1H), 8.03 (t, *J* = 8.4 Hz, 1H), 8.13 (d, *J* = 8.4 Hz, 1H), 8.21 (dd, *J* = 4.8, 6.8 Hz, 1H), 8.46 (d, *J* = 8.4 Hz, 1H), 9.48 (dd, *J* = 2.0, 4.8 Hz, 1H), 9.74 (dd, *J* = 2.0, 6.8 Hz, 1H). The ¹H NMR signals were assigned to each proton as shown in Figure by COSY analysis and NOE analysis.

Electrochemical oxidation of 2-pyrimidylbenzenes **4** followed by treatment with piperidine.

General Procedure. The anodic oxidation was carried out using an H-type divided cell (4G glass filter) equipped with a carbon felt anode (Nippon Carbon JF-20-P7, ca. 160 mg, dried at 300 °C/1 mmHg for 4 h before use) and a platinum plate cathode (20 mm × 20 mm). In the anodic chamber was placed a solution of substrate **4** (0.20 mmol) and K₂CO₃ (0.6 mmol) in LiClO₄/CH₃CN (0.3 M or 1.0 M, 10.0 mL). In the cathodic chamber were placed trifluoromethanesulfonic acid (150 μL) and LiClO₄/CH₃CN (0.3 M or 1.0 M, 10.0 mL). The constant current electrolysis (8.0 mA) was carried out at room temperature or 50 °C with magnetic stirring. After the electrolysis (2.5–4.0 *F*), piperidine (200 μL) was added to the reaction mixture. The reaction mixture was transferred to a round-bottom flask and stirred at 70 °C for 3 h. After removal of the solvent under reduced pressure, H₂O (20 mL) and ethyl acetate (10 mL) were added to the mixture. The mixture was extracted with ethyl acetate/hexane (2/1, 20 mL × 3), and the combined extracts were washed with water (20 mL) and brine (20 mL), and was dried over Na₂SO₄. After removal of the solvent under reduced pressure, the crude product was purified with flash chromatography or preparative GPC to obtain **6**.

2-Aminobenzoxazole (6a). Electrochemical oxidation (2.5 *F*, r.t.) of 2-pyrimidinylbenzene (**4a**) (0.20 mmol) in a 0.3 M solution of LiClO₄ in CH₃CN and subsequent treatment with piperidine gave the title compound (22.8 mg, 85%) as white solid, which was identified by comparison with their NMR spectra reported in the literature.²³

2-Amino-7-ethoxycarbonylbenzoxazole (6b). Electrochemical oxidation (2.5 *F*, r.t.) of ethyl 2-(2-pyrimidinylloxy)benzoate (**4b**) (0.20 mmol) in a 0.3 M solution of LiClO₄ in CH₃CN and subsequent treatment with piperidine gave the title compound (30.7 mg, 74%) as white solid. ¹H NMR (400 MHz, DMSO-*d*₆): δ 1.33 (t, *J* = 7.2 Hz, 3H), 4.33 (q, *J* = 7.1 Hz, 2H), 7.18 (t, *J* = 8.0 Hz, 1H), 7.41-7.47 (m, 2H), 7.62 (br, 2H); ¹³C NMR (150 MHz, DMSO-*d*₆): δ 14.1, 60.6, 112.5, 119.7, 120.9, 123.3, 145.1, 147.0, 163.4, 163.6; HRMS (ESI): calcd. for [M+H]⁺ C₁₀H₁₁N₂O₃, 207.0764; found, 207.0757.

2-Amino-5-ethoxycarbonylbenzoxazole (6c). Electrochemical oxidation (2.5 *F*, r.t.) of ethyl 4-(2-pyrimidinylloxy)benzoate (**4c**) (0.20 mmol) in a 0.3 M solution of LiClO₄ in CH₃CN and subsequent treatment with piperidine gave the title compound (36.6 mg, 89%) as white solid. ¹H NMR (400 MHz, DMSO-*d*₆): δ 1.30 (t, *J* = 7.0 Hz, 3H), 4.27 (q, *J* = 7.2 Hz, 2H), 7.41 (d, *J* = 8.4 Hz, 1H), 7.61-7.71 (m, 4H); ¹³C NMR (150 MHz, DMSO-*d*₆): δ 14.2, 60.6, 108.4, 115.7, 122.1, 125.6, 143.9, 151.2, 163.7, 165.9; HRMS (ESI): calcd. for [M+H]⁺ C₁₀H₁₁N₂O₃, 207.0764; found, 207.0761.

2-Amino-6-methoxycarbonylbenzoxazole (6da) and 2-amino-4-methoxycarbonylbenzoxazole (6db). Electrochemical oxidation (3.0 *F*, r.t.) of methyl 3-(2-pyrimidinylloxy)benzoate (**4d**) (0.20 mmol) in a 1.0 M solution of LiClO₄ in CH₃CN and subsequent treatment with piperidine gave **6da** (15.6 mg, 40%) and **6db** (15.3 mg, 40%) as white solids. Compound **6da** was identified by comparison with their NMR spectra reported in the literature.²⁴ **6db**: ¹H NMR (400 MHz, DMSO-*d*₆): δ 3.82 (s, 3H), 7.03 (t, *J* = 8.0 Hz, 1H), 7.55 (d, *J* = 8.0 Hz, 1H), 7.64 (d, *J* = 8.0 Hz, 1H), 7.86 (s, 2H); ¹³C NMR (100 MHz, DMSO-*d*₆): δ 51.6, 112.3, 116.6, 119.1, 125.1, 144.2, 148.8, 164.1, 165.7; HRMS (ESI): calcd. for [M+H]⁺ C₉H₉N₂O₃, 193.0608; found, 193.0603.

2-Amino-7-methylbenzoxazole (6e). Electrochemical oxidation (2.5 *F*, 50 °C.) of 2-methyl(2-pyrimidinylloxy)benzene (**4e**) (0.20 mmol) in a 1.0 M solution of LiClO₄ in CH₃CN and subsequent treatment with piperidine gave the title compound (14.2 mg, 48%) as white solid. ¹H NMR (400 MHz, CDCl₃): δ 2.41 (s, 3H), 4.20-6.00 (br, 2H), 6.88 (d, *J* = 7.6 Hz, 1H), 7.08 (dd, *J* = 7.6, 8.0 Hz, 1H), 7.17 (d, *J* = 8.0 Hz, 1H); ¹³C NMR (150 MHz, CDCl₃): δ 14.8, 113.6, 119.6, 123.0, 124.0, 141.1, 147.3, 161.5; HRMS (ESI): calcd. for [M+H]⁺ C₈H₉N₂O, 147.0709; found, 147.0707.

2-Amino-5-fluorobenzoxazole (6f). Electrochemical oxidation (2.5 *F*, r.t.) of 4-fluoro(2-pyrimidinylloxy)benzene (**4f**) (0.20 mmol) in a 0.3 M solution of LiClO₄ in CH₃CN and subsequent treatment with piperidine gave the title compound (31.1 mg,

>99%) as white solid. ^1H NMR (400 MHz, CDCl_3): δ 4.80-6.40 (br, 2H), 6.77(dt, J = 2.8, 8.8 Hz, 1H), 7.03 (dd, J = 2.8, 8.8 Hz, 1H), 7.15-7.19 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 103.6 (d, J = 26 Hz), 108.0 (d, J = 26 Hz), 109.0 (d, J = 10 Hz), 143.3 (d, J = 13 Hz), 144.7, 160.1 (d, J = 240 Hz), 163.0; HRMS (ESI): calcd. for $[\text{M}+\text{H}]^+$ $\text{C}_7\text{H}_6\text{N}_2\text{OF}$ 153.0459; found, 153.0455.

2-Amino-5-chlorobenzoxazole (6g). Electrochemical oxidation (2.5 F , r.t.) of 4-chloro(2-pyrimidinyloxy)benzene (**4g**) (0.20 mmol) in a 1.0 M solution of LiClO_4 in CH_3CN and subsequent treatment with piperidine gave the title compound (27.5 mg, 82%) as white solid, which was identified by comparison with their NMR spectra reported in the literature.²⁴

2-Amino-5-bromobenzoxazole (6h). Electrochemical oxidation (4.0 F , r.t.) of 4-bromo(2-pyrimidinyloxy)benzene (**4h**) (0.20 mmol) in a 1.0 M solution of LiClO_4 in CH_3CN and subsequent treatment with piperidine gave the title compound (29.1 mg, 68%) as white solid, which was identified by comparison with their NMR spectra reported in the literature.²⁵

2-Amino-5-trifluoromethylbenzoxazole (6i). Electrochemical oxidation (2.5 F , r.t.) of 4-trifluoromethyl(2-pyrimidinyloxy)benzene (**4i**) (0.20 mmol) in a 1.0 M solution of LiClO_4 in CH_3CN and subsequent treatment with piperidine gave the title compound (30.8 mg, 76%) as white solid. ^1H NMR (400 MHz, CDCl_3): δ 4.80-6.40 (br, 2H), 7.30-7.46 (br, 2H), 7.64 (br, 1H); ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$): δ 109.9, 112.6, 118.6, 125.2 (q, J = 260 Hz), 125.7 (q, J = 31 Hz), 144.3, 150.9, 165.0 (br); HRMS (ESI): calcd. for $[\text{M}+\text{H}]^+$ $\text{C}_8\text{H}_6\text{N}_2\text{OF}_3$ 203.0427; found, 203.0420.

2-Amino-5-cyanobenzoxazole (6j). Electrochemical oxidation (2.5 F , r.t.) of 4-cyano(2-pyrimidinyloxy)benzene (**4j**) (0.20 mmol) in a 0.3 M solution of LiClO_4 in CH_3CN and subsequent treatment with piperidine gave the title compound (24.8 mg, 78%) as white solid. ^1H NMR (400 MHz, CDCl_3): δ 7.42 (d, J = 8.4 Hz, 1H), 7.51 (d, J = 8.4 Hz, 1H), 7.63 (s, 1H), 7.80 (s, 2H); ^{13}C NMR (150 MHz, CDCl_3): δ 106.1, 109.6, 119.4, 119.5, 125.0, 144.4, 150.8, 164.0; HRMS (ESI): calcd. for $[\text{M}+\text{H}]^+$ $\text{C}_8\text{H}_6\text{N}_3\text{O}$, 160.0505; found, 160.0501.

2-Amino-5-acetylbenzoxazole (6k). Electrochemical oxidation (2.5 F , r.t.) of 4-acetyl(2-pyrimidinyloxy)benzene (**4k**) (0.20 mmol) in a 0.3 M solution of LiClO_4 in CH_3CN and subsequent treatment with piperidine gave the title compound (31.1 mg, 88%)

as white solid. ^1H NMR (400 MHz, CDCl_3): δ 2.56 (s, 3H), 7.42 (d, J = 8.4 Hz, 1H), 7.62-7.64 (m, 3H), 7.75 (s, 1H), 7.80 (d, J = 1.6 Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 26.8, 108.2, 115.0, 121.4, 133.1, 143.9, 151.1, 163.5, 197.2; HRMS (ESI): calcd. for $[\text{M}+\text{H}]^+$ $\text{C}_9\text{H}_9\text{N}_2\text{O}_2$, 177.0659; found, 177.0654.

2-Amino-5-benzoylbenzoxazole (6l). Electrochemical oxidation (2.5 F , r.t.) of 4-(2-pyrimidinylloxy)benzophenone (**4l**) (0.20 mmol) in a 0.3 M solution of LiClO_4 in CH_3CN and subsequent treatment with piperidine gave the title compound (46.9 mg, 98%) as white solid. ^1H NMR (400 MHz, CDCl_3): δ 5.71(s, 2H), 7.35 (d, J = 8.4 Hz, 1H), 7.46-7.51 (m, 2H), 7.57-7.64 (m, 2H), 7.79-7.82 (m, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 108.7, 118.7, 124.7, 128.2, 130.0, 132.2, 134.1, 138.0, 142.7, 151.5, 162.5, 196.4; HRMS (ESI): calcd. for $[\text{M}+\text{H}]^+$ $\text{C}_{14}\text{H}_{11}\text{N}_2\text{O}_2$, 239.0815; found, 239.0808.

2.0 mmol scale synthesis of 2-aminobenzoxazole (6a)

The anodic oxidation was carried out using an H-type divided cell (4G glass filter) equipped with a carbon felt anode (Nippon Carbon JF-20-P7, ca. 500 mg, dried at 300 °C/1 mmHg for 4 h before use) and a platinum plate cathode (20 mm $\times$ 20 mm). In the anodic chamber was placed a solution of substrate **4a** (2.0 mmol) and K_2CO_3 (6.0 mmol) in $\text{LiClO}_4/\text{CH}_3\text{CN}$ (1.0 M, 50 mL). In the cathodic chamber were placed trifluoromethanesulfonic acid (1.0 mL) and $\text{LiClO}_4/\text{CH}_3\text{CN}$ (1.0 M, 50 mL). The constant current electrolysis (40 mA) was carried out at room temperature with magnetic stirring. After the electrolysis (2.5 F), piperidine (2.0 mL) was added to the reaction mixture. The reaction mixture was transferred to a round-bottom flask and stirred at 70 °C for 3 h. After removal of the solvent under reduced pressure, H_2O (40 mL) and ethyl acetate (10 mL) were added to the mixture. The mixture was extracted with ethyl acetate/hexane (2/1, 30 mL $\times$ 3), and the combined extracts were washed with water (20 mL) and brine (20 mL), and was dried over Na_2SO_4 . After removal of the solvent under reduced pressure, the crude product was purified with flash chromatography **6a** (248 mg, 92%).

Preparation of 7.

Method A: To the 200 mL flask, thiophenol (10 mmol), 2-halopyrimidine (10 mmol), and H_2O (50 mL) were added. The mixture was stirred at 100 °C for 24 h. The mixture was extracted with $\text{EtOAc}/\text{Hexane}$ = 2/1 (20 mL $\times$ 3), and was dried over Na_2SO_4 . After removal of the solvent under reduced pressure, the crude product was purified with flash chromatography to obtain **7**.

2-Pyrimidinylthiobenzene (7a). Reaction of thiophenol with 2-chloropyrimidine gave the title compound (450 mg, 24%) as white solid, which was identified by comparison with their NMR spectra reported in the literature.²⁶

4-Fluoro(2-pyrimidinylthio)benzene (7c). Reaction of 4-fluorothiophenol with 2-bromopyrimidine gave the title compound (1.57 g, 76%) as white solid. ¹H NMR (400 MHz, CDCl₃): δ 6.97 (t, *J* = 4.8 Hz, 1H), 7.12-7.16 (m, 2H), 7.58-7.63 (m, 2H), 8.48 (d, *J* = 4.8 Hz, 2H); ¹³C NMR (150 MHz, CDCl₃): δ 116.4 (d, *J* = 22 Hz), 117.0, 124.6, 137.4 (d, *J* = 8.7 Hz) 157.5, 163.4 (d, *J* = 250 Hz), 172.6; HRMS (ESI): calcd. for [M+H]⁺ C₁₀H₈FN₂S, 207.0387; found, 207.0382.

Method B: To the 50 mL flask, aryl bromide (1 equiv), 2-pyrimidinethiol (1.0 equiv), CuI (20 mol%), Fe(acac)₃ (40 mol%), K₂CO₃ (1.6 equiv), and DMF (0.5 M) were added. The mixture was stirred at 135 °C for 24 h. After removal of the solvent under reduced pressure, the crude product was purified with flash chromatography to obtain 7.

4-Ethoxycarbonyl(2-pyrimidinylthio)benzene (7b). Reaction of ethyl 4-bromobenzoate (3 mmol) with 2-pyrimidinethiol gave the title compound (172 mg, 22%) as white solid. ¹H NMR (400 MHz, DMSO-*d*₆): δ 1.33 (t, *J* = 7.2 Hz, 3H), 4.33 (q, *J* = 7.1 Hz, 2H), 7.28 (t, *J* = 4.8 Hz, 1H), 7.75 (d, *J* = 8.4 Hz, 3H), 8.00 (d, *J* = 8.4 Hz, 2H), 8.62 (d, *J* = 4.8 Hz, 2H); ¹³C NMR (100 MHz, DMSO-*d*₆): δ 14.0, 60.9, 118.3, 129.6, 130.1, 134.5, 135.0, 158.2, 165.1, 170.0; HRMS (ESI): calcd. for [M+H]⁺ C₁₃H₁₃N₂O₂S, 261.0692; found, 261.0689.

4-Trifluoromethyl(2-pyrimidinylthio)benzene (7d). Reaction of 4-trifluoromethylthiophenol (4 mmol) with 2-bromopyrimidine gave the title compound (760 mg, 79%) as white solid. ¹H NMR (400 MHz, DMSO-*d*₆): δ 7.29 (t, *J* = 4.8 Hz, 1H), 7.79-7.86 (m, 4H), 8.63 (d, *J* = 4.8 Hz, 2H); ¹³C NMR (100 MHz, DMSO-*d*₆): δ 118.4, 121.2 (q, *J* = 270 Hz) 125.8 (m), 129.3 (q, *J* = 32 Hz), 134.4, 135.2, 158.2, 169.9; HRMS (ESI): calcd. for [M+H]⁺ C₁₁H₈F₃N₂S, 257.0355; found, 257.0348.

4-Cyano(2-pyrimidinylthio)benzene (7e). Reaction of 4-cyanophenol (5 mmol) with 2-bromopyrimidine gave the title compound (741 mg, 69%) as white solid, which was identified by comparison with their NMR spectra reported in the literature.²⁷

4-Benzoyl(2-pyrimidinylthio)benzene (7f). Reaction of 4-bromobenzophenone (5 mmol) with 2-pyrimidinethiol gave the title compound (882 mg, 60%) as white solid. ¹H NMR

(400 MHz, DMSO- d_6): δ 7.30 (t, J = 4.8 Hz, 1H), 7.58 (t, J = 7.8 Hz, 2H), 7.70 (t, J = 7.6 Hz, 1H), 7.71-7.80 (m, 6H), 8.65 (d, J = 4.8 Hz, 2H); ^{13}C NMR (100 MHz, DMSO- d_6): δ 118.3, 128.6, 129.6, 130.2, 132.8, 134.2, 134.4, 136.6, 137.1, 158.2, 170.0, 195.0; HRMS (ESI): calcd. for $[\text{M}+\text{H}]^+$ $\text{C}_{17}\text{H}_{13}\text{N}_2\text{OS}$, 293.0743; found, 293.0732.

Electrochemical oxidation of 2-pyrimidylthiobenzenes **7** followed by treatment with piperidine.

