JOC The Journal of Organic Chemistry

pubs.acs.org/joc Note

One-Pot Synthesis of Tertiary Amides from Organic Trichlorides through Oxygen Atom Incorporation from Air by Convergent Paired Electrolysis

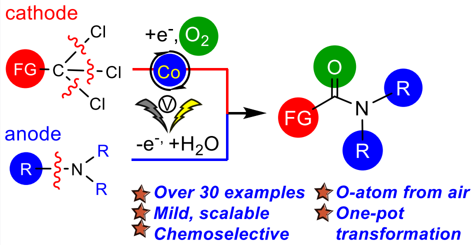
Zhongli Luo, Kenji Imamura, Yoshihito Shiota, Kazunari Yoshizawa, Yoshio Hisaeda,* and Hisashi Shimakoshi*

Cite This: *J. Org. Chem.* 2021, 86, 5983−5990

Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: A convergent paired electrolysis catalyzed by a B_{12} complex for the one-pot synthesis of a tertiary amide from organic trichlorides ($R-CCl_3$) has been developed. Various readily available organic trichlorides, such as benzotrichloride and its derivatives, chloroform, dichlorodiphenyltrichloroethane (DDT), trichloro-2,2,2-trifluoroethane (CFC-113a), and trichloroacetonitrile ($CNCCl_3$), were converted to amides in the presence of tertiary amines through oxygen incorporation from air at room temperature. The amide formation mechanism in the paired electrolysis, which was mediated by a cobalt complex, was proposed.



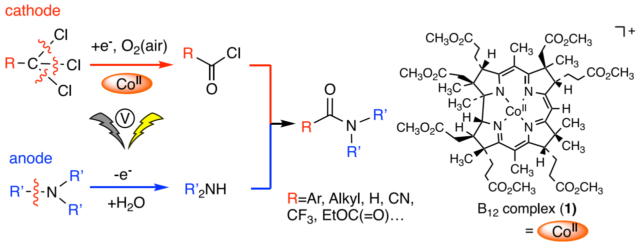
Over 30 examples
Mild, scalable
Chemoselective
O-atom from air
One-pot transformation

During the past decade, electroorganic synthesis has been recognized as a green and sustainable process in the field of synthetic organic chemistry.[1] The electrochemical method serves as a straightforward and powerful technique to electrochemically activate the substrate by an electrode process, the so-called direct electrolysis. As an electric current could replace the traditional chemical oxidants and reductants in electrochemistry, electroorganic synthesis offers a mild and efficient protocol for various molecular transformations in both academic and industrial chemistries.[2]

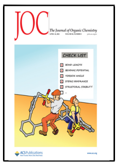
Other attention has focused on the electrochemical elimination of organic pollutants such as organohalogen waste since many organohalogen compounds, including organic trichlorides ($RCCl_3$) such as DDT or chlorofluorocarbons (CFCs), are dispersed in the environment.[3] Therefore, considerable interest has focused on the electrochemical reduction of such organic halides for both the degradation of these substances and a fundamental understanding of their redox behavior.[4] Recently, we reported the unique transformation of benzotrichloride to an ester or amide by aerobic electrolysis using the bioinspired cobalt complex, a B_{12} derivative, as a mediator (indirect electrolysis).[5] The electrochemically formed Co(I) species reacts with benzotrichloride to form oxygen-incorporated products, i.e., an ester or amide, in the presence of an alcohol or amine in air. Acyl chloride could be formed as an intermediate of these reactions. This unique molecular transformation prompted us to develop various tertiary amide syntheses in a green electrochemical method. As the amide is the key building block in natural products, agrochemicals, biologically and pharmaceutically active compounds, and functional materials, effective and efficient methodologies for amide synthesis have been studied, such as the oxidative amidation of alcohols or aldehydes with amines, the carbonylation of aryl iodides and tertiary amines using palladium catalyst, etc.[6]

We now describe the convergent paired electrochemical synthesis of tertiary amides from various organic trichlorides, including environmental pollutants, which is catalyzed by the B_{12} complex heptamethyl cobyrinate (**1**)[7] in air at room temperature as shown in Scheme 1. The paired electrolysis simultaneously produces products at both the cathode and the anode and also optimizes the energy efficiency of the oxidation and reduction processes.[8] The electricity on both electrodes is effectively utilized for the desired reactions. Among the paired

Scheme 1. Convergent Paired Electrolysis for the Amide from Organic Trichloride with a Tertiary Amine Catalyzed by a B_{12} Complex (1)



Received: January 21, 2021
Published: April 2, 2021

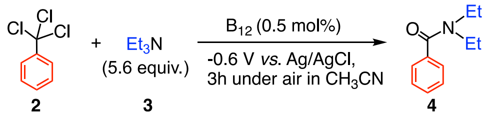


https://doi.org/10.1021/acs.joc.1c00161
J. Org. Chem. 2021, 86, 5983−5990

electrolyses, a convergent paired electrolysis produces intermediates at the cathode and the anode, and the subsequent reaction of the intermediates could produce the target product without any loss of the electricity.[8a,b] The direct synthesis of a tertiary amide with tertiary amines from organic trichlorides through oxygen incorporation from air by a convergent paired electrolysis is reported in this study.[9] The development of the substrate scope and mechanistic studies were also conducted.

Before the bulk electrolysis, cyclic voltammetry (CV) studies were conducted to investigate the cathodic and anodic process of **1** with $RCCl_3$ and a tertiary amine as shown in Figures S1 and S2, respectively. A reversible Co(II)/Co(I) redox couple of **1** was observed at −0.59 V vs. Ag/AgCl under N_2 in CH_3CN. The addition of 50 equiv mol of benzotrichloride (**2**) changed the voltammetric pattern of **1**, and a new irreversible wave was observed around −0.6 V vs. Ag/AgCl in air. The appearance of a large catalytic current peak implies the efficient reaction of the Co(I) species of **1** with **2**, while an irreversible anodic oxidation peak was observed for triethylamine (**3**) in CN_3CN in air. A tertiary amine is known to cause oxidative dealkylation to form a dialkyl amine and an aldehyde in the presence of H_2O.[10] These CV studies suggest the potential for the desired paired electrolysis of $RCCl_3$ and the tertiary amine mediated by **1** in air at room temperature.