The reactions were carried out in a similar way to the general procedure for the reactions of **4**.

2-Aminobenzothiazole (8a). Electrochemical oxidation (2.5 F , 50 $^{\circ}\text{C}$) of 2-phenylthiopyrimidine (**7a**) (0.20 mmol) in a 1.0 M solution of LiClO_4 in CH_3CN and subsequent treatment with piperidine gave the title compound (21.8 mg, 73%) as white solid, which was identified by comparison with their NMR spectra reported in the literature.²⁸

2-Amino-5-ethoxycarbonylbenzothiazole (8b). Electrochemical oxidation (4.0 F , r.t.) of ethyl 4-(2-pyrimidinylthio)benzoate (**7b**) (0.20 mmol) in a 0.3 M solution of LiClO_4 in CH_3CN and subsequent treatment with piperidine gave the title compound (30.2 mg, 68%) as white solid. ^1H NMR (400 MHz, DMSO- d_6): δ 1.31 (t, J = 7.2 Hz, 3H), 4.30 (q, J = 7.2 Hz, 2H), 7.59 (dd, J = 2.0, 8.4 Hz, 1H), 7.71 (s, 2H), 7.80 (d, J = 8.4 Hz, 1H), 7.83 (d, J = 2.0 Hz, 1H); ^{13}C NMR (150 MHz, DMSO- d_6): δ 14.1, 60.5, 117.6, 120.9, 121.3, 127.3, 136.5, 152.9, 165.9, 167.4; HRMS (ESI): calcd. for $[\text{M}+\text{H}]^+$ $\text{C}_{10}\text{H}_{11}\text{N}_2\text{O}_2\text{S}$, 223.0536; found, 223.0533.

2-Amino-5-fluorobenzothiazole (8c). Electrochemical oxidation (2.5 F , r.t.) of 4-fluoro(2-pyrimidinylthio)benzene (**7c**) (0.20 mmol) in a 0.3 M solution of LiClO_4 in CH_3CN and subsequent treatment with piperidine gave the title compound (24.2 mg, 72%) as white solid, which was identified by comparison with their NMR spectra reported in the literatures.²⁹

2-Amino-5-trifluoromethylbenzothiazole (8d). Electrochemical oxidation (2.5 F , 50 $^{\circ}\text{C}$) of 4-trifluoromethyl(2-pyrimidinylthio)benzene (**7c**) (0.20 mmol) in a 1.0 M solution of LiClO_4 in CH_3CN and subsequent treatment with piperidine gave the title compound (36.7 mg, 84%) as white solid. ^1H NMR (400 MHz, CDCl_3): δ 5.80-5.92 (br, 2H), 7.36 (dd, J = 0.8 Hz, 8.0 Hz, 1H), 7.68 (d, J = 8.0 Hz, 1H), 7.74 (d, J = 0.8 Hz, 1H); ^{13}C NMR (150

MHz, CDCl₃): δ 115.6 (q, J = 4.0 Hz), 118.5 (q, J = 3.7 Hz), 120.9, 124.1 (q, J = 270 Hz), 128.3 (q, J = 32 Hz), 134.9, 151.7, 167.0 ; HRMS (ESI): calcd. for [M+H]⁺ C₈H₆N₂SF₃ 219.0198; found, 219.0198.

2-Amino-5-cyanobenzothiazole (8e). Electrochemical oxidation (3.5 F , r.t.) of 4-cyano(2-pyrimidinylthio)benzene (**7e**) (0.20 mmol) in a 1.0 M solution of LiClO₄ in CH₃CN and subsequent treatment with piperidine gave the title compound (26.3 mg, 75%) as white solid. ¹H NMR (400 MHz, CDCl₃): δ 7.38 (d, J = 8.0 Hz, 1H), 7.71 (s, 1H), 7.84-7.88 (m, 3H); ¹³C NMR (150 MHz, CDCl₃): δ 107.8, 119.4, 120.3, 122.1, 123.7, 136.9, 152.9, 168.1; HRMS (ESI): calcd. for [M+H]⁺ C₈H₆N₃S₁, 176.0277; found, 176.0273.

2-Amino-5-benzoylbenzothiazole (8f). Electrochemical oxidation (2.5 F , r.t.) of 4-(2-pyrimidinylthio)benzophenone (**7f**) (0.20 mmol) and subsequent treatment with piperidine gave the title compound (40.9 mg, 80%) as white solid. ¹H NMR (400 MHz, CDCl₃): δ 7.38 (d, J = 8.4 Hz, 1H), 7.54-7.75 (m, 8H), 7.84 (d, J = 8.0 Hz, 1H); ¹³C NMR (150 MHz, CDCl₃): δ 118.3, 120.9, 122.2, 128.4, 129.4, 132.2, 134.5, 136.3, 137.5, 152.7, 167.5, 195.6; HRMS (ESI): calcd. for [M+H]⁺ C₁₄H₁₁N₂OS, 255.0587; found, 255.0579.

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Chapter 3

Chapter 4

Direct C–N Coupling of Imidazoles with Aromatic and Benzylic Compounds via Electrooxidative C–H Functionalization

Abstract

A method for the C–N coupling of imidazoles based on electrooxidative C–H functionalization of aromatic and benzylic compounds has been developed. The key to the success is the formation of protected imidazolium ions as initial products avoiding overoxidation. Deprotection under non-oxidative conditions affords *N*-substituted imidazoles. Various functional groups are compatible with the present transformation. To demonstrate the power of the method, a P450 17 inhibitor and an antifungal agent having *N*-substituted imidazole structures were synthesized.

Introduction

Imidazoles bearing organic substituent on the nitrogen atom are important motifs in natural products and medicinal compounds of various biological activities such as antiviral, anti-inflammatory, anticancer, and antifungal activities (Figure 1). Some *N*-substituted imidazoles are widely used as drugs.¹ For example, Losartan is the first orally available angiotensin II receptor antagonist and is used for treating hypertension.²

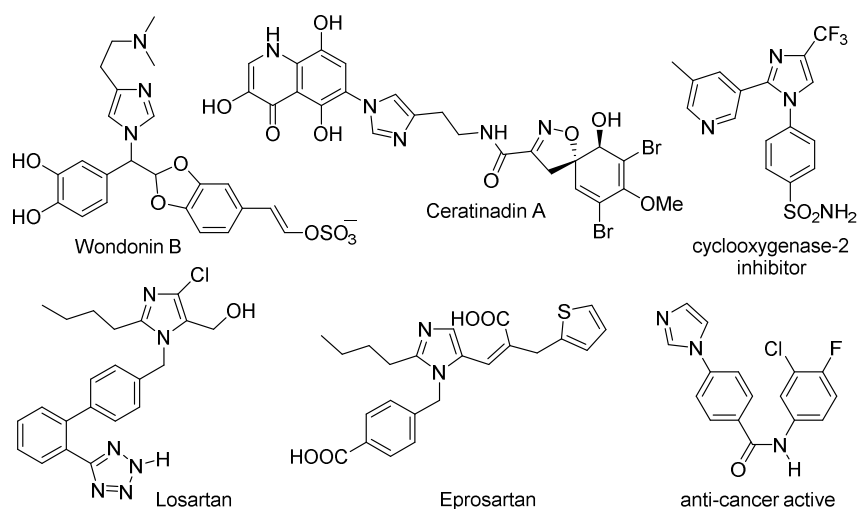


Figure 1. Selected examples of *N*-substituted imidazoles

Although various protocols for C–N coupling of imidazole derivatives and organic molecules have been developed, the most of them require prefunctionalization of organic molecules.^{3,4,5} Because direct C–N coupling⁶ between imidazoles and organic compounds serves as a straightforward method for construction of a wide variety of *N*-substituted imidazoles having intriguing chemical and biological functions, development of efficient methods for direct C–N coupling by C–H functionalization is highly desired. Recently, direct C–N coupling by functionalizing benzylic C–H or C–H bond adjacent to a hetero atom based on radical H-atom abstraction has been reported.⁷ Although it serves as a powerful method for synthesizing *N*-benzyl imidazoles, an excess amount of a benzylic compound is required presumably because C–N coupling products are also susceptible to H-atom abstraction.

Electrochemical oxidation^{8,9} serves as a powerful method for functionalizing C–H bonds of benzylic¹⁰ and aromatic¹¹ compounds by single electron transfer. Despite the usefulness of the method, it suffers from overoxidation when a product is also susceptible to electrochemical oxidation.¹² This is indeed the case, when benzylic and aromatic compounds are electrochemically oxidized in the presence of unprotected imidazole (Figure

2a).

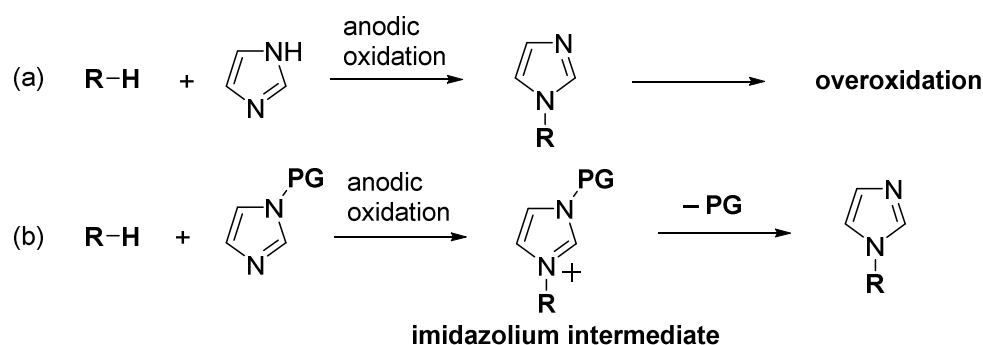


Figure 2. Electrooxidative C–N cross-coupling of imidazoles with benzylic and aromatic compounds. a) conventional approach. b) present approach.

This chapter describes a new approach to solve the problem; the C–N coupling of protected imidazoles based on electrooxidative C–H functionalization of organic counter parts (Figure 2b). This method is applicable not only to benzylic but also to aromatic compounds. The initial products are N -benzyl or N -aryl imidazolium ions, which can be easily converted to the corresponding N -benzyl or N -aryl imidazoles by a subsequent non-oxidative removal of the protecting group. The key to the success of the present approach is the intermediacy of the electrooxidatively inactive imidazolium ions which avoids overoxidation. Therefore, the reaction does not require an excess amount of a benzylic or aromatic compound.

Results and Discussions

Naphthalene (**1a**) was chosen to use because C–H functionalization of **1a** via the electrogenerated radical cation intermediate is well known.¹³ Because the choice of an appropriate protecting group of an imidazole is crucial for the success of the present approach, the electrochemical reactions of naphthalene in the presence of various N -protected imidazoles were examined. The electrochemical reactions were carried out with 0.20 mmol of naphthalene (**1a**) and 0.6 mmol of a N -protected imidazole (**2**) in an H-type divided cell equipped with an anode consisting of fine carbon fibers and a platinum plate cathode using a 1.0 M solution of $LiClO_4$ in CH_3CN at 20 °C under constant current conditions. In the anodic chamber **1a** was oxidized, and in the cathodic chamber, proton was reduced to generate hydrogen. Trifluoromethanesulfonic acid was added to the cathodic chamber prior to the electrolysis in order to promote the hydrogen generation. After 2.5 F of electricity was consumed, the reaction mixture was treated with piperidine at

70 °C for 12 h. The yields of the resulting C–N coupling product **3a** were determined by GC analysis. The use of unprotected imidazole **2a** gave no C–N coupling product presumably because of the overoxidation (Table 1, entry 1). In contrast, 1-acetylimidazole (**2b**) gave the C–N coupling product **3a** in 46% yield (entry 2). Among the examined (entries 2–7) *N*-methylsulfonyl-protected imidazole **2f** (1-mesylimidazole) gave the product in the highest yield (entry 6, 82%). The imidazolium intermediate **4f** could be characterized by NMR after electrolysis.

Table 1. Optimization of the Protecting Groups

entry	PG		yield of 3a (%) ^a	entry	PG		yield of 3a (%) ^a
1	H	2a	0	5	SO ₂ C ₆ H ₄ - <i>p</i> -CH ₃ (Ts)	2e	71
2	COCH ₃	2b	46	6	SO ₂ CH ₃ (Ms)	2f	82
3	CO ₂ NMe ₂	2c	62	7	SiMe ₃	2g	0
4	SO ₂ NMe ₂	2d	42				

^a Yields were determined by GC analysis using tridecane as an internal standard.

Various functional groups are compatible with the present transformation. To demonstrate high chemoselectivity of the present method, a robustness screen that was recently developed by Glorius group¹⁴ was applied. The reactions were performed in the presence of various compounds having given functional groups as additives. The conversion of naphthalene (**1a**), the yield of the product **3a**, and those of the unchanged additives were determined by GC analysis (Table 2). Electron-withdrawing groups such as ketone, ester, amide, cyano, and nitro groups survived the reaction (entries 2–4), although aldehydes could not tolerate the reaction conditions (entry 5). Benzylic C–H bond in non-electron-rich aromatic rings and allylic C–H bond were intact (entry 6). The observed chemoselectivity sharply contrasts with that for the radical H-atom abstraction.⁷ Aryl halides, which could be used for further transformation, also survived the reaction (entry 7). Some heterocycles such as coumarin, 2-acetylthiophene, and *N*-tosylmorpholine survived, although *N*-tosylpyrrole and 2-bromothiophene could not tolerate the reaction (entries 8–12).

Table 2. Robustness screen of C–N Coupling of *N*-methylsulfonylimidazole with Naphthalene

entry	additive	additive remaining (%)	yield of 3a (%)	naphthalene remaining (%)	run	additive	additive remaining (%)	yield of 3a (%)	naphthalene remaining (%)
1	—	—	82	0	7		92		
2		100	77	0			94	88	0
		90					92		
3		100	70	0	8		84	76	0
		98			9		42	39	45
4		100	77	0	10		76	27	23
5		52	41	0	11		96	88	0
		94	84	0	12		97	77	0
6		94							
		90							

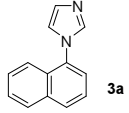
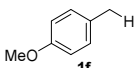
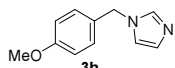
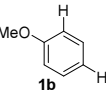
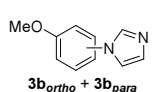
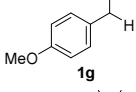
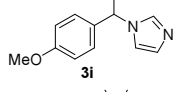
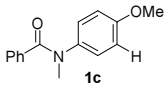
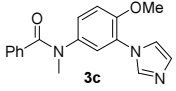
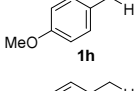
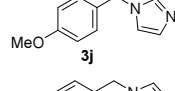
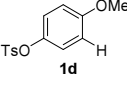
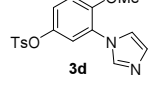
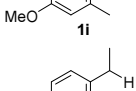
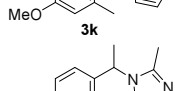
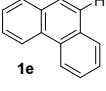
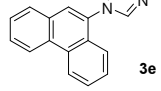
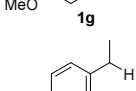
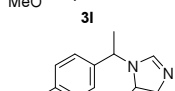
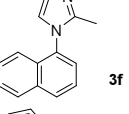
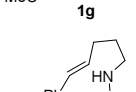
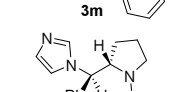
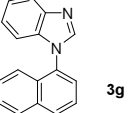
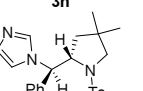
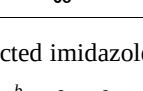
Yields of **3a**, the additives, and naphthalene (**1a**) after reaction were determined by GC analysis using tridecane as an internal standard. Color coding should help the ready assessment of the data: green (above 66%), yellow (34–66%), red (below 34%).

As shown in Table 3, the present method can be applied to other electron-rich aromatic compounds. Methoxybenzene derivatives gave the corresponding C–N coupling products in moderate to good yields (entries 2–4). In particular, *para*-substituted methoxybenzenes gave single regioisomers. π -Extended aromatic compounds such as phenanthrene (**1e**) were

effective in this reaction (entry 5). Furthermore, the method could also be applied to other imidazole derivatives such as *N*-methylsulfonyl-2-methylimidazole (**2h**) and *N*-methylsulfonylbenzimidazole (**2i**), which gave the corresponding C–N coupling products in good yields (entries 6–7).

Benzylic compounds are also effective for the C–N coupling (entries 8–12). Notably, primary, secondly, and tertiary benzylic C–H bonds were functionalized efficiently. The regioselectivity of the reaction of 4-methoxy-1,2-dimethylbenzene (**1i**) is interesting. The *para*-methyl group was selectively functionalized without affecting the *meta*-methyl group (entry 11). 2-Methylimidazole and benzimidazole could also be introduced by the present C–N coupling (entries 12 and 13).

Table 3. C–N Coupling of Imidazole Derivatives with Various Aromatic and Benzylic Compounds^a

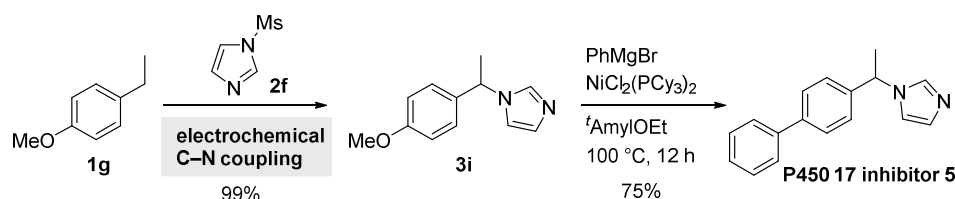
entry	aromatics	imidazole	product	yield (%) ^b	entry	aromatics	imidazole	product	yield (%) ^b
1				81	8 ^c				81
2 ^c				68 (<i>o/p</i> =1/2.0)	9				99
3 ^c				70	10				83
4				36	11 ^c				65
5				75	12				70
6				97	13				60
7				61	14 ^d				91
					15 ^{d,e}				77

^a 0.2 mmol of **1** was oxidized electrochemically in the presence of 0.6 mmol of *N*-protected imidazole **2** using 2.5 F/mol of electricity in a 1.0 M solution of LiClO₄ in CH₃CN at room temperature. ^b Isolated yields. ^c 1.0 mmol of *N*-protected imidazole was used with 3.0 F/mol of electricity. The reaction was carried out at 50 °C. ^d Electrolysis was carried out in 0.1 M solution of LiClO₄ in 1,2-dimethoxyethane/dichloromethane (1/5). The reaction was carried out at 0 °C with 2.2 F/mol of electricity. ^e 0.1 mmol of **1k** and 0.5 mmol of **2f** were used.

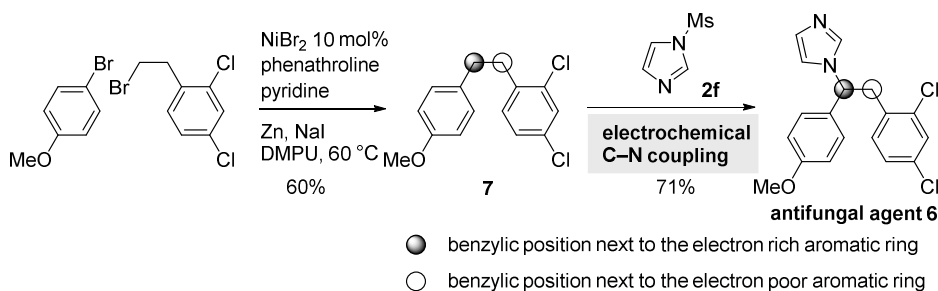
The present method can be integrated with electrooxidative alkene-cyclization reactions.¹⁵ For example, the electrochemical reaction of an alkene having a nucleophilic tosylamide group in the presence of **2f** followed by the treatment with piperidine gave the cyclized *N*-benzylimidazole (entries 14 and 15). Only the five-membered ring compound was formed, and a single diastereomer was observed by ¹H NMR analysis of the crude product. The stereochemistry was determined by JBCA¹⁶ and NOE analyses, and is consistent with a mechanism involving the back-side attack to a benzylic cation stabilized by the cyclized tosylamide group.^{10e}

The electrochemical reaction is facilitated by an electron donating group such as a methoxy group on the aromatic ring. The use of such an activating group gives us an added bonus, because a methoxy group can be used for further transformations such as transition metal catalyzed coupling reactions.¹⁷ For example, compound **3i** synthesized by the present electrochemical C–N coupling was reacted with PhMgBr in the presence of a catalytic amount of NiCl₂(PCy₃)₂ to give compound **5**, a P450 17 inhibitor¹⁸ in 75% yield (Scheme 1).

Scheme 1. Synthesis of P 450 17 Inhibitor **5** from **3i** Featuring Nickel Catalyzed C–O Bond Activation



The following synthesis of an antifungal agent¹⁹ **6** also demonstrates the power of the present method (Scheme 2). Compound **7**, which has two different benzylic positions, was prepared from commercially available compounds in one step.²⁰ The present electrochemical method functionalized the benzylic C–H bond next to the electron-rich aromatic ring substituted by a methoxy group selectively without affecting the benzylic C–H bond next to relatively electron poor aromatic ring substituted by two chloro groups. Thus, the electrochemical oxidation of **7** in the presence of 1-mesitylimidazole **2f** followed by treatment with piperidine gave desired **6** in 71% isolated yield.

Scheme 2. Synthesis of Antifungal Agent **6** Using Electrochemical C–N Coupling**Conclusion**

In conclusion, a new electrooxidative C–N coupling of *N*-mesylimidazole and its derivatives with aromatic and benzylic compounds was developed. The key to the success of the present method is the formation of electrochemically-inactive imidazolium ions as initial products, which is converted to the corresponding *N*-aryl or *N*-benzylimidazoles by subsequent treatment with piperidine. The method provides a straightforward highly chemoselective metal-free route to the *N*-substituted imidazoles.

Experimental Section

General: ^1H and ^{13}C NMR spectra were recorded in CDCl_3 on Varian MERCURY plus-400 (^1H 400 MHz, ^{13}C 100 MHz), or JEOL ECA-600P spectrometer (^1H 600 MHz, ^{13}C 150 MHz). Mass spectra were obtained on JEOL JMS SX-102A mass spectrometer. IR spectra were measured with a Shimadzu IRAffinity (FTIR). Merck precoated silica gel F₂₅₄ plates (thickness 0.25 mm) was used for thin-layer chromatography (TLC) analysis. Flash chromatography was carried out on a silica gel (Kanto Chem. Co., Silica Gel N, spherical, neutral, 40–100 μm). Preparative gel permeation chromatography (GPC) was carried out on Japan Analytical Industry LC-918 equipped with JAIGEL-1H and 2H using CHCl_3 as an eluent. All reactions were carried out under argon atmosphere unless otherwise noted. Compounds **3a**,²¹ **3b_{ortho}**,²² **3b_{para}**,²¹ **3e**,²³ **3g**,²⁴ **3h**,²⁵ **5**,²⁶ and **6**²⁷ were identified by comparison with their ^1H and ^{13}C NMR spectra reported in the literature. Compounds **1c**,²⁸ **1d**,²⁹ **1j**,³⁰ and **1k**³⁰ were prepared according to the reported procedures. Bu_4NBF_4 was purchased from TCI and dried at 50 °C/1 mmHg overnight. Unless otherwise noted, all materials were obtained from commercial suppliers and used without further purification.

Procedure of the C–N coupling of imidazoles with aromatic and benzylic compound

General procedure: The anodic oxidation was carried out using an H-type divided cell (4G glass filter) equipped with a carbon felt anode (Nippon Carbon JF-20-P7, ca. 160 mg, dried at 300 °C/1 mmHg for 4 h before use) and a platinum plate cathode (10 mm × 10 mm). In the anodic chamber was placed a solution of substrate **1** (0.20 mmol) and N-protected imidazole **2** (0.6 mmol or 1.0 mmol) in 1.0 M LiClO₄/CH₃CN (10.0 mL). In the cathodic chamber were placed trifluoromethanesulfonic acid (150 μL) and 1.0 M LiClO₄/CH₃CN (10.0 mL). The constant current electrolysis (8.0 mA) was carried out at T °C (0 < T < 50) with magnetic stirring. After X F (2.2 < X < 3.0) of electricity was consumed, the reaction mixture was transferred to a round-bottom flask. Then, piperidine (500 μL) was added to the reaction mixture. The resulting mixture was stirred at 70 °C for 12 h. After removal of the solvent under reduced pressure, NaOH aq (1%, 20 mL) and EtOAc (20 mL) were added to the mixture. The mixture was extracted with EtOAc/Hex (2/1, 20 mL x 3), and was dried over Na₂SO₄. After removal of the solvent under reduced pressure, the crude product was purified with flash chromatography or preparative GPC to obtain the N-substituted imidazole **3**.

1-naphthalen-1-yl-1H-imidazole (3a).²¹ Electrochemical oxidation (2.5 F, 20 °C) of naphthalene (**1a**) (0.20 mmol) in the presence of 1-mesyylimidazole (**2f**) (0.6 mmol) and subsequent treatment with piperidine gave the title compound (31.9 mg, 81%) as pale brown solid.

1-(2-methoxyphenyl)-1H-imidazole (3b_{ortho})²² and **1-(4-methoxyphenyl)-1H-imidazole (3b_{para})**¹. Electrochemical oxidation (3.0 F, 50 °C) of anisole (**1b**) (0.20 mmol) in the presence of 1-mesyylimidazole (**2f**) (1.0 mmol) and subsequent treatment with piperidine gave the mixture of **3b_{ortho}** and **3b_{para}** (23.7 mg, 68%) in 1:2.0 selectivity which was determined by ¹NMR analysis.

N-(3-(1H-imidazol-1-yl)-4-methoxyphenyl)-N-methylbenzamide (3c). Electrochemical oxidation (3.0 F, 50 °C) of N-(4-methoxyphenyl)-N-methylbenzamide (**1c**) (0.20 mmol) in the presence of 1-tosylimidazole (**2e**) (1.0 mmol) and subsequent treatment with piperidine gave the title compound (42.8 mg, 70%) as pale brown solid. ¹H NMR (400 MHz, CDCl₃): δ 3.48 (s, 3H), 3.80 (s, 3H), 6.87-6.93 (m, 3H), 7.08-7.11 (m, 2H), 7.23-7.31 (m, 5H), 7.52 (s, 1H); ¹³C NMR (150 MHz, CDCl₃): δ 38.3, 56.0, 112.5, 119.9, 124.3, 126.4, 128.0, 128.4, 128.9, 129.7, 135.8, 137.5, 137.9, 150.5, 170.6; HRMS (ESI): calcd. for [M+H]⁺ C₁₈H₁₈N₃O₂, 308.1394; found, 308.1386.

3-(1*H*-imidazol-1-yl)-4-methoxyphenyl 4-methylbenzenesulfonate (3d).

Electrochemical oxidation (3.0 *F*, 20 °C) of 4-methoxyphenyl-4-methylbenzenesulfonate (**1d**) (0.20 mmol) in the presence of 1-mesyylimidazole (**2f**) (1.0 mmol) and subsequent treatment with piperidine gave title compound (24.6 mg, 36%) as pale brown solids. ¹H NMR (600 MHz, CDCl₃): δ 2.47 (s, 3H), 3.83 (s, 3H), 6.84 (d, *J* = 2.8 Hz, 1H), 6.95 (d, *J* = 9.2 Hz, 1H), 7.03-7.07 (m, 3H), 7.35 (d, *J* = 7.6 Hz, 2H), 7.65 (m, 1H), 7.73 (d, *J* = 8.4 Hz, 2H); ¹³C NMR (150 MHz, CDCl₃): δ 21.7, 56.2, 112.6, 119.6, 119.9, 122.6, 122.7, 128.6, 129.1, 129.9, 132.0, 137.5, 142.6, 145.8, 151.2; HRMS (ESI): calcd. for [M+H]⁺ C₁₇H₁₇N₂O₄S, 345.0904; found, 345.0896.

1-(phenanthren-9-yl)-1*H*-imidazole (3e).²³ Electrochemical oxidation (2.5 *F*, 20 °C) of phenanthrene (**1e**) (0.2 mmol) in the presence of 1-mesyylimidazole (**2f**) (0.6 mmol) and subsequent treatment with piperidine gave the title compound (36.8 mg, 75%) as pale brown solid.

2-methyl-1-(naphthalen-1-yl)-1*H*-imidazole (3f). Electrochemical oxidation (2.5 *F*, 20 °C) of naphthalene (**1a**) (0.20 mmol) in the presence of 2-methyl-1-mesyylimidazole (**2h**) (0.6 mmol) and subsequent treatment with piperidine gave title compound (40.2 mg, 97%) as pale brown solids. ¹H NMR (400 MHz, CDCl₃): δ 2.16 (s, 3H), 7.05 (s, 1H), 7.14 (s, 1H), 7.31 (d, *J* = 8.4 Hz, 1H), 7.31 (d, *J* = 7.2 Hz, 1H), 7.47-7.58 (m, 3H), 7.93-7.98 (m, 2H); ¹³C NMR (150 MHz, CDCl₃): δ 13.1, 121.9, 122.5, 124.8, 125.2, 126.9, 127.6, 127.7, 128.2, 129.4, 130.2, 134.1, 134.3, 146.1; HRMS (ESI): calcd. for [M+H]⁺ C₁₄H₁₃N₂, 209.1073; found, 209.1070.

1-(naphthalen-1-yl)-1*H*-benzoimidazole (3g).²⁴ Electrochemical oxidation (2.5 *F*, 20 °C) of naphthalene (**1a**) (0.20 mmol) in the presence of 1-mesylbenzimidazole (**2i**) (0.6 mmol) and subsequent treatment with piperidine gave the title compound (29.7 mg, 61%) as pale brown solid.

1-(4-methoxybenzyl)-1*H*-imidazole (3h).²⁵ Electrochemical oxidation (3.0 *F*, 50 °C) of 4-methoxytoluene (**1f**) (0.20 mmol) in the presence of 1-mesyylimidazole (**2f**) (1.0 mmol) and subsequent treatment with piperidine gave the title compound (30.5 mg, 81%) as pale brown oil.

1-(1-(4-methoxyphenyl)ethyl)-1*H*-imidazole (3i). Electrochemical oxidation (2.5 *F*, 20 °C) of 4-ethylanisole (**1g**) (0.2 mmol) in the presence of 1-mesyylimidazole (**2f**) (0.6 mmol)

and subsequent treatment with piperidine gave title compound (40.1 mg, 99%) as pale brown oil. ^1H NMR (400 MHz, CDCl_3): δ 1.83 (d, J = 6.8 Hz, 3H), 3.80 (s, 3H), 5.29 (q, J = 6.8 Hz, 1H), 6.86-6.91 (m, 3H), 7.05-7.11 (m, 3H), 7.56 (s, 1H); ^{13}C NMR (150 MHz, CDCl_3): δ 22.1, 55.3, 56.0, 114.1, 117.8, 127.3, 129.3, 133.4, 135.9, 159.3; HRMS (APCI): calcd. for $[\text{M}+\text{H}]^+ \text{C}_{12}\text{H}_{15}\text{N}_2\text{O}$, 203.1179; found, 203.1175.

1-(2-(4-methoxyphenyl)propan-2-yl)-1H-imidazole (3j). Electrochemical oxidation (2.5 F , 20 $^\circ\text{C}$) of 4-isopropylanisole (**1h**) in the presence of 1-mesyylimidazole (**2f**) (0.6 mmol) and subsequent treatment with piperidine gave title compound (36.1 mg, 83%) as white solid. ^1H NMR (400 MHz, CDCl_3): δ 1.88 (s, 6H), 3.78 (s, 3H), 6.82 (d, J = 8.8 Hz, 2H), 6.88 (m, 1H), 7.00 (d, J = 8.8 Hz, 2H), 7.59 (s, 1H); ^{13}C NMR (150 MHz, CDCl_3): δ 30.5, 55.2, 59.5, 113.8, 117.7, 126.1, 129.1, 135.5, 138.0, 158.8; HRMS (ESI): calcd. for $[\text{M}+\text{H}]^+ \text{C}_{13}\text{H}_{17}\text{N}_2\text{O}$, 217.1335; found, 217.1332.

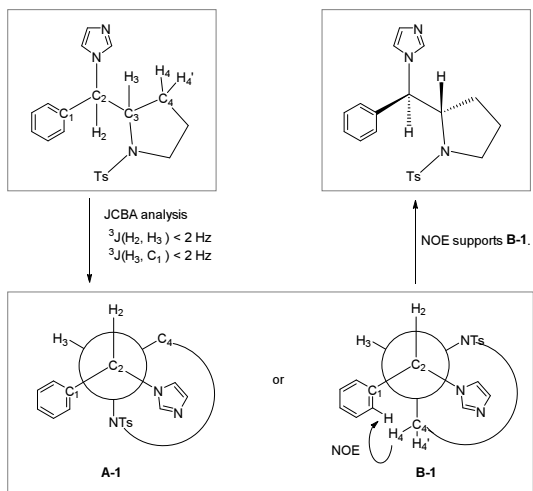
1-(4-methoxy-2-methylbenzyl)-1H-imidazole (3k). Electrochemical oxidation (3.0 F , 50 $^\circ\text{C}$) of 3,4-dimethylanisole (**1i**) in the presence of 1-mesyylimidazole (**2f**) (1.0 mmol) and subsequent treatment with piperidine gave title compound (26.1 mg, 65%) as pale brown oil. ^1H NMR (400 MHz, CDCl_3): δ 2.22 (s, 3H), 3.80 (s, 3H), 5.04 (s, 2H), 6.70-6.77 (m, 2H), 6.83 (s, 1H), 6.99 (d, J = 8.4 Hz, 1H), 7.06 (s, 1H), 7.45 (s, 1H); ^{13}C NMR (150 MHz, CDCl_3): δ 19.1, 48.6, 55.2, 111.3, 116.5, 119.0, 125.9, 129.5, 130.2, 137.2, 137.9, 159.7; HRMS (ESI): calcd. for $[\text{M}+\text{H}]^+ \text{C}_{12}\text{H}_{15}\text{N}_2\text{O}$, 203.1179; found, 203.1176.

1-(1-(4-methoxyphenyl)ethyl)-2-methyl-1H-imidazole (3l). Electrochemical oxidation (2.5 F , 20 $^\circ\text{C}$) of ethylanisole (**1g**) in the presence of 2-methyl-1-mesyylimidazole (**2h**) (0.6 mmol) and subsequent treatment with piperidine gave title compound (30.3 mg, 70%) as pale brown oil. ^1H NMR (400 MHz, CDCl_3): δ 1.77 (d, J = 7.2 Hz, 3H), 2.31 (s, 3H), 3.78 (s, 3H), 5.26 (q, J = 7.2 Hz, 1H), 6.84 (m, J = 8.8 Hz, 2H), 6.94-7.00 (m, 4H); ^{13}C NMR (150 MHz, CDCl_3): δ 13.3, 22.2, 54.5, 55.3, 114.2, 116.4, 126.6, 127.0, 133.5, 144.6, 159.1; HRMS (ESI): calcd. for $[\text{M}+\text{H}]^+ \text{C}_{13}\text{H}_{17}\text{N}_2\text{O}$, 217.1335; found, 217.1333.

1-(1-(4-methoxyphenyl)ethyl)-1H-benzimidazole (3m). Electrochemical oxidation (2.5 F , 20 $^\circ\text{C}$) of 4-ethylanisole (**1g**) in the presence of 1-mesybenzimidazole (**2i**) (0.6 mmol) and subsequent treatment with piperidine gave title compound (32.3 mg, 64%) as pale brown oil. ^1H NMR (400 MHz, CDCl_3): δ 1.96 (d, J = 6.8 Hz, 3H), 3.78 (s, 3H), 5.58 (q, J = 6.8 Hz, 1H), 6.85 (d, J = 8.4 Hz, 2H), 7.13 (d, J = 8.8 Hz, 2H), 7.18-7.27 (m, 3H), 7.80 (d, J = 8.8 Hz, 1H), 8.03 (s, 1H); ^{13}C NMR (150 MHz, CDCl_3): δ 21.5, 54.7, 55.2, 110.6, 114.2, 120.3, 122.2, 122.7, 127.3, 132.5, 133.5, 141.0, 144.0, 159.

3; HRMS (ESI): calcd. for $[M+H]^+$ $C_{16}H_{17}N_2O$, 253.1335; found, 253.1329.