Table 1. Reaction Optimization[a]



entry[a]	conditions	electrode	conversion (%)[b]	yield (%)[b]
1	as shown	C(−)–C(+)	99	95
2	as shown	Pt(−)–Pt (+)	64	61
3	as shown	C(−)–Pt(+)	99	73
4	as shown	Pt(−)–C(+)	55	53
5	as shown	C(−)–Zn(+)	99	12
6[c]	as shown	C(−)–C(+)	99	0[d]
7[e]	as shown	C(−)–C(+)	44	35
8	no catalyst	C(−)–C(+)	trace	trace
9	+1.3 V vs. Ag/AgCl	C(−)–C(+)	90	66
10	dry CH_3CN[f]	C(−)–C(+)	99	20
11[g]	as shown	C(−)–C(+)	60	41
12	no electricity	C(−)–C(+)	0	0
13[h]	as shown	C(−)–C(+)	92	89

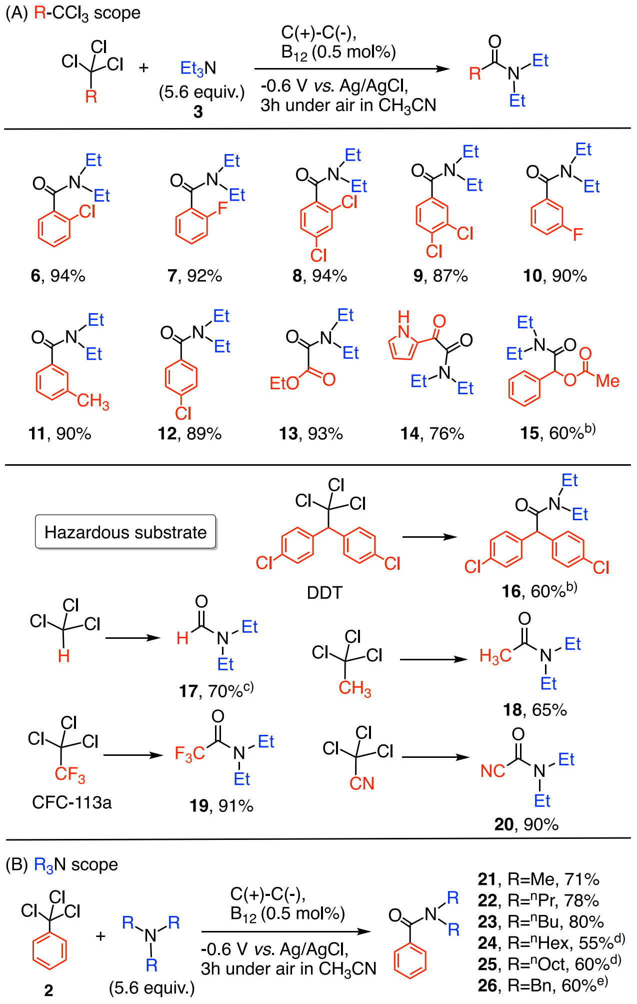
[a] Conditions are as follows: [**1**] = 1.25×10^{-4} M, [**2**] = 2.5×10^{-2} M, [**3**] = 1.4×10^{-1} M, [nBu_4NClO_4] = 1×10^{-1} M, and solvent CH_3CN at room temperature. Applied potentials were −0.6 V vs. Ag/AgCl for 3 h. [b] Conversions of **2** and the yields of the product (**4**) were based on the initial concentration of the substrate. [c] Electrolysis was carried out in the glovebox (O_2 < 1 ppm). [d] Mixture of (*Z*)- and (*E*)-1,2-dichlorostilbenes (**50** and **51**, respectively) were formed at 70% and 16%, respectively. [e] Under O_2. [f] H_2O < 100 ppm. [g] An imine/oxime-type cobalt complex (**5**) was used as the catalyst. [h] Gram scale electrolysis was carried out using 1.03 g of **2** in CH_3CN containing of 0.1 M nBu_4NPF_6.

The convergent paired electrolysis of **2** with **3** was carried out in an undivided cell equipped with a carbon felt (C) or a Pt mesh cathode and a C, Pt, or Zn plate anode in air at room temperature in 0.1 M $^{n}Bu_4NClO_4$, which contained CH_3CN. The optimization of the reaction, including the control reaction, is summarized in Table 1. When the electrolysis was carried out at −0.6 V vs. Ag/AgCl in air using the C(+)−C(−) electrode pair with 0.5 mol % **1**, *N*,*N*-diethylbenzamide (**4**) was obtained in a 95% yield with an excellent selectivity (Table 1, entry 1). The turnover number of catalyst **1** was 190. During the electrolysis, a +1.2 to +1.3 V vs. Ag/AgCl potential was charged on the noncontrolled counter anode, which allowed the oxidation of **3**.[11] The electrode materials had an influence on this reaction, and other electrode pairs afforded only moderate 53−73% yields of **4** (Table 1, entries 2−4). When Zn was used as the anode, the yield of **4** decreased to 12% since Zn worked as a sacrificial electrode that disturbed the oxidation of **3** (Table 1, entry 5). When the electrolysis was carried out under N_2 (in the glovebox, O_2 < 1 ppm), almost all of **2** was consumed after 3 h of electrolysis, and dechlorinated products, (*Z*)- and (*E*)-1,2-dichlorostilbenes (**50** and **51**, respectively), were obtained instead of **4** (Table 1, entry 6). In contrast, too much oxygen disturbed the reaction, and the conversion of **2** was only 44% after 3 h of electrolysis because oxygen quenched the labile Co(I) species (Table 1, entry 7). Without a catalyst, the reaction did not proceed under the same conditions (Table 1, entry 8). When the anodic potential was controlled at +1.3 V vs. Ag/AgCl based on the oxidation potential of **3** (Figure S2), 66% of **4** was obtained (Table 1, entry 9), while the ca. −0.8 V vs. Ag/AgCl potential was charged on the noncontrolled counter cathode during the electrolysis. The yield of **4** decreased to 20% in dry CH_3CN (H_2O < 100 ppm) since H_2O is necessary for the formation of diethyl amine by the hydrolysis of the oxidized intermediate of **3** (Table 1, entry 10).[10] The imine/oxime-type cobalt complex (**5**) [Co(III){(C_2C_3)(DO)(DOH)pn}Br_2] (see Chart S1 in the Supporting Information), which is a well-known functional model compound of B_{12},[12] showed a low reactivity with a 41% yield of the product (Table 1, entry 11), probably due to its low stability under aerobic electrolysis conditions.[13] The B_{12} complex **1** is a tough and excellent catalyst for the reaction. No desired product could be produced without electricity (Table 1, entry 12). Notably, the gram-scale electrolysis was easily designed due to the simple setup of the reaction system in the paired electrolysis, and a 20× substrate concentration with 1.03 g of **2** afforded an 89% yield of **4** using cheap C electrodes (Table 1, entry 13).