1-((R*)-phenyl((S*)-1-tosylpyrrolidin-2-yl)methyl)-1H-imidazole (3n). In the anodic chamber was placed a solution of (E)-N-tosyl-5-phenyl-4-pentenamine (**1j**) (0.20 mmol) and 1-mesylimidazole (**2f**) (1.0 mmol) in 0.1 M $LiClO_4/CH_2Cl_2:DME$ (5:1, 10.0 mL). In the cathodic chamber were placed trifluoromethanesulfonic acid (200 μ L) and 0.1 M $LiClO_4/CH_2Cl_2:DME$ (5:1, 10.0 mL). The constant current electrolysis (8.0 mA) was carried out at 0 °C with magnetic stirring. After 2.2 F of electricity was consumed, the reaction mixture was transferred to a round-bottom flask. Then, piperidine (500 μ L) was added to the reaction mixture. The resulting mixture was stirred at 70 °C for 12 h. After removal of the solvent under reduced pressure, NaOH aq (1%, 20 mL) and EtOAc (20 mL) were added to the mixture. The mixture was extracted with EtOAc/Hex (5/1, 20 mL x 3), and was dried over Na_2SO_4 . After removal of the solvent under reduced pressure, the crude product was purified with flash chromatography and following preparative GPC to obtain the title compound (69.8 mg, 91%) as white solid. 1H NMR (400 MHz, $CDCl_3$): δ 0.78 (m, 1H), 1.17 (m, 1H), 1.87 (m, 2H), 2.44 (s, 3H), 3.02 (m, 1H), 3.19 (m, 1H), 4.37 (m, 1H), 6.02 (m, 1H), 6.97 (s, 1H), 7.07 (s, 1H), 7.26-7.41 (m, 7H), 7.61 (s, 1H), 7.70 (d, J = 8.4 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$, 50 °C): δ 21.5, 23.7, 27.9, 49.2, 61.6, 64.8, 120.0, 127.7, 128.1, 128.3, 128.7, 129.1, 129.9, 134.1, 136.4, 137.8, 144.0; HRMS (ESI): calcd. for $[M+H]^+$ $C_{21}H_{24}N_3O_2S$, 382.1584; found, 382.1581.



The stereochemistry was determined by JBCA analysis³¹ and NOE analysis.

1-((R*)-phenyl((S*)-4,4-dimethyl-1-tosylpyrrolidin-2-yl) methyl)-1H-imidazole (3n). In the anodic chamber was placed a solution of (E)-N-tosyl-2,2-dimethyl-5-phenyl-4-pentenamine (**1k**) (0.10 mmol) and 1-mesylimidazole (**2f**) (0.5 mmol) in 0.1 M $LiClO_4/CH_2Cl_2:DME$ (5:1, 5.0 mL). In the cathodic chamber were

placed trifluoromethanesulfonic acid (200 μ L) and 0.1 M LiClO₄/CH₂Cl₂:DME (5:1, 5.0 mL). The constant current electrolysis (8.0 mA) was carried out at 0 °C with magnetic stirring. After 2.2 *F* of electricity was consumed, the reaction mixture was transferred to a round-bottom flask. Then, piperidine (250 μ L) was added to the reaction mixture. The resulting mixture was stirred at 70 °C for 12 h. After removal of the solvent under reduced pressure, NaOH aq (1%, 20 mL) and EtOAc (20 mL) were added to the mixture. The mixture was extracted with EtOAc/Hex (5/1, 20 mL x 3), and was dried over Na₂SO₄. After removal of the solvent under reduced pressure, the crude product was purified with flash chromatography and following preparative GPC to obtain the title compound (31.6 mg, 77%) as white solid. ¹H NMR (400 MHz, CDCl₃): δ 0.39 (s, 3H), 0.79 (s, 3H), 1.53 (dd, *J* = 12.8, 9.2 Hz, 1H), 1.88 (dd, *J* = 12.8, 9.2 Hz, 1H), 2.42 (s, 3H), 2.72 (d, *J* = 11.2 Hz, 1H), 3.15 (d, *J* = 11.2 Hz, 1H), 4.36 (m, 1H), 6.30 (d, *J* = 2.8 Hz, 1H), 7.06 (m, 2H), 7.31 (m, 4H), 7.41 (m, 3H), 7.57 (s, 1H), 7.70 (d, *J* = 8.4 Hz, 2H); ¹³C NMR (150 MHz, CDCl₃, 20 °C):

δ 21.5, 25.8, 25.9, 37.6, 41.0, 60.8, 62.6, 64.1, 120.2, 127.4, 128.2, 128.2, 128.7, 129.0, 129.9, 134.8, 136.0, 137.8, 144.0; HRMS (ESI): calcd. for [M+H]⁺ C₂₃H₂₈N₃O₂S, 410.1897; found, 410.1896.

NMR analysis of imidazolium intermediate **4f**

The anodic oxidation was carried out using an H-type divided cell (4G glass filter) equipped with a carbon felt anode (Nippon Carbon JF-20-P7, ca. 160 mg, dried at 300 °C/1 mmHg for 4 h before use) and a platinum plate cathode (10 mm $\times$ 10 mm). In the anodic chamber was placed a solution of naphthalene (0.20 mmol) and 1-mesylimidazole (0.6 mmol) in 0.1 M LiClO₄/CH₃CN (10.0 mL). In the cathodic chamber were placed trifluoromethanesulfonic acid (150 μ L) and 0.1 M LiClO₄/CH₃CN (10.0 mL). The constant current electrolysis (8.0 mA) was carried out at 20 °C with magnetic stirring. After 2.5 *F* of electricity was consumed, the reaction mixture was transferred to a round-bottom flask. After removal of the solvent under reduced pressure, the intermediate **4f** was observed by NMR analysis using CD₃CN as solvent.

Robustness Screen of C–N coupling of *N*-(methylsulfonyl)-imidazole with naphthalene

General procedure for the screening: The anodic oxidation was carried out using an H-type divided cell (4G glass filter) equipped with a carbon felt anode (Nippon Carbon JF-20-P7, ca. 160 mg, dried at 300 °C/1 mmHg for 4 h before use) and a platinum plate cathode (10 mm $\times$ 10 mm). In the anodic chamber was placed a solution of naphthalene **1a**

(0.20 mmol) and 1-mesylimidazole **2f** (0.6 mmol), and the respective additives (Amount of each additives is 0.2 mmol.) in 1.0 M LiClO₄/CH₃CN (10.0 mL). In the cathodic chamber were placed trifluoromethanesulfonic acid (150 μ L) and 1.0 M LiClO₄/CH₃CN (10.0 mL). The constant current electrolysis (8.0 mA) was carried out at 20 °C with magnetic stirring. After 2.5 *F* of electricity was consumed, the reaction mixture was transferred to a round-bottom flask. Then, piperidine (500 μ L) was added to the reaction mixture. The resulting mixture was stirred at 70 °C for 12 h. The yield was determined by GC analysis using tridecane as internal standard.

Synthesis of P450 inhibitor 5

3i (20.2 mg, 0.1 mmol), NiCl₂(PCy₃)₂ (20 mg, 0.03 mmol), PhMgBr in Et₂O (3.0 M, 200 μ L), ^tAmylOEt (0.2 mL) and Et₂O (0.2 mL) were added to the sealed tube. The mixture was stirred at 100 °C for 12 h. After the mixture was cooled to room temperature, water (20 mL) and EtOAc (20 mL) were added. The mixture was extracted with EtOAc (20 mL x 3), and was dried over Na₂SO₄. After removal of the solvent under reduced pressure, the crude product was purified with preparative GPC to obtain P450 17 inhibitor **5**²⁶ (18.7 mg, 75%) as white solid.

Synthesis of antifungal agent 6

To the 50 mL flask, *p*-bromoanisole (224 mg, 1.2 mmol), 1-(2-bromoethyl)-2,4-dichlorobenzene (254 mg, 1.0 mmol), NiBr₂ (21.9 mg, 0.1 mmol), phenanthroline (18.0 mg, 0.1 mmol), pyridine (7.9 mg, 0.1 mmol), Zn (163 mg, 2.5 mmol), NaI (45 mg, 0.3 mmol), and N,N'-dimethylpropyleneurea (3 mL) were added. The mixture was stirred at 60 °C for 24 h. After removal of the solvent under reduced pressure, the crude product was purified with flash chromatography to obtain **7** (169 mg, 60%) as colorless oil.

The anodic oxidation was carried out using an H-type divided cell (4G glass filter) equipped with a carbon felt anode (Nippon Carbon JF-20-P7, ca. 160 mg, dried at 300 °C/1 mmHg for 4 h before use) and a platinum plate cathode (10 mm $\times$ 10 mm). In the anodic chamber was placed a solution of **7** (56.2 mg, 0.20 mmol) and 1-mesylimidazole **2f** (146 mg, 1.0 mmol) in 1.0 M LiClO₄/CH₃CN (10.0 mL). In the cathodic chamber were placed trifluoromethanesulfonic acid (150 μ L) and 1.0 M LiClO₄/CH₃CN (10.0 mL). The constant current electrolysis (8.0 mA) was carried out at 20 °C with magnetic stirring. After 2.5 *F* of electricity was consumed, the reaction mixture was transferred to a round-bottom flask. Then, piperidine (500 μ L) was added to the reaction mixture. The resulting mixture was

stirred at 70 °C for 12 h. After removal of the solvent under reduced pressure, NaOH aq (1%, 20 mL) and EtOAc (20 mL) were added to the mixture. The mixture was extracted with EtOAc/Hex (2/1, 20 mL x 3), and was dried over Na₂SO₄. After removal of the solvent under reduced pressure, the crude product was purified with flash chromatography to obtain the antifungal agent **6**²⁷ (49.0 mg, 71%).

2,4-dichloro-1-(4-methoxyphenethyl)benzene (7). ¹H NMR (400 MHz, CDCl₃): δ 2.81-2.86 (m, 2H), 2.94-2.99 (m, 2H), 3.80 (s, 3H), 6.84 (d, *J* = 8.8 Hz, 2H), 7.02-7.15 (m, 3H), 7.38 (d, *J* = 2.0 Hz, 1H); ¹³C NMR (150 MHz, CDCl₃): δ 34.9, 35.5, 55.2, 113.8, 126.9, 129.2, 129.4, 131.3, 132.2, 133.1, 134.5, 137.8, 157.9; HRMS (ESI): calcd. for [M+H]⁺ C₁₂H₁₄OCl₂, 280.0421; found, 280.0414.

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Chapter 5

Heterocyclization Approach for Electrooxidative Coupling of Functional Primary Alkylamines with Aromatics

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.

Introduction

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. electrochemical^{6,7} As described in chapter 2-4, electrochemical C–H amination⁸ which enables direct introduction of nitrogen functionalities into electron-rich aromatic compounds selectively has been developed. 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 In this chapter, 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 is described.

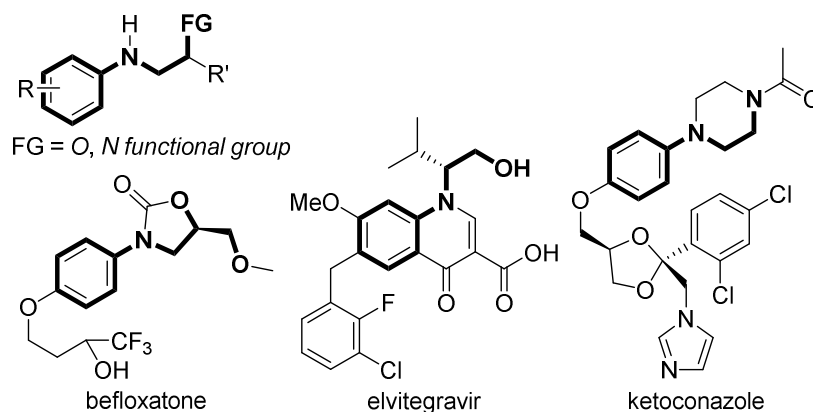


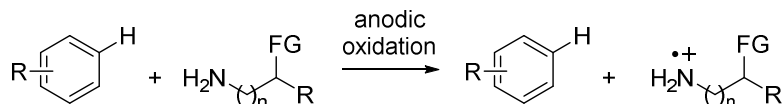
Figure 1. Aromatic compounds bearing functional alkylamino groups.

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 nucleophilicity 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, overoxidation¹² 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

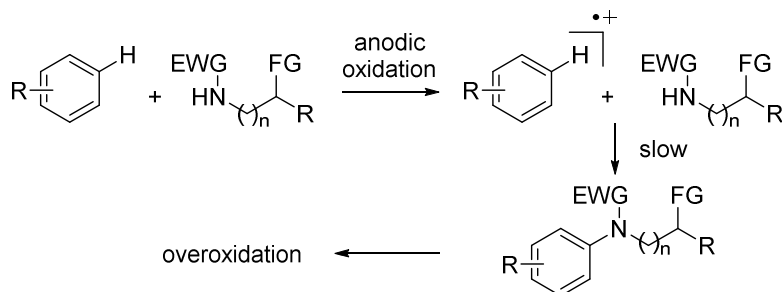
OH and NHR groups might be problematic for the electrooxidative reaction because of their undesired nucleophilic attack on the radical cation of an aromatic compound.

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

A) direct use of primary alkylamines bearing a functional group

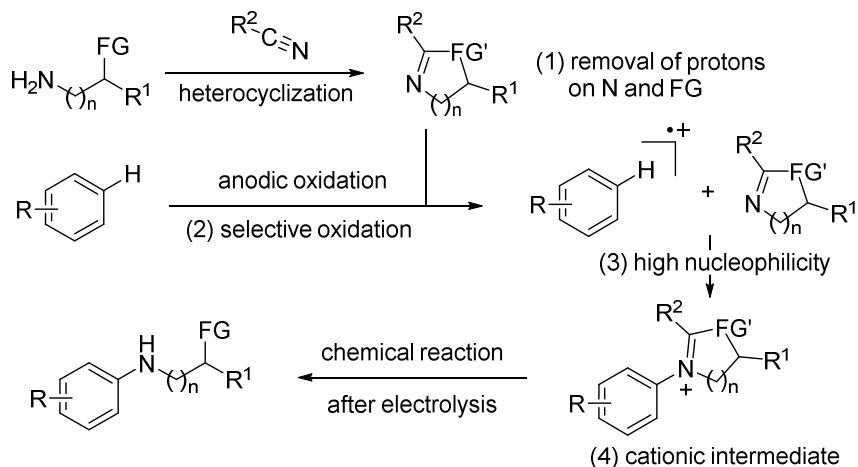


B) use of *N*-protected primary alkylamines bearing a functional group



As described in chapters 2-4, 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, it is reasonable to consider that an initial heterocyclization of a functional primary alkylamine 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 2. Present approach for electrooxidative coupling of functional primary alkylamines with aromatics

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 potential¹⁵ 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 heterocycles 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.

Results and Discussions

First, the reaction of naphthalene (**1a**) ($E_{\text{ox}}=1.52$ V, vs. Ag/Ag^+) with 2-methyloxazoline (**2a**) ($E_{\text{ox}}=1.73$ V, vs. Ag/Ag^+) which can be derived from 2-hydroxyethylamine (Table 1, entry 1) was examined. The anodic oxidation led to the formation of a corresponding cationic intermediate **4a**, which was characterized by ^1H NMR. 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-hydroxyethylamino)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

Reaction scheme showing the synthesis of 3 from 1a and 2 via intermediate 4:

1a + 2 $\xrightarrow[\text{CH}_3\text{CN}, 0^\circ\text{C}]{\text{anodic oxidation, 0.3 M LiClO}_4}$ 4 $\xrightarrow{\text{chemical reaction}}$ 3

General structure of 2:

General structure of 4:

General structure of 3:

entry	2	chemical reaction	NR ³ R ⁴ of product, yield
1		A	 3aa 75%
2		B	 3aa' 79%
3		B	 3ab 67%
4 ^a		B	 3ac 74%
5		A	 3ad 64%
6		B	 3ad' 80%
7		A	 3ae 90%
8		B	 3af 65%
9		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 LiClO₄ in CH₃CN at 0 °C unless otherwise stated, and the resulting solution was subjected to the chemical reaction: A, *aq* NaHCO₃; 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.

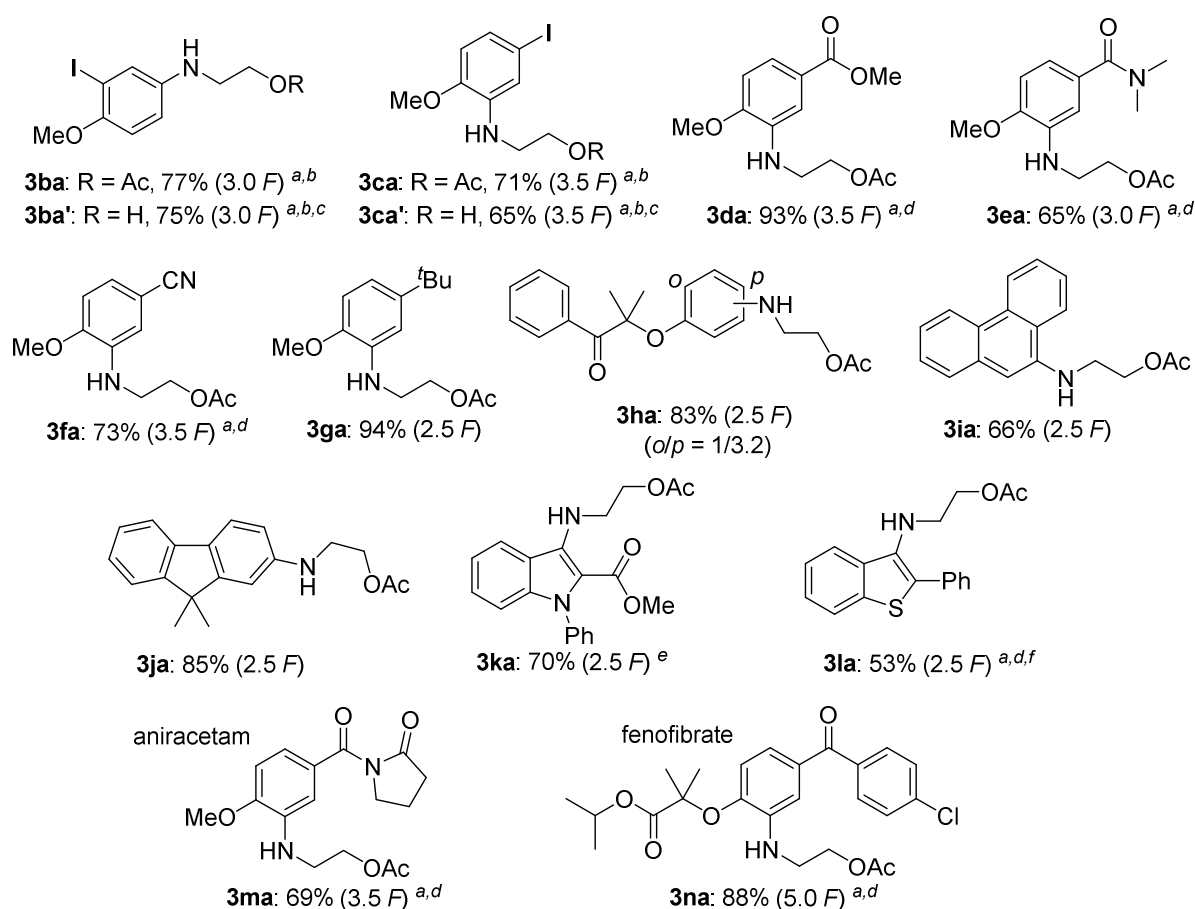


Figure 2. Electrooxidative coupling of various aromatic and heteroaromatic compounds with 2-methyloxazoline.