With the optimized reaction conditions in hand,[14] the aerobic convergent paired electrolysis for the formation of an amide was applied to other substrates, i.e., benzotrichloride derivatives, DDT, chloroform ($CHCl_3$), 1,1,1-trichloroethane (CH_3CCl_3), CFC-113a (CF_3CCl_3), trichloroacetonitrile ($CNCCl_3$), etc., as shown in Scheme 2A. The corresponding diethylamides (**6**−**20**) were obtained in moderate to good yields. When 3-methylbenzotrichloride was used as the substrate, *N*,*N*-diethyl-3-methylbenzamide (**11**) was obtained in a 90% yield as a mosquito repellent, DEET.[15] From trichloroacetonitrile ($CNCCl_3$), cyanoformamide (**20**) was obtained in a 90% yield. The tertiary amine scope was also investigated, as shown in Scheme 2B. A variety of the tertiary amides (**4** and **21**−**26**) were obtained from **2** with the symmetric tertiary amines in moderate to good yields.

When the asymmetric tertiary amines (**27**−**30**) were used as the anodic substrate, asymmetric dialkylamides (**35**−**37**, respectively) were obtained with symmetric dialkylamides (**21** and **4**) as byproducts, as shown in Scheme 3. From the cyclic asymmetric tertiary amines (**31**−**33**), cyclic dialkylamides (**38**−**40**) were obtained in moderate yields. Notably, *N*-acylpiperidine (**39**), a more promising mosquito repellent than

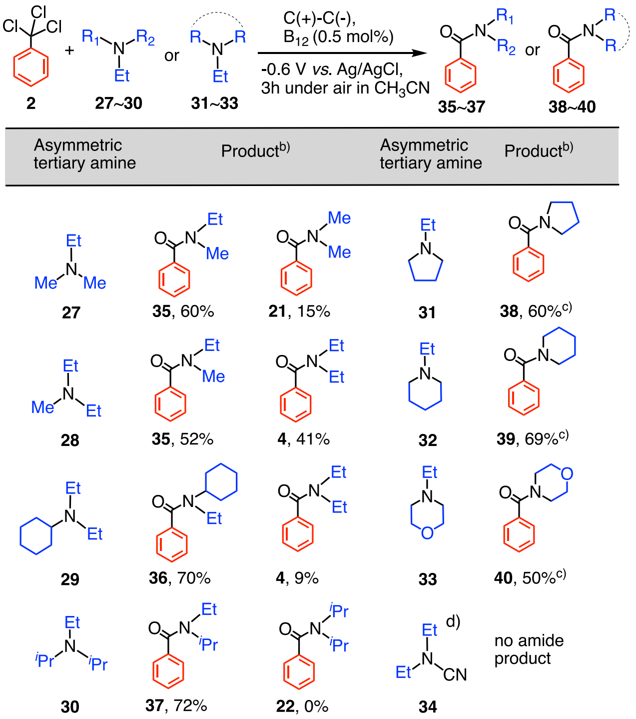
Scheme 2. Reaction Scope[a]



[a]Conditions are as follows: $[\mathbf{1}] = 1.25 \times 10^{-4}$ M, $[\mathrm{R{-}CCl_3}] = 2.5 \times 10^{-2}$ M, $[\mathbf{3}] = 1.4 \times 10^{-1}$ M, and $[{}^n\mathrm{Bu_4NClO_4}] = 1 \times 10^{-1}$ M at room temperature. Applied potentials were −0.6 V vs. Ag/AgCl for 3 h. The yields of the product were based on the initial concentration of the substrate. [b]Applied potentials were −1.1 V vs. Ag/AgCl for 3 h. [c]Conditions are as follows: $[\mathbf{1}] = 2.5 \times 10^{-4}$ M, $[\mathrm{R{-}CCl_3}] = 5.0 \times 10^{-2}$ M, and $[\mathbf{3}] = 7 \times 10^{-1}$ M. Applied potentials were −0.9 V vs. Ag/AgCl for 3 h. [d]Solvent DMF. [e]The applied potential was −0.8 V vs. Ag/AgCl.

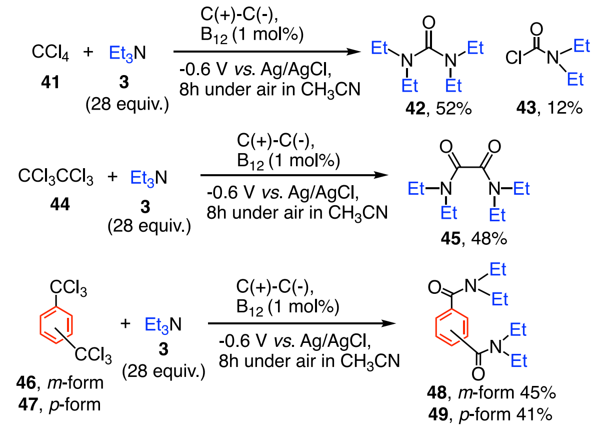
DEET, was obtained by this method.[16] It is noted that no amide product was obtained when diethyl cyanoamine (**34**) was used as the anodic substrate, since the oxidation potential of **34** is over +1.8 V vs. Ag/AgCl in CH_3CN (Figure S15) and no desired diamine could be formed by the anodic reaction. Moreover, the paired electrolysis was applied for the bifunctional substrate with 1 mol % B_{12} catalyst, as shown in Scheme 4. From carbon tetrachloride (**41**) with **3**, tetraethylurea (**42**) and diethylcarbamoyl chloride (**43**) were obtained under optimized conditions in 52% and 12% yields, respectively. From 1,1,1,2,2,2-hexachloroethane (**44**) with **3**, *N,N,N′,N′*-tetraethyl oxamide (**45**) was obtained in a 48% yield. As ureas and oxamides are important carbonyl compounds in organic synthesis, the one-pot synthesis of these compounds under mild conditions should have a significant impact in both the academic and industrial chemistries.[17]

Scheme 3. Asymmetric Tertiary Amine Scope[a]



[a]Conditions are as follows: $[\mathbf{1}] = 1.25 \times 10^{-4}$ M, $[\mathbf{2}] = 2.5 \times 10^{-2}$ M, $[\mathrm{amine}] = 1.4 \times 10^{-1}$ M, and $[{}^n\mathrm{Bu_4NClO_4}] = 1 \times 10^{-1}$ M at room temperature. Applied potentials were −0.6 V vs. Ag/AgCl for 3 h. [b]The conversion of substrate $PhCCl_3$ and the yield of the product were based on the initial concentration of the substrate. [c]No other amide product was obtained. [d]The oxidation potential (E_{pa}) of **34** is > +1.8 V vs. Ag/AgCl in CH_3CN (Figure S4).