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 LiClO₄ in CH₃CN at room temperature unless otherwise stated, and the resulting solution was treated with aq NaHCO₃. ^a1.0 mmol of 2-methyloxazoline was used. ^b1.0 M solution of LiClO₄ was used. ^cThe reaction mixture obtained by the electrolysis was treated with ethylenediamine. ^d0.2 M solution of Mg(ClO₄)₂ was used. ^e0.3 M solution of NaClO₄ was used. ^fElectrolysis was carried out at 50 °C.

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).

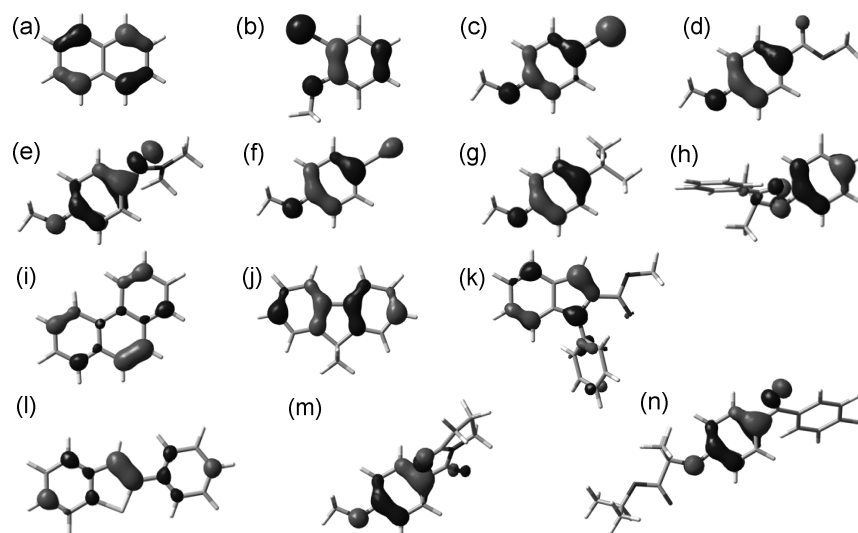
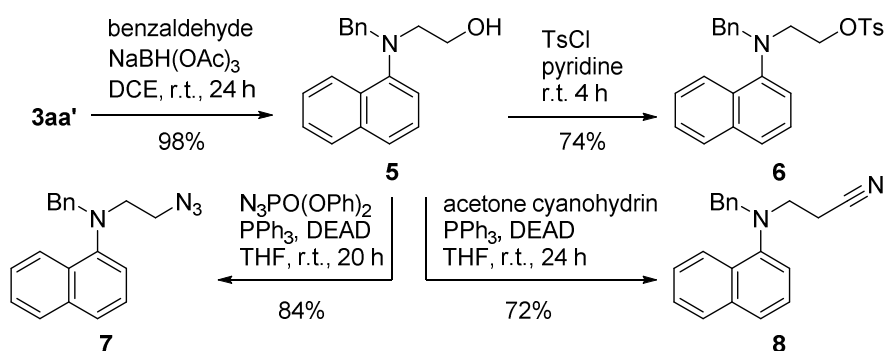


Figure 3. The lowest unoccupied molecular orbitals (β -LUMOs) of radical cation of (a) **1a**,^{8a} (b) **1b**,^{8a} (c) **1c**,^{8a} (d) **1d**, (e) **1e**, (f) **1f**, (g) **1g**, (h) **1h**, (i) **1i**, (j) **1j**, (k) **1k**, (l) **1l**, (m) **1m**, and (n) **1n** obtained by DFT calculations.

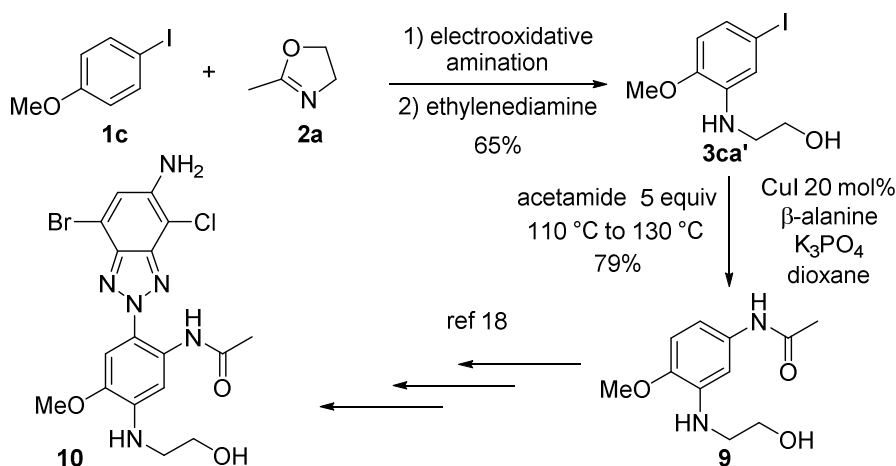
It is also noteworthy that the hydroxyl group attached to the alkylamino group in the products can be used for further transformations. For example, after benzyl protection of the amino group, the hydroxyl group was successfully converted to various functional groups such as tosylate, azide, and cyano 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, a key intermediate **9** for the synthesis of a mutagen **10** isolated from blue cotton-adsorbed materials in the Nikko River in Japan was synthesized (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 literature¹⁸ 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 **10** with the overall yield of 51%.

Scheme 4. Synthesis of mutagen 10



Conclusion

In summary, an effective method for C–H amination of aromatic compounds with functionalized primary alkylamines via heterocyclization was developed 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.

Experimental Section

General: ^1H and ^{13}C NMR spectra were recorded in CDCl_3 on Varian MERCURY plus-400 (^1H 400 MHz, ^{13}C 100 MHz), or JEOL ECA-600P spectrometer (^1H 600 MHz, ^{13}C 150 MHz). Mass spectra were obtained on JEOL JMS SX-102A mass spectrometer. Merck precoated silica gel F₂₅₄ plates (thickness 0.25 mm) was used for thin-layer chromatography (TLC) analysis. Flash chromatography was carried out on a silica gel (Kanto Chem. Co., Silica Gel N, spherical, neutral, 40-100 μm). Preparative gel permeation chromatography (GPC) was carried out on Japan Analytical Industry LC-918 equipped with JAIGEL-1H and 2H using CHCl_3 as an eluent. All reactions were carried out under argon atmosphere unless otherwise noted. Unless otherwise noted, all materials were obtained from commercial suppliers and used without further purification.

The anodic oxidation was carried out using an H-type divided cell (4G glass filter) equipped with a carbon felt anode (Nippon Carbon JF-20-P7, ca. 160 mg, dried at 300 °C/1 mmHg for 4 h before use) and a platinum plate cathode (20 mm $\times$ 20 mm). Although we used the cell of our original design, similar electrochemical cells are commercially available at EC Frontier., Inc. and Adams & Chitenden Scientific Glass. Kikusui PMC350-0.2A was used as a DC power supply for the electrolysis.

Oxidation potentials of naphthalene (**1a**) and 2-methyloxazoline (**2a**) were determined by rotating-disk electrode (RDE) voltammetry using BAS 600C and BAS RRDE-3 rotating disk electrodes. Measurements of an oxidation potential of substrate (0.02 M) were carried out in 0.3 M $\text{LiClO}_4/\text{CH}_3\text{CN}$ using a glassy carbon disk working electrode, a platinum wire counter electrode, and an Ag/AgNO_3 reference electrode with sweep rate of 100 mVs^{-1} at 3000 rpm.

^1H NMR analysis of the cationic intermediate.

In the anodic chamber was placed a solution of naphthalene (**1a**) (0.20 mmol) and 2-methyloxazoline (**2a**) (0.6 mmol) in 0.3 M $\text{LiClO}_4/\text{CH}_3\text{CN}$ (10.0 mL). In the cathodic chamber were placed trifluoromethanesulfonic acid (150 μL) and 0.3 M $\text{LiClO}_4/\text{CH}_3\text{CN}$ (10.0 mL). The constant current electrolysis (8.0 mA) was carried out at 0 °C with magnetic stirring. After the electrolysis (2.5 *F*), the reaction mixture was transferred to a round-bottom flask. After removal of the solvent under reduced pressure, the cationic intermediate **4a** was observed by ^1H NMR analysis using CD_3CN as solvent. ^1H NMR (400 MHz, CDCl_3): δ 2.20 (s, 3H), 4.44-4.49 (m, 1H), 4.61-4.69 (m, 1H), 5.20-5.29 (m, 2H), 7.64-7.79 (m, 3H), 7.77 (d, *J* = 7.2 Hz, 1H), 7.98 (d, *J* = 7.2 Hz, 1H), 8.08 (d, *J* = 8.4 Hz, 1H), 8.16 (d, *J* = 8.0 Hz, 1H).

Preparation of heterocycles

2-methyloxazoline (**2a**) was commercially available. 2-methyl-1-tosylimidazoline (**2d**),¹⁹ 2-phenyl-1-tosyl-1,4,5,6-tetrahydro-pyrimidine (**2e**),²⁰ and 2-phenyl-4a,5,6,7,8,8a-hexahydro-4H-1,3-benzoxazine (**2f**)²¹ were synthesized according to the reported literature.

2-methyl-5-phenyloxazoline (2b). To a 30 mL screw cap tube, 2-hydroxy-2-phenylethylamine (10 mmol), acetonitrile (30 mmol), ZnCl₂ (1 mmol), and chlorobenzene (5 mL) were added. The mixture was stirred at 140 °C for 24 h. After removal of the solvent under reduced pressure, the mixture was extracted with ethyl acetate/hexane (2/1, 20 mL x 3), and the combined extracts were washed with water (20 mL) and brine (20 mL), and was dried over Na₂SO₄. Removal of the solvent under reduced pressure gave the title compound **2b** (1.37 g, 85%), which was identified by comparison with their NMR spectra reported in the literature.²²

2-phenyl-5,6-dihydro-4H-1,3-oxazine (2c). To a 30 mL screw cap tube, 3-amino-propan-1-ol (30 mmol), benzonitrile (30 mmol), ZnCl₂ (3 mmol), and chlorobenzene (15 mL) were added. The mixture was stirred at 140 °C for 24 h. After removal of the solvent under reduced pressure, the mixture was extracted with ethyl acetate/hexane (2/1, 20 mL x 3), and the combined extracts were washed with water (20 mL) and brine (20 mL), and was dried over Na₂SO₄. After removal of the solvent under reduced pressure, the crude product was purified with flash chromatography to obtain the title compound **2c** (2.45 g, 51%), which was identified by comparison with their NMR spectra reported in the literature.²³

6-hexyl-2-phenyl-5,6-dihydro-4H-1,3-oxazine (2g). To a 100 mL flask, 1-octene (20 mmol), N-(hydroxymethyl)benzamide (15 mmol), acetic acid (12 mL), and H₂SO₄ (2 mL) were added. The mixture was stirred at 140 °C for 24 h. After removal of the solvent under reduced pressure, water and NaHCO₃ were added to neutralize the mixture. The mixture was extracted with ethyl acetate/hexane (2/1, 20 mL x 3), and the combined extracts were washed with water (20 mL) and brine (20 mL), and was dried over Na₂SO₄. After removal of the solvent under reduced pressure, the crude product was purified with flash chromatography to obtain the title compound **2g** (470 mg, 10%). ¹H NMR (400 MHz, CDCl₃): δ 0.91 (t, *J* = 6.8 Hz, 3H), 1.31-1.77 (m, 11H), 1.91-1.97 (m, 1H), 3.51-3.70 (m, 2H), 4.16-4.22 (m, 1H), 7.33-7.42 (m, 3H), 7.90-7.93 (m, 2H); ¹³C NMR (150 MHz, CDCl₃): δ 14.0, 22.6, 24.9, 27.3, 29.2, 31.7, 35.6, 43.0, 74.8, 126.8, 127.9, 130.1, 134.2,

155.8; HRMS (ESI): calcd. for $[M+H]^+$ $C_{16}H_{24}NO$, 246.1852; found, 246.1852.

Procedure of the electrooxidative coupling of naphthalene with heterocycles

General procedue of electrolysis. In the anodic chamber was placed a solution of naphthalene (**1a**) (0.20 mmol) and heterocycle **2** (0.6 or 1.0 mmol) in $LiClO_4/CH_3CN$ (0.3 M, 10.0 mL). In the cathodic chamber were placed trifluoromethanesulfonic acid (150 μ L) and $LiClO_4/CH_3CN$ (0.3 M, 10.0 mL). The constant current electrolysis (8.0 mA) was carried out at 0 °C with magnetic stirring. After the electrolysis (2.5 *F*), the reaction mixture was treated with chemical reaction A or chemical reaction B described as follows.

General procedue of chemical reaction A. After the electrolysis, the reaction mixture was transferred to a round-bottom flask. After removal of the solvent under reduced pressure, ethyl acetate/hexane (2/1, 10 mL), H_2O (20 mL) and saturated solution of $NaHCO_3/H_2O$ (3 mL) were added to the mixture. The mixture was extracted with ethyl acetate/hexane (2/1, 20 mL x 3), and the combined extracts were washed with water (20 mL) and brine (20 mL), and was dried over Na_2SO_4 . After removal of the solvent under reduced pressure, the crude product was purified with flash chromatography or preparative GPC to obtain coupling product **3**.

General procedue of chemical reaction B. After the electrolysis, ethylenediamine (1.0 mmol) was added and the reaction mixture was stirred at room temperature for 10 m. The reaction mixture was transferred to a round-bottom flask and stirred at 70 °C for 3 h. After removal of the solvent under reduced pressure, ethyl acetate/hexane (2/1, 10 mL), and H_2O (20 mL) were added to the mixture. The mixture was extracted with ethyl acetate/hexane (2/1, 20 mL x 3), and the combined extracts were washed with water (20 mL) and brine (20 mL), and was dried over Na_2SO_4 . After removal of the solvent under reduced pressure, the crude product was purified with flash chromatography or preparative GPC to obtain coupling product **3**.

***N*-(2-acetoxyethyl)-1-naphthylamine (3aa).** Electrooxidative coupling of naphthalene (**1a**) and 2-methyloxazoline (**2a**) (0.6 mmol) followed by treatment of chemical reaction A gave the title compound **3aa** (34.3 mg, 75%) as pale brown oil. 1H NMR (400 MHz, $CDCl_3$): δ 2.13 (s, 3H), 3.57 (t, *J* = 5.6 Hz, 4H), 4.47 (t, *J* = 5.6 Hz, 4H), 6.62 (d, *J* = 7.6 Hz, 1H), 7.27 (d, *J* = 8.8 Hz, 1H), 7.37 (t, *J* = 7.8 Hz, 1H), 7.45-7.50 (m, 2H) 7.78-7.85 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.0, 43.5, 63.0, 104.3, 117.9, 120.0, 123.5, 124.8, 125.8, 126.5, 128.6, 134.3, 142.9, 171.5; HRMS (ESI): calcd. for $[M+H]^+$

C₁₄H₁₆N₁O₂, 230.1176; found, 230.1172.

***N*-(2-hydroxyethyl)-1-naphthylamine (3aa').** Electrooxidative coupling of naphthalene (**1a**) and 2-methyloxazoline (**2a**) (0.6 mmol) followed by treatment of chemical reaction B gave the title compound **3aa'** (29.5 mg, 79%) as white solid, which was identified by comparison with their NMR spectra reported in the literature.²⁴

***N*-(2-hydroxy-2-phenylethyl)-1-naphthylamine (3ab').** Electrooxidative coupling of naphthalene (**1a**) and 2-methyl-5-phenyloxazoline (**2b**) (1.0 mmol) followed by treatment of chemical reaction B gave the title compound **3ab'** (35.5 mg, 67%) as white solid, which was identified by comparison with their NMR spectra reported in the literature.²⁵

***N*-(2-hydroxyethyl)-1-naphthylamine (3ac').** Electrooxidative coupling of naphthalene (**1a**) and 2-phenyl-5,6-dihydro-4H-1,3-oxazine (**2c**) (0.6 mmol) followed by treatment of chemical reaction B gave the title compound **3ac'** (29.6 mg, 74%) as white solid, which was identified by comparison with their NMR spectra reported in the literature.²⁶

***N*-acetyl-*N*-(2-tosylamidethyl)-1-naphthylamine (3ad).** Electrooxidative coupling of naphthalene (**1a**) and 2-methyl-1-tosylimidazoline (**2d**) (0.6 mmol) followed by treatment of chemical reaction A gave the title compound **3ad'** (48.7 mg, 64%) as white solid. ¹H NMR (400 MHz, CDCl₃): δ 1.73 (s, 3H), 2.42 (s, 3H), 3.11-3.28 (m, 3H), 4.28-4.46 (m, 1H), 5.87 (t, *J* = 5.0 Hz, 1H), 7.07 (d, *J* = 7.2 Hz, 1H), 7.29 (d, *J* = 8.4 Hz, 2H), 7.43 (t, *J* = 7.8 Hz, 1H), 7.53-7.57 (m, 2H), 7.68-7.72 (m, 1H), 7.75 (d, *J* = 8.4 Hz, 2H), 7.88 (d, *J* = 8.4 Hz, 1H), 7.92-7.95 (m, 1H); ¹³C NMR (150 MHz, CDCl₃): δ 21.4, 22.1, 42.5, 47.6, 121.8, 125.7, 126.5, 126.8, 127.1, 127.7, 128.8, 129.2, 129.6, 129.6, 134.8, 136.9, 138.1, 143.2, 173.2; HRMS (ESI): calcd. for [M+H]⁺ C₂₁H₂₃N₂O₃S, 383.1424; found, 383.1412.