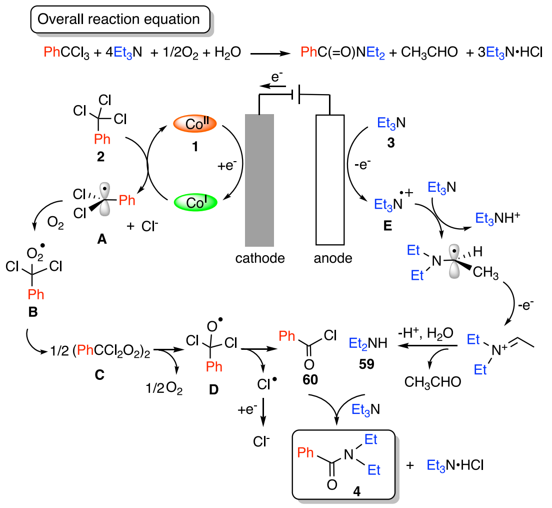
Scheme 4. Application of the Paired Electrolysis for Dual Amidation



The proposed reaction mechanism is shown in Scheme 5. The dichloromethylbenzene radical (**A**) should be formed from the trichloromethylbenzene (**2**) by the Co(I) species of **1**.[5,9] The radical **A** may rapidly react with oxygen to form the peroxy radical (**B**).[18] The coupling and subsequent elimination of oxygen may form the oxy radical **D**. The disproportionation of **D** should form the acyl chloride as an intermediate.[19] At the same time, the tertiary amine was oxidized at the anode to give a radical cation (**E**), which would decompose into the dialkylamine (**59**) by hydrolysis.[20] The acyl chloride species should react with the dialkylamine to form the tertiary amides.

https://doi.org/10.1021/acs.joc.1c00161
J. Org. Chem. 2021, 86, 5983−5990

Scheme 5. Proposed Mechanism



The actual formation of the acyl chloride (**56**) was confirmed by GC-MS during the electrolysis of 3,4-dichlorobenzotrichloride (**55**) in the absence of a tertiary amine, as shown in Scheme S1B (see Figure S17). To support this mechanism, an ESR spin-trapping experiment was also conducted using 5,5-dimethylpyrroline *N*-oxide (DMPO), and the ESR signal for the oxygen-centered radical-trapped DMPO (**58**)[21] ($g = 2.009$, $A_N = 13.5$ G, and $A_H = 7.7$ G) was observed during the electrolysis of 4-chlorobenzotrichloride (**57**) in air, as shown in Scheme S1C. Under this condition, the yield of **10** decreased to 5%. To help understand the reaction of the carbon-centered radical **A** with O_2 to form acyl chloride, we performed DFT calculations using the B3LYP functional combined with the 6-31G** basis. All the calculated energies are summarized in Figure 1. The DFT calculations support the proposed mechanism of the energetically preferred acyl chloride formation. Thus, the formed acyl chloride should react with the dialkylamine to form the tertiary amide.[22] Finally, the incorporation of oxygen into the amide was confirmed using $^{18}O_2$. In the MS analysis for the electrolysis of **2**, the parent peak was observed at m/z 177 for **4** in air, while corresponding parent peak for **4′** (^{18}O) observed at m/z 179 under $^{18}O_2$, as shown in Scheme S1D (see Figure S18).

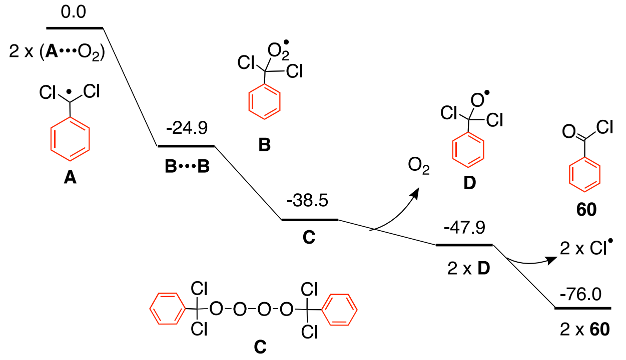


Figure 1. Computed energy diagrams for the acyl chloride (**60**) formation step. Units are in kilocalories per mole.

In summary, we have developed a convergent paired electrolysis method for the direct synthesis of tertiary amides from organic trichlorides under mild conditions. Both the cathodic and anodic reactions are effectively utilized for the desired organic synthesis without the need for sacrificial redox reagents. Notably, this method can also be scaled up for the practical synthesis of amides using cheap carbon- felt electrodes in a simple undivided cell. Further applications of the paired electrolysis reactions are ongoing in our laboratory.

■ EXPERIMENTAL SECTION

Chemicals. All solvents and chemicals used in this study were of reagent grade and used without further purification unless otherwise noted. Dry CH_3CN was purchased from Kanto Kagaku, and the water content was measured before use of ca. 100 ppm. The heptamethyl cobyrinate perchlorate (**1**) (Chart S1) was synthesized by a previously reported method.[24] The cobalt complex Co(III){(C_2C_3)(DO)(DOH)pn}Br_2 (**5**) (Chart S1) ((C_2C_3)(DO)(DOH)pn is the deprotonated form of 4,10-dipropyl-5,9-diazatrideca-4,9-diene-3,10-dione dioxime) was prepared according to the literature.[25] Authentic samples of the amide products from the catalytic reactions were purchased from Aldrich or Tokyo Kasei Kogyo (TCI). Other compounds were isolated by chromatography (Silica Gel 60N, spherical, neutral) using dichloromethane/*n*-hexane (1:1) as the eluent and identified by GC-MS, ^1H NMR, ^{13}C NMR, HR-MS (EI), and IR techniques. Oxygen gas ($^{18}O_2$) (97.0% atom ^{18}O) was purchased from Shoko Co., Ltd. and used as received. 3-Methylbenzotrichloride, the substrate for the electrochemical synthesis of DEET (**11**), was synthesized according to the literature.[26]

Measurements. The elemental analyses were obtained from the Service Center of Elementary Analysis of Organic Compounds at Kyushu University. The NMR spectra were recorded by a Bruker Avance 500 spectrometer and a Bruker Avance NEO 400 spectrometer at the Center of Advanced Instrumental Analysis of Kyushu University. The ESR spectra were measured using a Bruker EMX-Plus X-band spectrometer at room temperature. The UV−vis absorption spectra were measured by a Hitachi U-3300 spectrophotometer at room temperature. The MALDI-TOF mass spectra were obtained by a Bruker autoflex II instrument using 6-aza-2-thiothymine as the matrix. The high resolution-mass spectra of the new compounds (**15**, **35**, and **36**) were obtained by a JEOL JMS-700 instrument using *m*-nitrobenzylalcohol as the matrix. The gas chromatography−mass spectra (GC-MS) were obtained using a Shimadzu GCMS-QP5050A instrument equipped with a J&W Scientific DB-1 column (length of 30m, ID of 0.25 mm, and film of 0.25 μm) and helium as the carrier gas. For the measurement, the injector and detector temperatures were 250 °C, and the oven temperature was initially held at 100 °C for 2 min and then increased to 240 °C at a rate of 10 °C/min. The gas chromatography (GC) data were obtained using a Shimadzu GC-2010 instrument equipped with a J&W Scientific DB-1 column (length of 30m, ID of 0.25 mm, and film of 0.25 μm) and argon as the carrier gas. For the measurement, the injector and detector temperatures were 250 °C, and the oven temperature was initially held at 100 °C for 2 min and then increased to 240 °C at a rate of 10 °C/min. The IR spectra were recorded by a JASCO FT-IR 460 plus KH spectrophotometer using KBr discs. The cyclic voltammogram (CV) was obtained using a BAS CV 50 W electrochemical analyzer. A three-electrode cell equipped with a 3.0 mm diameter glassy carbon (GC) rod and a 1.6 mm diameter platinum (Pt) wire as the working and counter electrodes, respectively, were used. An Ag/AgCl (3.0 M NaCl) electrode served as the reference. Acetonitrile solutions containing **1** (1.0×10^{-3} M) and $^nBu_4NClO_4$ (1.0×10^{-1} M) were deaerated prior to each measurement, and the inside of the cell was maintained under a nitrogen atmosphere throughout each measurement. With this setup, the $E_{1/2}$ value of ferrocene/ferrocenium (Fc/Fc^+) was +0.44 V vs. Ag/AgCl. The water content in the CH_3CN solvent was measured by a Karl Fischer moisture analyzer (Metrohm 831 KF).

General Procedure for Paired Electrolysis. The controlled-potential electrolysis of benzotrichloride (**2**) was carried out in a one-compartment cell equipped with a carbon felt cathode and anode (1 × 3 cm^2) at −0.6 V vs. Ag/AgCl in the presence of **1** at room temperature in 0.14 M triethylamine (**3**) and 0.1 M ^{n}Bu$_4$NClO$_4$ that contained 10 mL of CH$_3$CN in air at room temperature. The applied potential for the electrolysis between the working and reference electrodes was kept constant using a Hokuto Denko HA BF-501A potentiostat, and the electrical quantity was also recorded. The concentrations of the catalyst (**1**) and substrate (**2**) were 1.25×10^{-4} and 2.5×10^{-2} M, respectively. After the electrolysis, the electrolyte solution was passed through silica gel using a CHCl$_3$ eluent, then analyzed by GC-MS, ^{1}H NMR, and ^{13}C NMR. All other products in the paired electrolysis were purified by the same method.

Gram-Scale Paired Electrolysis. A 20× scale-up of the electrolysis of **2** (1.03 g, 1.25×10^{-4} M) was carried out at −0.6 V vs. Ag/AgCl in the presence of **1** (1.25×10^{-4} M) at room temperature in 0.1 M ^{n}Bu$_4$NPF$_6$ and 0.14 M **3** that contained 200 mL of CH$_3$CN with same reaction conditions as general procedure. After electrolysis, the product was purified by silica gel chromatograph (CHCl$_3$ eluent), and 0.788 g (89% yield) of **4** was obtained.

ESR Spin-Trapping Experiment. The ESR spectra of the DMPO spin-adduct were observed after 1 h of electrolysis at −0.6 V vs. Ag/AgCl in 0.1 M ^{n}Bu$_4$NClO$_4$ that contained CH$_3$CN in air at room temperature, where [**1**] = 1.25×10^{-4} M, [**2**] = 2 0.5×10^{-2} M, [**3**] = 1.4×10^{-1} M, and [DMPO] = 6.25×10^{-2} M. The settings for the ESR measurements were as follows: a frequency of 9.78 GHz, a power of 1.0 mW, a center field of 3515 G, a sweep width of 150 G, a modulation amplitude of 3.0 G, a time constant of 40 ms, and a sweep time of 20 s.

Theoretical Calculations. Geometry optimizations were performed using the hybrid (Hartree−Fock/DFT) B3LYP functional[27,28] combined with the 6-31G** basis set.[29] The RB3LYP functional was used for the closed-shell molecules. The solvent effects were estimated for methanol using the PCM method. The Gaussian 09 program[30] was used for all the calculations. After the structural optimization, the vibration frequencies were systematically computed to ensure that the potential-energy surface on each optimized geometry corresponded to a local minimum with no imaginary frequencies.

Analytical Data of the Compounds. *2-Chloro-N,N-diethylbenzamide (**6**).*[31] Colorless oil, 48 mg, 94% yield. GC-MS *m*/*z* 211. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.40−7.38 (m, 1H), 7.32−7.28 (m, 3H), 3.80−3.78 (m, 1H), 3.42−3.37 (m, 1H), 3.19−3.12 (m, 2H), 1.29−1.25 (t, J = 8.0 Hz, 3H), 1.08−1.04 (t, J = 8.0 Hz, 3H). ^{13}C{^{1}H} NMR (125 MHz, CDCl$_3$): δ 167.7, 136.8, 130.3, 129.8, 129.6, 127.5, 126.9, 42.7, 38.9, 13.9, 12.6.

*2-Fluoro-N,N-diethylbenzamide (**7**).*[32] Yellow oil, 45 mg, 92% yield. GC-MS *m*/*z* 195. ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.38−7.31 (m, 2H), 7.20−7.17 (m, 1H), 7.11−7.08 (m, 1H), 3.60−3.57 (m, 2H), 3.24−3.19 (q, J = 7.2 Hz, 2H), 1.18−1.15 (t, J = 7.2 Hz, 3H), 1.10−1.07 (t, J = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (125 MHz, CDCl$_3$): δ 66.1, 158.1 (C−F, $^{1}J_{\mathrm{C-F}}$ = 246.5 Hz), 130.6 (C−F, $^{3}J_{\mathrm{C-F}}$ = 7.3 Hz), 128.5 (C−F, $^{3}J_{\mathrm{C-F}}$ = 4.5 Hz), 125.5 (C−F, $^{2}J_{\mathrm{C-F}}$ = 18.3 Hz), 124.4 (C−F, $^{4}J_{\mathrm{C-F}}$ = 3.7 Hz), 115.8 (C−F, $^{2}J_{\mathrm{C-F}}$ = 21.9 Hz), 43.0, 39.2, 13.9, 12.8.

*2,4-Dichloro-N,N-diethylbenzamide (**8**).*[33] Yellow oil, 58 mg, 94% yield. GC-MS *m*/*z* 246. ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.42−7.41 (m, 1H), 7.31−7.29(m, 1H), 7.22−7.21 (m, 1H), 3.81−3.80 (m, 1H), 3.41−3.38 (m, 1H), 3.18−3.11 (m, 2H), 1.28−1.25(t, J = 7.2 Hz, 3H), 1.08−1.05 (t, J = 7.2 Hz, 3H). ^{13}C NMR{^{1}H} (125 MHz, CDCl$_3$): δ 166.8, 135.3, 135.1, 131.3, 129.6, 128.4, 127.4, 42.7, 39.1, 13.9, 12.6.