***N*-(2-tosylamidethyl)-1-naphthylamine (3ad').** Electrooxidative coupling of naphthalene (**1a**) and 2-methyl-1-tosylimidazoline (**2d**) (0.6 mmol) followed by treatment of chemical reaction B gave the title compound **3ad'** (54.3 mg, 80%) as white solid. ¹H NMR (400 MHz, CDCl₃): δ 2.33 (s, 3H), 3.24-3.29 (m, 2H), 3.33-3.37 (m, 2H), 4.77 (s, 1H), 5.35 (s, 1H), 6.44 (d, *J* = 7.2 Hz, 1H), 7.14 (d, *J* = 8.0 Hz, 2H), 7.21-7.28 (m, 2H), 7.36-7.48 (m, 2H), 7.71 (d, *J* = 8.0 Hz, 2H), 7.76-7.80 (m, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 21.4, 41.9, 43.3, 104.1, 117.7, 120.1, 123.5, 124.8, 125.8, 126.9, 128.4, 129.7, 134.2, 136.4, 142.6, 143.5; HRMS (ESI): calcd. for [M+H]⁺ C₁₉H₂₁N₂O₂S, 341.1318; found, 341.1313.

N-benzyl-N-(2-tosylamidpropyl)-1-naphthylamine (3ae). Electrooxidative coupling of naphthalene (**1a**) and 2-phenyl-1-tosyl-1,4,5,6-tetrahydro-pyrimidine (**2e**) (0.6 mmol) followed by treatment of chemical reaction A gave the title compound **3ae** (82.1 mg, 90%) as white solid. ^1H NMR (400 MHz, CDCl_3): δ 2.41 (s, 3H), 2.61-2.76 (m, 2H), 3.99 (d, $J = 10.4$ Hz, 1H), 4.55-4.72 (m, 2H), 4.88-4.94 (m, 1H) 6.73-6.80 (m, 2H), 6.99-7.02 (m, 3H), 7.22-7.29 (m, 3H), 7.40 (d, $J = 8.4$ Hz, 2H), 7.50-7.53 (m, 1H), 7.64-7.69 (m, 3H), 7.77 (d, $J = 8.4$ Hz, 1H), 7.82 (d, $J = 7.6$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 20.6, 21.9, 45.3, 52.6, 120.0, 125.6, 125.8, 126.7, 126.9, 126.9, 127.0, 127.3, 127.9, 128.4, 128.5, 129.1, 130.2, 130.3, 130.4, 131.2, 133.0, 133.8, 136.4, 147.0, 166.6; HRMS (ESI): calcd. for $[\text{M}-\text{OH}]^+ \text{C}_{27}\text{H}_{25}\text{N}_2\text{O}_2\text{S}_1$, 441.1631; found, 441.1629.

2-((naphthalen-1-ylamino)methyl)cyclohexan-1-ol (3af'). Electrooxidative coupling of naphthalene (**1a**) and 2-phenyl-4a,5,6,7,8,8a-hexahydro-4H-1,3-benzoxazine (**2f**) (0.6 mmol) followed by treatment of chemical reaction B gave the title compound **3af'** (33.3 mg, 65%) as pale brown oil. ^1H NMR (400 MHz, CDCl_3): δ 1.22-1.39 (m, 1H), 1.42-1.84 (m, 7H), 1.87-1.99 (m, 1H), 3.27 (dd, $J = 5.2, 12.4$ Hz, 1H), 3.44 (dd, $J = 7.6, 12.4$ Hz, 1H), 4.12-4.15 (m, 1H), 6.65 (d, $J = 7.6$ Hz, 1H), 7.25 (d, $J = 8.0$ Hz, 1H), 7.34-7.39 (m, 1H) 7.41-7.46 (m, 2H), 7.77-7.85 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 20.6, 25.0, 25.3, 33.0, 40.2, 46.8, 69.0, 104.4, 117.2, 120.0, 123.6, 124.6, 125.7, 126.6, 128.6, 134.3, 143.7; HRMS (ESI): calcd. for $[\text{M}+\text{H}]^+ \text{C}_{17}\text{H}_{22}\text{NO}$, 256.1696; found, 256.1689.

N-(3-hydroxynonyl)-1-naphthylamine (3ag'). Electrooxidative coupling of naphthalene (**1a**) and 6-hexyl-2-phenyl-5,6-dihydro-4H-1,3-oxazine (**2g**) (0.6 mmol) followed by treatment of chemical reaction B gave the title compound **3ag'** (48.5 mg, 85%) as white solid. ^1H NMR (400 MHz, CDCl_3): δ 0.90-0.95 (m, 3H), 1.31-1.56 (m, 10H), 1.80-1.87 (m, 1H), 1.91-1.98 (m, 1H), 3.34-3.49 (m, 2H), 3.83-3.89 (m, 1H), 6.64 (d, $J = 7.2$ Hz, 1H), 7.27 (d, $J = 8.4$ Hz, 1H), 7.35-7.49 (m, 3H), 7.78-7.84 (m, $J = 2$ H); ^{13}C NMR (100 MHz, CDCl_3): δ 14.1, 22.6, 25.5, 29.3, 31.8, 35.7, 37.9, 42.2, 72.0, 104.4, 117.4, 120.0, 123.6, 124.6, 125.6, 126.6, 128.5, 134.2, 143.6; HRMS (ESI): calcd. for $[\text{M}+\text{H}]^+ \text{C}_{19}\text{H}_{28}\text{NO}$, 286.2165; found, 286.2162.

Preparation of aromatic substrates.

o-Iodoanisole (**1b**), *p*-iodoanisole (**1c**), methyl *p*-anisate (**1d**), *p*-cyanoanisole (**1f**), *p*-*tert*-butylanisole (**1g**), phenanthrene (**1i**), 9,9-dimethylfluorene (**1j**), aniracetam (**1m**), and fenofibrate (**1n**) were purchased from commercial supplier.

N,N-dimethyl-4-methoxybenzamide (**1e**)²⁷ and 2-methyl-2-phenoxy-1-phenyl-propan-1-one (**1h**)²⁸ were synthesized according to the reported literature.

2-methoxycarbonyl-1-phenylindole (1k). To a 300 mL flask, methyl 1H-indole-2-carboxylate (5 mmol), bromobenzene (10 mmol), CuI (3 mmol), K₃PO₄ (8 mmol), *N,N'*-dimethylethylenediamine (6 mmol), and toluene (50 mL) were added. The mixture was stirred at 120 °C for 24 h. After removal of the solvent under reduced pressure, the crude product was purified with flash chromatography to obtain the title compound **1k** (460 mg, 37%) as white solid. ¹H NMR (400 MHz, CDCl₃): δ 3.78(s, 3H), 7.10 (d, *J* = 8.4 Hz, 1H), 7.20 (t, *J* = 7.0 Hz, 1H), 7.28 (t, *J* = 7.2 Hz, 1H), 7.33-7.36 (m, 2H), 7.45 (s, 1H), 7.46-7.55 (m, 3H), 7.74 (d, *J* = 8.0 Hz, 1H); ¹³C NMR (150 MHz, CDCl₃): δ 51.6, 111.5, 111.5, 121.2, 122.4, 125.5, 126.1, 128.0, 128.1, 128.6, 129.0, 138.4, 140.6, 161.7; HRMS (ES): calcd. for [M+H]⁺ C₁₆H₁₄NO₂, 252.1019; found, 252.1014.

2-phenylbenzo[*b*]thiophene (1l). To a 100 mL flask, benzo[*b*]thiophene-2-carboxylic acid (2.8 mmol), iodobenzene (2.7 mmol), Pd(PPh₃)₄ (0.2 mmol), Na₂CO₃ (11 mmol), toluene (7.5 mL), H₂O (7.5 mL), and EtOH (10 mL) were added. The mixture was refluxed for 24 h. The mixture was extracted with ethyl acetate/hexane (2/1, 20 mL x 3), and the combined extracts were washed with water (20 mL) and brine (20 mL), and was dried over Na₂SO₄. After removal of the solvent under reduced pressure, the crude product was purified with flash chromatography to obtain the title compound **1l** (430 mg, 76%) as white solid, which was identified by comparison with their NMR spectra reported in the literature.²⁹

Procedure of the electrooxidative coupling of aromatics with 2-methyloxazoline

General procedue. In the anodic chamber was placed a solution of aromatic compound **1** (0.20 mmol) and 2-methyloxazoline (**2a**) (0.6 or 1.0 mmol) in electrolyte/CH₃CN (0.3 M or 1.0 M, 10.0 mL). In the cathodic chamber were placed trifluoromethanesulfonic acid (150 μL) and electrolyte/CH₃CN (0.3 M or 1.0 M, 10.0 mL). The constant current electrolysis (8.0 mA) was carried out at room temperature or 50 °C with magnetic stirring. After the electrolysis (2.5–5.0 *F*), the reaction mixture was treated with chemical reaction A or chemical reaction B as described before.

***N*-(2-acetoxyethyl)-3-iodo-4-methoxyaniline (3ba).** Electrooxidative coupling (3.0 *F*, r.t., 1.0 M solution of LiClO₄) of *o*-iodoaniline (**1b**) and 2-methyloxazoline (**2a**) (1.0 mmol) followed by treatment of chemical reaction A gave the title compound **3ba** (51.4 mg, 77%) as pale brown oil. ¹H NMR (400 MHz, CDCl₃): δ 2.07 (s, 3H), 3.31 (t, *J* = 5.2 Hz, 2H),

3.78 (s, 3H), 4.24 (t, $J = 5.4$ Hz, 2H), 6.60 (dd, $J = 2.8, 8.4$ Hz, 1H), 6.70 (d, $J = 8.4$ Hz, 1H), 7.09 (d, $J = 2.8$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 20.9, 43.5, 57.1, 63.0, 87.0, 112.5, 113.9, 124.0, 143.0, 151.0, 171.0; HRMS (ESI): calcd. for $[\text{M}+\text{H}]^+$ $\text{C}_{11}\text{H}_{15}\text{IN}_2\text{O}_3$, 336.0091; found, 336.0081.

***N*-(2-hydroxyethyl)-3-iodo-4-methoxyaniline (3ba').** Electrooxidative coupling (3.0 F, r.t., 1.0 M solution of LiClO_4) of *o*-iodoanisole (**1b**) and 2-metyloxazoline (**2a**) (1.0 mmol) followed by treatment of chemical reaction B gave the title compound **3ba'** (43.7 mg, 75%) as white solid. ^1H NMR (400 MHz, CDCl_3): δ 3.20 (t, $J = 5.0$ Hz, 6H), 3.73-3.80 (m, 5H), 6.61 (dd, $J = 2.8, 8.8$ Hz, 1H), 6.70 (d, $J = 8.8$ Hz, 1H), 7.10 (d, $J = 2.8$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 46.8, 57.1, 61.0, 87.0, 112.5, 114.4, 124.3, 143.5, 151.1; HRMS (ESI): calcd. for $[\text{M}+\text{H}]^+$ $\text{C}_9\text{H}_{13}\text{INO}$, 293.9985; found, 293.9976.

***N*-(2-acetoxyethyl)-3-iodo-6-methoxyaniline (3ca).** Electrooxidative coupling (3.0 F, r.t., 1.0 M solution of LiClO_4) of *o*-iodoanisole (**1c**) and 2-metyloxazoline (**2a**) (1.0 mmol) followed by treatment of chemical reaction A gave the title compound **3ca** (47.3 mg, 71%) as pale brown oil. ^1H NMR (400 MHz, CDCl_3): δ 2.08 (s, 1H), 3.37 (t, $J = 5.4$ Hz, 2H), 3.81 (s, 3H), 4.27 (t, $J = 5.6$ Hz, 2H), 6.49 (d, $J = 8.0$ Hz, 1H), 6.86 (d, $J = 2.0$ Hz, 1H), 6.96 (dd, $J = 2.0, 8.0$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 20.9, 42.3, 55.5, 63.0, 83.9, 111.3, 118.1, 125.4, 139.1, 146.7, 171.0; HRMS (ESI): calcd. for $[\text{M}+\text{H}]^+$ $\text{C}_{11}\text{H}_{15}\text{IN}_2\text{O}_3$, 336.0091; found, 336.0082.

***N*-(2-hydroxyethyl)-3-iodo-6-methoxyaniline (3ca').** Electrooxidative coupling (3.0 F, r.t., 1.0 M solution of LiClO_4) of *o*-iodoanisole (**1c**) and 2-metyloxazoline (**2a**) (1.0 mmol) followed by treatment of chemical reaction B gave the title compound **3ca'** (38.2 mg, 65%) as white solid. ^1H NMR (400 MHz, CDCl_3): δ 3.28 (t, $J = 5.2$ Hz, 2H), 3.81 (s, 3H), 3.84 (t, $J = 5.2$ Hz, 2H), 4.53 (s, 1H), 6.49 (d, $J = 8.0$ Hz, 1H), 6.87 (s, 1H), 6.97 (dd, $J = 2.0, 8.0$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 45.5, 55.5, 61.0, 84.0, 111.3, 118.3, 125.4, 149.5, 146.9; HRMS (ESI): calcd. for $[\text{M}+\text{H}]^+$ $\text{C}_9\text{H}_{13}\text{INO}_2$, 293.9985; found, 293.9977.

***N*-(2-acetoxyethyl)-2-methoxy-5-methoxycarbonylaniline (3da).** Electrooxidative coupling (3.5 F, r.t., 0.2 M solution of $\text{Mg}(\text{ClO}_4)_2$) of methyl *p*-anisate (**1d**) and 2-metyloxazoline (**2a**) (1.0 mmol) followed by treatment of chemical reaction A gave the title compound **3da** (49.7 mg, 93%) as pale brown solid. ^1H NMR (400 MHz, CDCl_3): δ 2.07 (s, 3H), 3.46 (t, $J = 5.6$ Hz, 2H), 3.86 (s, 3H), 3.89 (s, 3H), 4.30 (t, $J = 5.6$ Hz, 2H), 4.49 (s, 1H), 6.76 (d, $J = 8.0$ Hz, 1H), 7.26 (d, $J = 2.4$ Hz, 1H), 7.43 (dd, $J = 2.4, 8.0$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 20.8, 42.4, 51.7, 55.5, 63.1, 108.5, 110.2, 119.7,

122.9, 137.2, 150.5, 167.3, 171.0; HRMS (ESI): calcd. for $[M+H]^+$ $C_{13}H_{18}NO_5$, 268.1179; found, 268.1175.

***N*-(2-acetoxyethyl)-3-dimethylaminocarbonyl-6-methoxyaniline (3ea).** Electrooxidative coupling (3.0 F, r.t., 0.2 M solution of $Mg(ClO_4)_2$) of *N,N*-dimethyl-*p*-methoxybenzamide (**1e**) and 2-metyloxazoline (**2a**) (1.0 mmol) followed by treatment of chemical reaction A gave the title compound **3ea** (36.2 mg, 65%) as pale brown solid. 1H NMR (400 MHz, $CDCl_3$): δ 2.06 (3, 3H), 3.02 (br, 6H), 3.40 (t, $J = 5.4$ Hz, 2H), 3.84 (s, 3H), 4.26 (t, $J = 5.4$ Hz, 2H), 4.49 (s, 1H), 6.67 (d, $J = 1.2$ Hz, 1H) 6.68-6.75 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.8, 35.4, 39.7, 42.2, 55.5, 62.9, 108.5, 108.7, 116.2, 128.9, 137.3, 147.7, 171.0, 172.1; HRMS (ESI): calcd. for $[M+H]^+$ $C_{14}H_{21}N_2O_4$, 281.1496; found, 281.1492.

***N*-(2-acetoxyethyl)-3-cyano-6-methoxyaniline (3fa).** Electrooxidative coupling (3.5 F, r.t., 0.2 M solution of $Mg(ClO_4)_2$) of *p*-cyanoanisole (**1f**) and 2-metyloxazoline (**2a**) (1.0 mmol) followed by treatment of chemical reaction A gave the title compound **3fa** (34.0 mg, 73%) as pale brown oil. 1H NMR (400 MHz, $CDCl_3$): δ 2.08 (s, 3H), 3.37-3.42 (m, 2H), 3.89 (s, 3H), 4.29 (t, $J = 5.6$ Hz, 1H), 4.63 (s, 1H), 6.75 (d, $J = 8.0$ Hz, 1H), 6.76 (s, 1H) 7.01 (dd, $J = 1.6, 8.0$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.9, 42.2, 55.7, 62.7, 104.2, 109.2, 111.3, 120.0, 122.2, 138.0, 150.0, 171.0; HRMS (ESI): calcd. for $[M+H]^+$ $C_{12}H_{15}N_2O_3$, 235.1077; found, 235.1073.

***N*-(2-acetoxyethyl)-2-methoxy-5-*tert*-butylaniline (3ga).** Electrooxidative coupling (2.5 F, r.t., 0.3 M solution of $LiClO_4$) of *p-tert*-butylanisole (**1g**) and 2-metyloxazoline (**2a**) (1.0 mmol) followed by treatment of chemical reaction A gave the title compound **3ga** (49.9 mg, 94%) as pale brown oil. 1H NMR (400 MHz, $CDCl_3$): δ 1.31 (s, 9H), 2.09 (s, 3H), 3.45 (t, $J = 5.6$ Hz, 2H), 3.84 (s, 3H), 4.32 (t, $J = 5.6$ Hz, 2H), 6.72 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.9, 31.5, 34.3, 42.6, 55.4, 63.2, 107.7, 109.0, 113.4, 136.9, 144.1, 144.9, 171.1; HRMS (ESI): calcd. for $[M+H]^+$ $C_{15}H_{24}NO_3$, 266.1751; found, 266.1740.