*3,4-Dichloro-N,N-diethylbenzamide (**9**).*[34] Pale green oil, 54 mg, 87% yield. GC-MS *m*/*z* 246. ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.49−7.47 (m, 2H), 7.22−7.20(m, 1H), 3.53 (bs, 2H), 3.25 (bs, 2H), 1.24−1.13 (m, 6H). ^{13}C NMR{^{1}H} (125 MHz, CDCl$_3$): δ 168.8, 137.1, 133.5, 132.9, 130.5, 128.6, 125.7, 43.3, 39.5, 14.1, 12.9.

*3-Fluoro-N,N-diethylbenzamide (**10**).*[35] Yellow oil, 44 mg, 90% yield. GC-MS *m*/*z* 195. ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.39−7.36 (m, 1H), 7.14−7.07 (m, 2H), 3.54 (bs, 2H), 3.52 (bs, 2H), 1.25−1.12 (m, 6H). ^{13}C NMR{^{1}H} (125 MHz, CDCl$_3$): δ 169.8, 162.5 (C−F, $^{1}J_{\mathrm{C-F}}$ = 248.3 Hz), 139.4 (C−F, $^{3}J_{\mathrm{C-F}}$ = 6.2 Hz), 130.2 (C−F, $^{3}J_{\mathrm{C-F}}$ = 8.2 Hz), 122.0 (C−F, $^{4}J_{\mathrm{C-F}}$ = 3.7 Hz), 116.1 (C−F, $^{2}J_{\mathrm{C-F}}$ = 21.0 Hz), 113.7 (C−F, $^{2}J_{\mathrm{C-F}}$ = 21.9 Hz), 43.2, 39.4, 14.2, 12.9.

*4-Chloro-N,N-diethylbenzamide (**12**).*[36] Yellow oil, 47 mg, 89% yield. GC-MS *m*/*z* 211. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.39−7.36 (m, 2H), 7.33−7.31 (m, 2H), 3.53 (bs, 2H), 3.24 (bs, 2H), 1.24 (bs, 3H), 1.12 (bs, 3H). ^{13}C{^{1}H} NMR (125 MHz, CDCl$_3$): δ 170.2, 135.7, 135.1, 128.7, 127.8, 43.3, 39.4, 14.2, 12.9.

*N,N-Diethyl-2-oxo Butyramide (**13**).*[34] Colorless oil, 47 mg, 93% yield. GC-MS *m*/*z* 173. ^{1}H NMR (500 MHz, CDCl$_3$): δ 4.36−4.31 (q, J = 7.25 Hz, 2H), 3.45−3.41 (q, J = 7.25 Hz, 2H), 3.31−3.27 (q, J = 7.25 Hz, 2H), 1.38−1.35 (t, J = 7.25 Hz, 3H), 1.25−1.17 (m, 6H). ^{13}C{^{1}H} NMR (125 MHz, CDCl$_3$): δ 163.3, 161.5, 61.8, 42.4, 39.1, 14.2, 14.0, 12.5.

*N,N-Diethyl-α-oxo-1H-pyrrole-2-acetamide (**14**).*[34] Colorless oil, 37 mg 76% yield. GC-MS *m*/*z* 194. ^{1}H NMR (500 MHz, CDCl$_3$): δ 9.58 (bs, 1H), 7.13 (s, 1H), 7.00 (s, 1H), 6.35−6.33 (m, 1H), 3.54−3.50 (q, J = 7.25 Hz, 2H), 3.36−3.32 (q, J = 7.25 Hz, 2H), 127−1.24 (t, J = 7.25, 3H), 1.21−1.18 (t, J = 7.25 Hz, 3H). ^{13}C NMR{^{1}H} (125 MHz, CDCl$_3$): δ 180.0, 166.3, 129.6, 126.9, 120.4, 111.7, 42.4, 39.2, 14.3, 12.7.

*α-(Acetyloxy)-N,N-diethylbenzeneacetamide (**15**).* White solid, 37 mg, 60% yield. GC-MS *m*/*z* 248 (M-1). ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.46−7.39 (m, 5H), 6.18 (s, 1H), 3.154−3.50 (m, 1H), 1.31−3.24 (m, 2H), 319−3.14 (m, 1H), 2.16 (s, 3H), 1.12−1.09 (t, J = 7.25 Hz, 3H), 1.05−1.02 (t, J = 7.25 Hz, 3H). ^{13}C NMR{^{1}H} (125 MHz, CDCl$_3$): δ 170.7, 166.9, 134.6, 129.2, 129.0, 128.6, 73.5, 41.5, 40.6, 20.9, 13.5, 12.7. HRMS (EI) *m*/*z*: [M]$^{+}$ Calcd for C$_{14}$H$_{19}$NO$_3$ 249.1365. Found: 249.1371.

*2,2-Bis(4-chlorophenyl)-N,N-diethylacetamide (**16**).*[34] White solid, 50 mg, 60% yield. GC-MS *m*/*z* 335. ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.29−7.27 (m, 4H), 7.18−7.16 (m, 4H), 5.08 (s, 1H), 3.44−3.39 (q, J = 7.0 Hz, 2H), 3.31−3.27 (q, J = 7.0 Hz, 2H), 1.18−1.12 (m, 6H). ^{13}C{^{1}H} NMR (125 MHz, CDCl$_3$): δ 170.0, 138.0, 133.1, 130.2, 128.8, 53.1, 42.2, 40.8, 14.7, 12.8.

*N,N-Diethyl Cyanoformamide (**20**).*[37] Colorless oil, 28 mg, 90% yield. GC-MS *m*/*z* 126. ^{1}H NMR (500 MHz, CDCl$_3$): δ 3.64 (q, J = 7.25 Hz, 2H), 3.46 (q, J = 7.25 Hz, 2H), 1.31(t, J = 7.25 Hz, 3H), 1.19 (t, J = 7.25 Hz, 3H). ^{13}C{^{1}H} NMR (125 MHz, CDCl$_3$): δ 144.4, 110.7, 43.6, 40.0, 14.4, 12.4.

*N,N-Dipropylbenzamide (**22**).*[38] Yellow oil, 40 mg, 78% yield. GC-MS *m*/*z* 205. ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.38−7.35 (m, 5H), 3.46 (bs, 2H), 3.16 (bs, 2H), 1.69 (bs, 2H), 1.53 (bs, 2H), 0.99−0.97 (t, J = 7.2 Hz, 3H), 0.75−0.73 (t, J = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (125 MHz, CDCl$_3$): δ 171.8, 137.4, 129.0, 128.3, 126.5, 50.7, 46.4, 21.9, 20.7, 11.3, 11.0.

*N,N-Dibutylbenzamide (**23**).*[39] Colorless oil, 47 mg, 80% yield. GC-MS *m*/*z* 233. ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.38−7.33 (m, 5H), 3.49 (bs, 2H), 3.19 (bs, 2H), 1.48−1.41 (m, 4H), 1.13 (bs, 2H), 0.98−0.78 (m, 6H). ^{13}C{^{1}H} NMR (125 MHz, CDCl$_3$): δ 171.6, 137.5, 128.9, 128.3, 126.5, 50.7, 48.8, 44.4, 30.9, 29.7, 20.3, 19.8, 13.9, 13.6.

*N,N-Dihexylbenzamide (**24**).*[40] Colorless oil, 40 mg, 55% yield. GC-MS *m*/*z* = 289. ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.38−7.33 (m, 5H), 3.48 (bs, 2H), 3.18 (bs, 2H), 1.65−1.11 (m, 16H), 0.91−0.83 (m, 6H). ^{13}C NMR{^{1}H} (125 MHz, CDCl$_3$): δ 171.6, 137.0, 128.9, 128.34, 126.5, 49.0, 44.8, 31.6, 31.3, 28.7, 27.5, 26.7, 26.2, 22.5, 13.9.

*N,N-Dioctylbenzamide (**25**).*[38] Colorless oil, 52 mg, 60% yield. GC-MS *m*/*z* 345. ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.38−7.33 (m, 5H), 3.47 (bs, 2H), 3.18 (bs, 2H), 1.65−1.19 (m, 24H), 6.09 (bs, 6H). ^{13}C{^{1}H} NMR (125 MHz, CDCl$_3$): δ 171.6, 137.5, 128.9, 128.3, 126.5, 31.7, 29.2, 22.6, 14.0.

*N,N-Diphenylbenzamide (**26**).*[38] White solid, 45 mg, 60% yield. GC-MS *m*/*z* 301. ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.51−7.50 (m, 2H), 7.39−7.27 (m, 11H), 7.16−7.14 (m, 2H), 4.71 (bs, 2H), 4.41 (bs, 2H). ^{13}C{^{1}H} NMR (125 MHz, CDCl$_3$): δ 172.2, 137.0, 136.4, 136.2, 129.6, 128.8, 128.7, 128.5, 128.4, 128.3, 127.6, 127.0, 126.7, 51.5, 46.8.

*N-Ethyl-N-methylbenzamide (**35**).* Colorless oil, 25 mg, 60% yield. GC-MS *m*/*z* 163 (M). ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.40 (bs, 5H), 3.62−3.58, 3.31−3.26 (q, J = 7.25 Hz, 2H), 3.08, 2.94 (s, 3H), 1.26−123, 1.15−1.12 (t, J = 6.94 Hz). ^{13}C{^{1}H} NMR (125 MHz, CDCl$_3$): δ 171.7, 171.0, 136.8, 129.3, 128.3, 126.8, 126.4, 45.9, 42.1, 36.7, 32.2,

https://doi.org/10.1021/acs.joc.1c00161

13.6, 12.1. HRMS (EI) m/z: $[M]^+$ Calcd for $C_{10}H_{13}NO$ 163.0997. Found: 163.0988.

N-Cyclohexyl-N-ethylbenzamide (***36***). Yellow oil, 41 mg, 70% yield. GC-MS m/z 231. ^1H NMR (500 MHz, $CDCl_3$ at 40 °C): δ 7.39−7.37, 7.34−7.32 (bs, 5H), 3.44, 3.21 (m, 3H), 1.37−1.04 (m, 13H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$ at 40 °C): δ 171.4, 137.9, 128.8, 128.4, 126.0, 58.8, 36.4, 31.7, 25.8, 25.3, 14.9. HRMS (EI) m/z: $[M]^+$ Calcd for $C_{15}H_{21}NO$ 231.1623. Found: 231.1619.

N-Ethyl-N-isopropylbenzamide (***37***).[41] Yellow oil, 34 mg, 72% yield. GC-MS m/z 191. ^1H NMR (500 MHz, $CDCl_3$): δ 7.40−7.26 (m, 5H), 3.95 (bs, 1H), 3.42−3.23 (m, 2H), 1.29−1.15 (m, 9H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 171.2, 137.9, 128.8, 128.4, 126.0, 50.1, 35.3, 21.0, 14.9.

Phenyl(pyrrolidin-1-yl)methanone (***38***).[38] Yellow oil, 26 mg, 60% yield. GC-MS m/z 175. ^1H NMR (500 MHz, $CDCl_3$): δ 7.52−7.50 (m, 2H), 7.40−7.38 (m, 2H), 3.67−3.64 (t, J = 7.0 Hz, 2H), 3.44−3.41 (t, J = 7.0 Hz, 2H), 1.99−1.94 (m, 2H), 1.90−1.85 (m, 2H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 169.7, 137.4, 129.7, 128.2, 127.1, 49.5, 46.1, 26.4, 24.4.

4-Morpholinylphenylmethanone (***40***).[38] Yellow oil, 24 mg, 50% yield. GC-MS m/z 191. ^1H NMR (500 MHz, $CDCl_3$): δ 7.41−7.40 (m, 5H), 3.77−3.46 (m, 8H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 170.5, 135.4, 129.8, 128.5, 127.1, 66.9, 48.2, 42.8.

1,1,3,3-Tetraethylurea (***42***).[42] Yellow oil, 28 mg, 52% yield. GC-MS m/z 172. ^1H NMR (500 MHz, $CDCl_3$): δ 3.16 (q, J = 7.13 Hz, 8H), 1.11 (t, J = 7.13 Hz, 12H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 164.9, 42.2, 13.2.

Diethylcarbamoyl Chloride (***43***).[43] Yellow oil, 8 mg, 12% yield. GC-MS m/z 135. ^1H NMR (500 MHz, $CDCl_3$): δ 3.51−3.39 (m, 4H), 1.26−1.19 (m, 6H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 148.6, 45.7, 44.4, 13.7, 12.8.

Tetraethyloxalamide (***45***).[44] Yellow oil, 24 mg, 48% yield. GC-MS m/z 200. ^1H NMR (500 MHz, $CDCl_3$): δ 3.47−3.44 (q, J = 7.25 Hz, 4H), 3.30−3.26 (q, J = 7.25 Hz, 4H), 1.23−1.17 (m, 12H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 164.8, 42.3, 38.3, 14.0, 12.5.