***N*-(2-acetoxyethyl)-2-(1-benzoyl-1-methylethoxy)aniline (3ha_{ortho}) and *N*-(2-acetoxyethyl)-4-(1-benzoyl-1-methylethoxy)aniline (3ha_{para}).** Electrooxidative coupling (2.5 F, r.t., 0.3 M solution of $LiClO_4$) of 2-methyl-2-phenoxy-1-phenyl-propan-1-one (**1h**) and 2-metyloxazoline (**2a**) (0.6 mmol) followed by treatment of chemical reaction A gave the title compounds **3ha_{ortho}** (13.6 mg, 20%) and **3ha_{para}** (43.7 mg, 64%) as pale brown oils. **3ha_{ortho}**: 1H NMR (400 MHz, $CDCl_3$): δ 1.17 (s, 3H), 1.26 (s, 3H), 1.99 (s, 3H), 3.29 (s, 1H), 3.30-3.38 (m, 1H), 3.50-3.58 (m, 1H), 4.17-4.35 (m, 2H), 6.78 (ddd, $J = 1.6, 7.6, 7.6$ Hz, 1H), 6.88-6.91 (m,

2H), 6.95-6.99 (m, 1H), 7.31-7.38 (m, 3H), 7.52 (br, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 20.9, 22.9, 23.0, 45.2, 62.6, 78.5, 113.2, 117.5, 119.1, 122.4, 127.7, 128.0, 128.1, 128.2, 134.7, 139.4, 142.2, 171.0; HRMS (ESI): calcd. for $[\text{M}+\text{Na}]^+ \text{C}_{20}\text{H}_{23}\text{NO}_4\text{Na}$, 364.1519; found, 364.1510. **3ha_{para}**: ^1H NMR (400 MHz, CDCl_3): δ 1.61 (s, 6H), 2.04 (s, 3H), 3.28 (t, $J = 5.4$ Hz, 2H), 4.22 (t, $J = 5.4$ Hz, 2H), 6.45 (d, $J = 8.8$ Hz, 2H), 6.64 (d, $J = 8.8$ Hz, 2H), 7.41 (t, $J = 7.8$ Hz, 2 H), 7.50 (t, $J = 7.8$ Hz, 1 H), 8.35 (d, $J = 7.8$ Hz, 2 H); ^{13}C NMR (100 MHz, CDCl_3): δ 20.8, 25.8, 43.4, 63.1, 85.0, 113.6, 121.0, 128.3, 132.8, 143.1, 147.2, 171.1, 202.6; HRMS (ESI): calcd. for $[\text{M}+\text{Na}]^+ \text{C}_{20}\text{H}_{23}\text{NO}_4\text{Na}$, 364.1519; found, 364.1509.

N-(2-acetoxyethyl)-9-phenanthrylamine (3ia). Electrooxidative coupling (2.5 F, r.t., 0.3 M solution of LiClO_4) of phenanthrene (**1i**) and 2-metyloxazoline (**2a**) (1.0 mmol) followed by treatment of chemical reaction A gave the title compound **3ia** (36.7 mg, 66%) as white solid. ^1H NMR (400 MHz, CDCl_3): δ 2.15 (s, 3H), 3.64 (t, $J = 5.4$ Hz, 2H), 4.53 (t, $J = 5.4$ Hz, 2H), 4.73 (s 1H), 6.78 (s, 1H), 7.42 (t, $J = 7.0$ Hz, 1H), 7.51 (t, $J = 7.4$ Hz, 1H), 7.63-7.73 (m, 3H), 7.92 (d, $J = 6.0$ Hz, 1H), 8.55 (d, $J = 8.4$ Hz, 1H), 8.71 (d, $J = 7.6$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 21.0, 43.5, 63.0, 102.1, 120.3, 122.3, 123.0, 123.4, 125.3, 125.4, 126.3, 126.6, 126.6, 126.9, 131.0, 133.4, 140.7, 171.6; HRMS (ESI): calcd. for $[\text{M}+\text{H}]^+ \text{C}_{18}\text{H}_{18}\text{NO}_2$, 280.1332; found, 280.1334.

N-(2-acetoxyethyl)-9,9-dimethyl-2-fluorenylamine (3ja). Electrooxidative coupling (2.5 F, r.t., 0.3 M solution of LiClO_4) of 9,9-dimethylfluorene (**1j**) and 2-metyloxazoline (**2a**) (1.0 mmol) followed by treatment of chemical reaction A gave the title compound **3ja** (50.1 mg, 85%) as white solid. ^1H NMR (400 MHz, CDCl_3): δ 1.47 (s, 6H), 2.11 (s, 3H), 3.49 (br, 2H), 4.07 (br, 1H), 4.35 (t, $J = 5.6$ Hz, 2H), 6.62 (d, $J = 7.6$ Hz, 1H), 6.73 (s, 1H), 7.22 (t, $J = 7.2$ Hz, 1H), 7.30 (dt, $J = 1.2, 7.4$ Hz, 1H), 7.38 (d, $J = 7.6$ Hz, 1H), 7.55 (d, $J = 8.4$ Hz, 1H), 7.59 (d, $J = 7.6$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 20.9, 27.3, 43.2, 46.6, 63.2, 107.1, 111.7, 118.6, 120.9, 122.2, 125.4, 126.8, 129.6, 139.6, 147.5, 152.6, 155.5, 171.1; HRMS (ESI): calcd. for $[\text{M}+\text{H}]^+ \text{C}_{19}\text{H}_{22}\text{N}_1\text{O}_2$, 296.1645; found, 296.1637.

3-(2-acetoxyethylamino)-2-methoxycarbonyl-1-phenylindole (3ka). Electrooxidative coupling (2.5 F, r.t., 0.3 M solution of NaClO_4) of 2-methoxycarbonyl-1-phenylindole (**1k**) and 2-metyloxazoline (**2a**) (1.0 mmol) followed by treatment of chemical reaction A gave the title compound **3ka** (49.3 mg, 70%) as pale brown solid. ^1H NMR (400 MHz, CDCl_3): δ 2.03 (s, 3H), 3.62 (s, 3H), 3.93 (t, $J = 5.4$ Hz, 2H), 4.35 (t, $J = 5.4$ Hz, 2H), 6.51 (br, 1H), 7.05 (t, $J = 8.8$ Hz, 2H), 7.22-7.28 (m, 3H), 7.35-7.39 (m, 1H), 7.46 (t, $J = 7.4$ Hz, 2H), 7.87 (d, $J = 7.6$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 20.8, 45.2, 50.7, 63.8, 111.2, 111.6, 118.6, 119.4, 122.0, 126.9, 127.1, 127.7, 128.7, 139.7, 139.9, 140.2, 163.3, 171.0;

HRMS (ESI): calcd. for $[M+H]^+$ $C_{20}H_{21}N_2O_4$, 353.1496; found, 353.1493.

3-(2-acetoxyethylamino)-2-methoxycarbonyl-1-phenylindole (3la). Electrooxidative coupling (2.5 F, r.t., 0.3 M solution of $NaClO_4$) of 2-phenylbenzo[*b*]thiophene (**1l**) and 2-metyloxazoline (**2a**) (1.0 mmol) followed by treatment of chemical reaction A gave the title compound **3la** (32.7 mg, 53%) as pale brown solid. 1H NMR (400 MHz, $CDCl_3$): δ 1.93 (s, 3H), 3.39 (t, J = 5.2 Hz, 2H), 4.08 (t, J = 5.2 Hz, 2H), 4.15 (br, 1H), 7.33-7.42 (m, 3H), 7.46 (t, J = 7.6 Hz, 2H), 7.62 (d, J = 6.8 Hz, 2H), 7.72 (d, J = 6.4 Hz, 1H) 7.79 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.7, 47.0, 63.6, 120.9, 122.7, 123.7, 124.0, 124.6, 127.6, 128.8, 129.0, 134.0, 135.6, 136.0, 137.7, 170.9; HRMS (ESI): calcd. for $[M+H]^+$ $C_{18}H_{18}NO_2S$, 312.1053; found, 312.1045.

(2-acetoxyethylamino)aniracetam (3ma). Electrooxidative coupling (3.5 F, r.t., 0.2 M solution of $Mg(ClO_4)_2$) of aniracetam **1m** and 2-metyloxazoline (**2a**) (1.0 mmol) followed by treatment of chemical reaction A gave the title compound **3ma** (44.1 mg, 69%) as pale brown solid. 1H NMR (400 MHz, $CDCl_3$): δ 2.07-2.15 (m, 5H), 2.59 (t, J = 8.0 Hz, 2H), 3.41 (t, J = 5.6 Hz, 2H), 3.88 (s, 3H), 3.91 (t, J = 7.2 Hz, 2H), 4.28 (t, J = 5.8 Hz, 2H), 6.74 (d, J = 8.0 Hz, 1H), 6.95 (d, J = 1.6 Hz, 1H), 7.06 (dd, J = 1.6, 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.7, 20.9, 33.4, 42.4, 46.9, 55.5, 62.9, 108.0, 110.4, 120.0, 126.6, 136.9, 150.2, 170.8, 171.0, 174.6; HRMS (APCI): calcd. for $[M+H]^+$ $C_{16}H_{21}N_2O_5$, 321.1145; found, 321.1437.

(2-acetoxyethylamino)fenofibrate (3na). Electrooxidative coupling (5.0 F, r.t., 0.2 M solution of $Mg(ClO_4)_2$) of aniracetam **1n** and 2-metyloxazoline (**2a**) (1.0 mmol) followed by treatment of chemical reaction A gave the title compound **3na** (81.7 mg, 88%) as pale brown solid. 1H NMR (400 MHz, $CDCl_3$): δ 1.22 (d, J = 6.0 Hz, 6H), 1.64 (s, 6H), 2.07 (s, 3H), 3.45 (t, J = 5.4 Hz, 2H), 4.30 (t, J = 5.4 Hz, 2H), 5.08 (sep, J = 6.2 Hz, 1H), 6.66 (d, J = 8.4 Hz, 1H), 6.95 (dd, J = 2.0, 8.8 Hz, 1H), 7.13 (d, J = 2.0 Hz, 1H), 7.42 (d, J = 8.4 Hz, 2H), 7.70 (d, J = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.8, 21.5, 42.4, 62.8, 69.3, 80.2, 111.0, 115.2, 120.2, 128.3, 131.1, 131.5, 136.6, 138.1, 140.0, 146.4, 171.0, 173.1, 194.9; HRMS (ESI): calcd. for $[M+H]^+$ $C_{24}H_{29}ClNOO_6$, 462.1678; found, 462.1668.

DFT calculations.

DFT calculations were performed with the Gaussian 09 program.³⁰

Cartesian coordinates (Å) of the optimized structure for the radical cation of naphthalene (**1a**) (D_2 symmetry) calculated at the UB3LYP/6-31G(d) level.^{8a}

Atom	X	Y	Z	Atom	X	Y	Z
C	0.000000	0.716377	0.000000	C	-1.236176	-1.402353	0.000000
C	0.000000	-0.716377	0.000000	H	1.243374	-2.488976	0.000000
C	1.236176	-1.402353	0.000000	H	3.389914	-1.242832	0.000000
C	2.452416	-0.696227	0.000000	H	3.389914	1.242832	0.000000
C	2.452416	0.696227	0.000000	H	1.243374	2.488976	0.000000
C	1.236176	1.402353	0.000000	H	-1.243374	2.488976	0.000000
C	-1.236176	1.402353	0.000000	H	-3.389914	1.242832	0.000000
C	-2.452416	0.696227	0.000000	H	-3.389914	-1.242832	0.000000
C	-2.452416	-0.696227	0.000000	H	-1.243374	-2.488976	0.000000

Cartesian coordinates (Å) of the optimized structure for the radical cation of o-iodoanisole (**1b**) (C_s symmetry) calculated at the UB3LYP/3-21G(d) level.^{8a}

Atom	X	Y	Z	Atom	X	Y	Z
C	-2.872644	0.147704	0.000000	H	-4.288220	-1.447612	0.000000
C	-3.239187	-1.178925	0.000000	H	-2.568054	-3.246606	0.000000
C	-2.255364	-2.210174	0.000000	H	-0.158123	-2.676815	0.000000
C	-0.905117	-1.894417	0.000000	H	-1.258076	3.784621	0.000000
C	-0.504828	-0.552510	0.000000	H	-2.555911	2.930476	-0.903150
C	-1.503043	0.499657	0.000000	H	-2.555911	2.930476	0.903150
C	-1.941643	2.939445	0.000000	O	-1.037958	1.749298	0.000000
H	-3.628266	0.920650	0.000000	I	1.513787	-0.029042	0.000000

Cartesian coordinates (Å) of the optimized structure for the radical cation of p-iodoanisole (**1c**) (C_s symmetry) calculated at the UB3LYP/3-21G(d) level.^{8a}

Atom	X	Y	Z	Atom	X	Y	Z
C	-0.847198	-0.903105	0.000000	H	-0.955713	-3.028462	0.000000
C	-0.303857	-2.166035	0.000000	H	3.025030	-1.336763	0.000000
C	1.109289	-2.327959	0.000000	H	2.053673	0.955354	0.000000
C	1.955524	-1.175472	0.000000	H	1.809586	-5.548155	0.000000
C	1.412381	0.084152	0.000000	H	0.406069	-4.885318	0.903161
C	0.000000	0.240245	0.000000	H	0.406069	-4.885318	-0.903161
C	1.015453	-4.805898	0.000000	O	1.743726	-3.501470	0.000000
H	-1.921375	-0.775060	0.000000	I	-0.845711	2.147923	0.000000

Cartesian coordinates (Å) of the optimized structure for the radical cation of methyl p-anisate (**1d**) (C_s symmetry) calculated at the UB3LYP/6-31G(d) level.

Atom	X	Y	Z	Atom	X	Y	Z
C	1.233561	-1.401022	0.000000	H	-2.154864	0.541779	0.000000
C	-0.018457	-2.115364	0.000000	H	2.162007	0.529463	0.000000
C	-1.263587	-1.410928	0.000000	H	-0.623276	-5.309803	0.000000
C	-1.239288	-0.040444	0.000000	H	-1.642265	-4.141818	0.902978

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C	0.000000	0.670120	0.000000	H	-1.642265	-4.141818	-0.902978
C	1.233138	-0.028468	0.000000	H	2.205464	4.453509	0.000000
C	-0.078600	2.170937	0.000000	H	0.647767	4.562647	-0.893340
C	-1.050787	-4.309638	0.000000	H	0.647767	4.562647	0.893340
C	1.150441	4.186967	0.000000	O	0.100011	-3.417696	0.000000
H	2.148923	-1.983643	0.000000	O	1.126712	2.733694	0.000000
H	-2.203930	-1.949130	0.000000	O	-1.144705	2.751903	0.000000

Cartesian coordinates (Å) of the optimized structure for the radical cation of *N,N*-dimethyl-*p*-methoxybenzamide (**1e**) (C_1 symmetry) calculated at the UB3LYP/6-31G(d) level.

Atom	X	Y	Z	Atom	X	Y	Z
C	1.493505	-1.139806	-0.840423	H	-0.512103	-1.601821	-1.410279
C	2.348426	-0.237764	-0.131548	H	5.575939	-0.196302	0.255305
C	1.803509	0.884488	0.548041	H	4.613119	1.296479	0.031246
C	0.443765	1.090296	0.511635	H	4.443753	0.325768	1.540465
C	-0.416556	0.163891	-0.143385	H	-4.784880	-0.644542	-0.501573
C	0.137363	-0.926713	-0.862294	H	-4.743662	0.410560	0.936216
C	-1.865342	0.506413	-0.244929	H	-4.256294	1.053119	-0.657134
C	4.625914	0.292140	0.462891	H	-1.601457	-1.567167	1.279521
C	-4.250033	0.174969	-0.011784	H	-3.069553	-2.299256	0.583498
C	-2.662535	-1.412294	1.080031	H	-3.182597	-1.272249	2.033174
H	1.951358	-1.980982	-1.350033	N	-2.860926	-0.230199	0.241463
H	2.445630	1.580700	1.073648	O	3.631462	-0.537210	-0.182582
H	0.010716	1.961254	0.991974	O	-1.982910	1.558724	-0.905627

Cartesian coordinates (Å) of the optimized structure for the radical cation of *p*-cyanoanisole (**1f**) (C_s symmetry) calculated at the UB3LYP/6-31G(d) level.

Atom	X	Y	Z	Atom	X	Y	Z
C	0.000000	1.244651	0.000000	H	2.137348	1.215689	0.000000
C	1.224406	0.629485	0.000000	H	0.227972	-2.685465	0.000000
C	1.315743	-0.800465	0.000000	H	-2.014904	-1.569048	0.000000
C	0.137607	-1.604632	0.000000	H	-3.785340	2.382713	0.000000
C	-1.090994	-1.000324	0.000000	H	-2.290290	2.788979	0.903741
C	-1.181790	0.435391	0.000000	H	-2.290290	2.788979	-0.903741
C	2.589820	-1.413261	0.000000	N	3.644728	-1.916755	0.000000
C	-2.698897	2.330998	0.000000	O	-2.400322	0.904820	0.000000
H	-0.070386	2.325812	0.000000				

Cartesian coordinates (Å) of the optimized structure for the radical cation of *p*-*tert*-butylanisole (**1g**) (C_s symmetry) calculated at the UB3LYP/6-31G(d) level.

Atom	X	Y	Z	Atom	X	Y	Z
C	-0.901684	-1.488752	0.000000	H	-2.089543	0.262572	0.000000
C	0.426874	-2.007885	0.000000	H	-1.283239	3.713225	1.262280

C	1.546631	-1.111501	0.000000	H	-0.527334	2.401250	2.184437
C	1.339634	0.244500	0.000000	H	-2.041708	2.118752	1.301045
C	0.024677	0.793137	0.000000	H	-1.283239	3.713225	-1.262280
C	-1.078923	-0.129524	0.000000	H	-2.041708	2.118752	-1.301045
C	-0.246612	2.284248	0.000000	H	-0.527334	2.401250	-2.184437
C	-1.078923	2.637728	1.268944	H	0.285746	-5.255968	0.000000
C	-1.078923	2.637728	-1.268944	H	-0.886135	-4.244219	-0.902121
C	-0.274617	-4.323423	0.000000	H	-0.886135	-4.244219	0.902121
C	1.041187	3.128315	0.000000	H	0.775703	4.189272	0.000000
H	-1.756616	-2.154462	0.000000	H	1.652780	2.947635	-0.890728
H	2.542287	-1.543016	0.000000	H	1.652780	2.947635	0.890728
H	2.196558	0.906042	0.000000	O	0.737651	-3.283143	0.000000

Cartesian coordinates (Å) of the optimized structure for the radical cation of 2-methyl-2-phenoxy-1-phenyl-propan-1-one (**1h**) (C_1 symmetry) calculated at the UB3LYP/3-21G(d) level.

Atom	X	Y	Z	Atom	X	Y	Z
C	3.384449	0.231135	-1.081219	H	1.535088	-0.292638	1.800022
C	2.302767	0.352427	-0.147468	H	3.410372	-1.825097	2.237147
C	2.330067	-0.395913	1.076282	H	5.256981	-2.052430	0.588943
C	3.384733	-1.249197	1.318013	H	5.235857	-0.736136	-1.528465
C	4.431805	-1.377894	0.382538	H	-0.934794	2.428880	1.602177
C	4.422370	-0.629124	-0.818484	H	0.822677	2.526666	1.604323
C	0.025100	1.354100	-0.027517	H	0.003880	1.053001	2.174836
C	-0.609417	-0.084248	-0.211561	H	-0.038288	3.322642	-0.909356
C	-0.022760	1.853790	1.432166	H	-0.454666	2.017731	-2.040837
C	-0.567545	2.370571	-1.012212	H	-1.626663	2.538755	-0.818565
C	-2.071001	-0.307568	-0.099789	H	-1.837442	-2.271281	-0.958326
C	-2.544868	-1.558948	-0.548871	H	-4.250696	-2.830400	-0.829733
C	-3.896630	-1.868305	-0.472734	H	-5.853160	-1.185378	0.126522
C	-4.796451	-0.942716	0.064673	H	-5.034416	1.009574	0.951366
C	-4.338314	0.294140	0.524936	H	-2.662503	1.577954	0.814732
C	-2.987065	0.616408	0.438870	O	1.401595	1.250778	-0.497979
H	3.337917	0.825197	-1.987305	O	0.149207	-1.008152	-0.468673

Cartesian coordinates (Å) of the optimized structure for the radical cation of phenanthrene (**1i**) (C_{2v} symmetry) calculated at the UB3LYP/3-21G(d) level.

Atom	X	Y	Z	Atom	X	Y	Z
C	0.000000	1.502357	-1.562590	C	0.000000	-3.587786	-0.282385
C	0.000000	0.732741	-0.397179	C	0.000000	-2.904641	-1.508458
C	0.000000	-0.732741	-0.397179	H	0.000000	1.233832	3.008759
C	0.000000	-1.502357	-1.562590	H	0.000000	-1.233832	3.008759
C	0.000000	1.429851	0.860687	H	0.000000	3.466060	-2.437933
C	0.000000	0.700524	2.062221	H	0.000000	4.672233	-0.259485
C	0.000000	-0.700524	2.062221	H	0.000000	3.358571	1.853931

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C	0.000000	-1.429851	0.860687	H	0.000000	-3.358571	1.853931
C	0.000000	2.904641	-1.508458	H	0.000000	-4.672233	-0.259485
C	0.000000	3.587786	-0.282385	H	0.000000	-3.466060	-2.437933
C	0.000000	2.857973	0.889848	H	0.000000	1.029726	-2.538134
C	0.000000	-2.857973	0.889848	H	0.000000	-1.029726	-2.538134

Cartesian coordinates (Å) of the optimized structure for the radical cation of 9,9-dimethylfluorene (**1j**) (C_{2v} symmetry) calculated at the UB3LYP/3-21G(d) level.

Atom	X	Y	Z	Atom	X	Y	Z
C	0.000000	3.425227	-0.344958	H	0.000000	4.493682	-0.149436
C	0.000000	2.529229	0.737156	H	0.000000	2.909169	1.754079
C	0.000000	1.172616	0.473334	H	0.000000	1.270959	-2.999713
C	0.000000	0.711676	-0.888523	H	0.000000	3.704666	-2.493899
C	0.000000	1.625926	-1.974048	H	0.000000	-2.909169	1.754079
C	0.000000	2.975188	-1.690640	H	0.000000	-4.493682	-0.149436
C	0.000000	0.000000	1.447047	H	0.000000	-3.704666	-2.493899
C	0.000000	-0.711676	-0.888523	H	0.000000	-1.270959	-2.999713
C	0.000000	-1.172616	0.473334	H	1.282923	0.883754	2.977582
C	0.000000	-2.529229	0.737156	H	1.282923	-0.883754	2.977582
C	0.000000	-3.425227	-0.344958	H	2.183292	0.000000	1.728585
C	0.000000	-2.975188	-1.690640	H	-1.282923	-0.883754	2.977582
C	0.000000	-1.625926	-1.974048	H	-1.282923	0.883754	2.977582
C	1.270302	0.000000	2.331692	H	-2.183292	0.000000	1.728585
C	-1.270302	0.000000	2.331692				

Cartesian coordinates (Å) of the optimized structure for the radical cation of 2-methoxycarbonyl-1-phenylindole (**1k**) (C_1 symmetry) calculated at the UB3LYP/6-31G(d) level.

Atom	X	Y	Z	Atom	X	Y	Z
C	-4.350414	0.187658	0.105867	H	-5.427301	0.315483	0.134575
C	-3.806276	-1.095882	0.114016	H	-4.464118	-1.958238	0.150623
C	-2.407852	-1.310641	0.084278	H	-2.003007	-2.315336	0.123467
C	-1.599646	-0.189800	0.014812	H	-3.938370	2.317937	0.098737
C	-2.128056	1.124730	0.034155	H	-1.034444	3.092928	0.025220
C	-3.517967	1.317252	0.076503	H	1.796174	-0.562965	1.745414
C	0.152688	1.238794	0.023679	H	3.226790	-2.584547	1.791725
C	-1.020624	2.012090	0.037874	H	2.919436	-4.367618	0.087411
C	1.546179	1.754773	-0.122718	H	1.176460	-4.128443	-1.669691
C	0.677808	-1.222488	0.015983	H	-0.261306	-2.108066	-1.721679
C	1.672204	-1.340216	1.000555	H	2.624145	4.799432	-0.021360
C	2.466576	-2.478516	1.024708	H	3.532551	3.362248	0.563140
C	2.287659	-3.485063	0.067632	H	3.204109	3.555069	-1.181573
C	1.300305	-3.357143	-0.916374	N	-0.183164	-0.089429	-0.000652
C	0.482479	-2.233305	-0.941582	O	2.518616	1.067523	-0.341805

C	2.822940	3.740442	-0.175365	O	1.539261	3.086478	-0.006394
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Cartesian coordinates (Å) of the optimized structure for the radical cation of 2-phenylbenzo[*b*]thiophene (**1l**) (C_s symmetry) calculated at the UB3LYP/6-31G(d) level.

Atom	X	Y	Z	Atom	X	Y	Z
C	1.313843	-4.153596	0.000000	C	1.176235	2.607265	0.000000
C	-0.076641	-4.389513	0.000000	H	1.998110	-4.995272	0.000000
C	-1.009351	-3.336562	0.000000	H	-0.442400	-5.411890	0.000000
C	-0.521487	-2.042476	0.000000	H	-2.073974	-3.546385	0.000000
C	0.882739	-1.773511	0.000000	H	2.870054	-2.664791	0.000000
C	1.802263	-2.861280	0.000000	H	2.163501	0.000936	0.000000
C	0.000000	0.419722	0.000000	H	-2.206683	2.016283	0.000000
C	1.157382	-0.400344	0.000000	H	-2.237833	4.470937	0.000000
C	-0.033230	1.855098	0.000000	H	-0.104905	5.751287	0.000000
C	-1.267643	2.561659	0.000000	H	2.073805	4.552401	0.000000
C	-1.289291	3.943983	0.000000	H	2.134876	2.101828	0.000000
C	-0.083915	4.665685	0.000000	S	-1.459449	-0.549901	0.000000
C	1.145203	3.991052	0.000000				

Cartesian coordinates (Å) of the optimized structure for the radical cation of aniracetam **1m** (C_1 symmetry) calculated at the UB3LYP/6-31G(d) level.

Atom	X	Y	Z	Atom	X	Y	Z
C	-2.180985	-0.567647	0.867815	H	-3.044505	1.517552	-1.737456
C	-0.848555	-0.251712	0.953511	H	-6.007250	-1.078738	0.081630
C	-0.259923	0.700206	0.062634	H	-4.566492	-2.106898	0.358353
C	-1.068105	1.366891	-0.891668	H	-4.985294	-0.797074	1.525373
C	-2.396209	1.045180	-1.007103	H	3.695257	1.105445	1.363374
C	-2.973270	0.068088	-0.128834	H	3.928589	1.296425	-0.382444
C	1.152570	1.186422	0.252289	H	5.312978	-0.682522	-0.048165
C	-4.994223	-1.108141	0.477630	H	4.335890	-1.216053	1.322944
C	3.592868	0.605939	0.398540	H	3.356676	-2.679718	-0.356564
C	4.291078	-0.767772	0.325814	H	3.670821	-1.526629	-1.652417
C	3.388075	-1.613780	-0.594702	N	2.175889	0.256616	0.162579
C	2.016965	-0.987613	-0.441254	O	-4.253744	-0.156240	-0.325588
H	-2.616858	-1.293166	1.543490	O	1.350014	2.362424	0.495418
H	-0.228900	-0.726732	1.706455	O	0.931463	-1.430262	-0.793029
H	-0.625720	2.128060	-1.525067				

Cartesian coordinates (Å) of the optimized structure for the radical cation of fenofibrate **1n** (C_1 symmetry) calculated at the UB3LYP/6-31G(d) level.

Atom	X	Y	Z	Atom	X	Y	Z
C	-6.614759	0.381694	-0.392487	H	-5.533580	2.171548	-0.892130
C	-6.509511	-0.918014	0.121792	H	-1.043887	2.692254	1.090129
C	-5.276787	-1.440786	0.529414	H	1.336524	2.078065	1.177660

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C	-4.135956	-0.657220	0.409724	H	0.532670	-1.284277	-1.444805
C	-4.220533	0.647888	-0.110159	H	-1.888918	-0.666957	-1.496638
C	-5.473809	1.161446	-0.500142	H	4.883743	2.074116	0.141501
C	-3.047004	1.512893	-0.214367	H	3.838370	1.801419	-1.262707
C	-1.631847	1.016589	-0.146315	H	3.184548	2.560434	0.208144
C	-0.685601	1.814551	0.563447	H	4.482637	0.527398	2.310057
C	0.645318	1.479175	0.602551	H	3.198874	-0.691344	2.220734
C	1.093780	0.342815	-0.135284	H	2.789581	1.037058	2.335692
C	0.147541	-0.430559	-0.896963	H	6.574442	-2.159574	-0.136471
C	-1.182112	-0.087888	-0.911821	H	8.854194	-1.608481	0.786884
C	3.562417	0.405065	0.379734	H	7.579655	-1.262148	1.969026
C	3.873068	1.800635	-0.169063	H	8.336172	0.066029	1.058254
C	3.489645	0.315867	1.907322	H	8.297350	-1.335771	-1.777697
C	4.604016	-0.620703	-0.154393	H	6.660242	-0.842816	-2.235410
C	6.957093	-1.136353	-0.105699	H	7.771143	0.331493	-1.479051
C	7.989441	-0.970987	0.996988	O	-3.094075	2.725728	-0.435278
C	7.444818	-0.714144	-1.484491	O	2.314684	-0.116968	-0.224372
H	-7.581554	0.765833	-0.698319	O	4.325345	-1.571389	-0.843382
H	-5.222165	-2.443871	0.937356	O	5.815257	-0.275977	0.283125
H	-3.184246	-1.057033	0.746833	Cl	-7.937105	-1.897430	0.262441

Further transformation of the coupling product **3aa'**.

To a 100 mL flask, **3aa'** (1.8 mmol), benzaldehyde (2.7 mmol), NaBH(OAc)₃ (3.6 mmol), and 1,2-dichloroethane (8 mL) were added. The mixture was stirred at room temperature for 24 h. The mixture was extracted with ethyl acetate/hexane (2/1, 20 mL x 3), and the combined extracts were washed with water (20 mL) and brine (20 mL), and was dried over Na₂SO₄. After removal of the solvent under reduced pressure, the crude product was purified with flash chromatography to obtain the title compound **5** (487 mg, 98%) as colorless oil. ¹H NMR (400 MHz, CDCl₃): δ 2.10 (s, 1H), 3.34 (t, *J* = 5.4 Hz, 2H), 3.66 (t, *J* = 5.4 Hz, 2H), 4.38 (s, 2H), 7.12 (d, *J* = 7.2 Hz, 1H), 7.23-7.41 (m, 6H), 7.51-7.55 (m, 2H), 7.65 (d, *J* = 8.0 Hz, 1H), 7.90 (d, *J* = 8.0 Hz, 1H), 8.47 (d, *J* = 8.4 Hz, 1H); ¹³C NMR (150 MHz, CDCl₃): δ 53.7, 59.4, 60.0, 118.9, 123.0, 124.5, 125.4, 125.9, 125.9, 127.2, 128.2, 128.5, 128.8, 130.2, 134.9, 137.6, 146.6; HRMS (ESI): calcd. for [M+H]⁺ C₁₉H₂₀NO, 278.1539; found, 278.1532.

To a 20 mL flask, **5** (0.1 mmol), TsCl (0.15 mmol), and pyridine (0.2 mL) were added. The mixture was stirred at room temperature for 4 h. The crude product was purified with flash chromatography to obtain the title compound **6** (32.1 mg, 74%) as white solid. ¹H NMR (400 MHz, CDCl₃): δ 2.36 (s, 3H), 3.39 (t, *J* = 5.8 Hz, 2H), 4.02 (t, *J* = 5.8 Hz, 2H), 4.30 (s, 2H), 6.99 (d, *J* = 7.8 Hz, 1H), 7.10 (d, *J* = 8.0 Hz, 2H), 7.23-7.31 (m, 6H), 7.46-7.49 (m,

2H), 7.53-7.58 (m, 3H), 7.80-7.83 (m, 1H), 8.26-8.29 (m, 1H); ^{13}C NMR (150 MHz, CDCl_3): δ 21.6, 50.3, 59.5, 67.4, 118.6, 123.5, 124.3, 125.3, 125.7, 126.0, 127.2, 127.7, 128.3, 128.3, 128.5, 129.6, 130.1, 132.6, 134.9, 137.8, 144.5, 146.3.; HRMS (ESI): calcd. for $[\text{M}+\text{H}]^+$ $\text{C}_{26}\text{H}_{26}\text{NO}_3\text{S}$, 432.1628; found, 432.1620.

To a 20 mL flask, **5** (0.1 mmol), PPh_3 (0.12 mmol), THF (1 mL), and 40% solution of diethyl azodicarboxylate in toluene (0.12 mmol) were added. $\text{N}_3\text{PO}(\text{OPh})_2$ (0.12 mmol) was added to the mixture. The mixture was stirred at room temperature for 20 h. After removal of the solvent under reduced pressure, the crude product was purified with flash chromatography to obtain the title compound **7** (25.4 mg, 84%) as white solid. ^1H NMR (400 MHz, CDCl_3): δ 3.30 (t, $J = 6.4$ Hz, 2H), 3.36 (t, $J = 6.4$ Hz, 2H), 4.36 (s, 2H), 7.15 (d, $J = 7.2$ Hz, 1H), 7.26-7.35 (m, 5H), 7.41 (t, $J = 7.8$ Hz, 1H), 7.49-7.59 (m, 2H), 7.63 (d, $J = 8.0$ Hz, 1H), 7.87 (d, $J = 7.6$ Hz, 1H), 8.46 (d, $J = 8.4$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 48.7, 51.0, 60.1, 118.5, 123.7, 124.5, 125.4, 125.8, 127.3, 128.3, 128.3, 128.6, 130.3, 135.0, 137.9, 146.6, 150.3; HRMS (APCI): calcd. for $[\text{M}+\text{H}]^+$ $\text{C}_{19}\text{H}_{19}\text{N}_4$, 303.1604; found, 303.1602.

To a 20 mL flask, **5** (0.1 mmol), PPh_3 (0.3 mmol), THF (1 mL), and 40% solution of diethyl azodicarboxylate in toluene (0.3 mmol) were added. Acetone cyanohydrin (0.4 mmol) was added to the mixture. The mixture was stirred at room temperature for 24 h. After removal of the solvent under reduced pressure, the crude product was purified with preparative GPC to obtain the title compound **8** (20.5 mg, 72%) as colorless oil. ^1H NMR (400 MHz, CDCl_3): δ 2.40 (t, $J = 7.0$ Hz, 2H), 3.46 (d, $J = 7.0$ Hz, 2H), 4.33 (s, 2H), 7.18 (d, $J = 7.6$ Hz, 1H), 7.28-7.44 (m, 6H), 7.51-7.59 (m, 2H), 7.67 (d, $J = 8.4$ Hz, 1H), 7.88 (d, $J = 8.8$ Hz, 1H), 8.49 (d, $J = 8.0$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 15.6, 47.7, 59.7, 118.7, 123.4, 125.1, 125.3, 126.1, 126.3, 127.5, 128.3, 128.5, 128.5, 130.5, 134.9, 137.5, 145.6; HRMS (ESI): calcd. for $[\text{M}+\text{H}]^+$ $\text{C}_{20}\text{H}_{19}\text{N}_2$, 287.1543; found, 287.1544.

Synthesis of a mutagen in the Nikko River in Japan **10**.

To a 10 mL sealed tube, **3ca'** (0.1 mmol), acetoamide (0.5 mmol), CuI (0.02 mmol), β -alanine (0.08 mmol), K_3PO_4 (1.0 mmol), and dioxane (1 mL) were added. The mixture was stirred at 110 $^\circ\text{C}$ for 24 h and at 130 $^\circ\text{C}$ for 24 h. After removal of the solvent under reduced pressure, the crude product was purified with flash chromatography to obtain the title compound **9** (17.8 mg, 79%) as white solid, which was identified by comparison with their NMR spectra reported in the literature.¹⁸ Synthesis of a mutagen **10** from **9** was also reported in the literature.¹⁸

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List of Publications

1. Metal- and Chemical-Oxidant-Free C–H/C–H Cross-Coupling of Aromatic Compounds: The Use of Radical-cation Pools
Morofuji, T.; Shimizu, A.; Yoshida, J. *Angew. Chem., Int. Ed.* **2012**, *51*, 7259-7262.
(Chapter 1)
2. Electrochemical C–H Amination: Synthesis of Aromatic Primary Amines via *N*-Arylpyridinium Ions
Morofuji, T.; Shimizu, A.; Yoshida, J. *J. Am. Chem. Soc.* **2013**, *135*, 5000-5003.
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3. Electrochemical Intramolecular C–H Amination: Synthesis of Benzoxazoles and Benzothiazoles
Morofuji, T.; Shimizu, A.; Yoshida, J. *Chem. Eur. J.* **2015**, *21*, 3211-3214.
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4. Direct C–N Coupling of Imidazoles with Aromatic and Benzylic compounds via Electrooxidative C–H Functionalization
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(Chapter 4)
5. Heterocyclization Approach for Electrooxidative Coupling of Functional Primary Alkylamines with Aromatics
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Other Publications

1. Direct Dendronization of Polystyrenes Using Dendritic Diarylcarbenium Ion Pools
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