N^1,N^1,N^3,N^3-Tetraethylisophthalamide (***48***).[35] White solid, 31 mg, 45% yield. GC-MS m/z 276. ^1H NMR (400 MHz, $CDCl_3$): δ 7.46−7.37 (m, 4H), 3.54 (m, 4H), 3.26 (m, 4H), 1.25 (m, 6H), 1.10 (m, 6H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 170.5, 137.6, 128.6, 127.0, 124.4, 43.4, 39.3, 14.2, 12.9.

N^1,N^1,N^4,N^4-Tetraethylterephthalamide (***49***).[9b] White solid, 28 mg, 41% yield. GC-MS m/z 276. ^1H NMR (500 MHz, $CDCl_3$): δ 1.10 (bs, 6H), 1.26 (bs, 6H), 3.25 (bs, 4H), 3.56 (bs, 4H), 7.40 (s, 4H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 13.2, 14.4, 39.5, 43.4, 126.6, 138.3, 170.9.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.1c00161.

> CVs of **1** and tertiary amines, GC-MS and GC data, NMR (^1H and ^{13}C) of the compounds, reaction setup details, and computational results (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

Yoshio Hisaeda − *Department of Chemistry and Biochemistry, Graduate School of Engineering, Kyushu University, Fukuoka 819-0395, Japan;* orcid.org/0000-0001-9196-8006; Email: yhisatcm@mail.cstm.kyushu-u.ac.jp

Hisashi Shimakoshi − *Department of Chemistry and Biochemistry, Graduate School of Engineering, Kyushu University, Fukuoka 819-0395, Japan;* orcid.org/0000-0003-4644-2392; Email: shimakoshi@mail.cstm.kyushu-u.ac.jp

Authors

Zhongli Luo − *Department of Chemistry and Biochemistry, Graduate School of Engineering, Kyushu University, Fukuoka 819-0395, Japan*

Kenji Imamura − *Institute for Materials Chemistry and Engineering, Kyushu University, Fukuoka 819-0395, Japan*

Yoshihito Shiota − *Institute for Materials Chemistry and Engineering, Kyushu University, Fukuoka 819-0395, Japan;* orcid.org/0000-0003-2054-9845

Kazunari Yoshizawa − *Institute for Materials Chemistry and Engineering, Kyushu University, Fukuoka 819-0395, Japan;* orcid.org/0000-0002-6279-9722

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.joc.1c00161

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This study was partially supported by a Grant-in-Aid for Scientific Research (B) (JP19H02735) from the Japan Society for the Promotion of Science (JSPS). Part of the study was performed under the Cooperative Research Program of "Dynamic Alliance for Open Innovation Bridging Human, Environment and Materials" (20203024) and a grant from the Nippon Sheet Glass Foundation (HAKF541800).

■ REFERENCES

(1) (a) Heard, D. M.; Lennox, A. J. J. Electrode Materials in Modern Organic Electrochemsitry. *Angew. Chem., Int. Ed.* **2020**, *59*, 18866−18884. (b) Wang, H.; Gao, X.; Lv, Z.; Abdelilah, T.; Lei, A. Recent Advances in Oxidative R^1-H/R^2-H Cross-Coupling with Hydrogen Evolution via Photo-/Electrochemistry. *Chem. Rev.* **2019**, *119*, 6769−6787. (c) Elsherbini, M.; Wirth, T. Electroorganic Synthesis under Flow Conditions. *Acc. Chem. Res.* **2019**, *52*, 3287−3296. (d) Wiebe, A.; Gieshoff, T.; Möhle, S.; Rodrigo, E.; Zirbes, M. S.; Waldvogel, R. Electrifying Organic Synthesis. *Angew. Chem., Int. Ed.* **2018**, *57*, 5594−5619. (e) Moeller, K. D. Using Physical Organic Chemistry to Shape the Course of Electrochemical Reactions. *Chem. Rev.* **2018**, *118*, 4817−4833. (f) Jiang, Y.; Xu, K.; Zeng, C. Use of Electrochemistry in the Synthesis of Heterocyclic Structures. *Chem. Rev.* **2018**, *118*, 4485−4540. (g) Yan, M.; Kawamata, Y.; Baran, P. S. Synthetic Organic Electrochemical Methods Since 2000: On the Verge of a Renaissance. *Chem. Rev.* **2017**, *117*, 13230−13319. (h) Francke, R.; Little, R. D. Redox Catalysis in Organic Electrosynthesis: Basic Principles and Recent Developments. *Chem. Soc. Rev.* **2014**, *43*, 2492−2521.

(2) (a) Yoshida, J.; Kataoka, K.; Horcajada, R.; Nagaki, A. Modern Strategies in Electroorganic Synthesis. *Chem. Rev.* **2008**, *108*, 2265−2299. (b) Sperry, J. B.; Wright, D. L. The Application of Cathodic Reductions and Anodic Oxidations in the Synthesis of Complex Molecules. *Chem. Soc. Rev.* **2006**, *35*, 605−621.

(3) Martin, E. T.; McGuire, C. M.; Mubarak, M. S.; Peters, D. G. Electroreductive Remediation of Halogenated Environmental Pollutants. *Chem. Rev.* **2016**, *116*, 15198−15234.

(4) Savéant, J.-M. Molecular Catalysis of Electrochemical Reactions. Mechanistic Aspects. *Chem. Rev.* **2008**, *108*, 2348−2378.

(5) Shimakoshi, H.; Luo, Z.; Inaba, T.; Hisaeda, Y. Electrolysis of Trichloromethylated Organic Compounds under Aerobic Conditions Catalyzed by the B_{12} Model Complex for Ester and Amide Formation. *Dalton Trans.* **2016**, *45*, 10173−10180. In this paper, we mainly reported ester formation by a cathodic process using the sacrificial anode system in an undivided cell.

(6) (a) Mane, R. S.; Bhanage, B. M. Pd/C-Catalyzed Aminocarbonylation of Aryl Iodides via Oxidative C-N Bond Activation of Tertiary Amines to Tertiary Amides. *Asian J. Org. Chem.* **2018**, *7*,

160−164. (b) Mane, R. S.; Bhanage, B. M. Carbonylative Tertiary Amide Synthesis from Aryl Iodides and Tertiary Amines via Oxidant-Free C-N Bond Cleavage Catalyzed by Palladium (II) Chloride in Polyethlene Glycol/Water. *Adv. Synth. Catal.* **2017**, *359*, 2621−2629. (c) Allen, C. L.; Williams, J. M. J. Metal-Catalysed Approaches to Amide Bond Formation. *Chem. Soc. Rev.* **2011**, *40*, 3405−3415. (d) Pattabiraman, V. R.; Bode, J. W. Rethinking Amide Bond Synthesis. *Nature* **2011**, *480*, 471−479. (e) Valeur, E.; Bradley, M. Amide Bond Formation: Beyond the Myth of Coupling Reagents. *Chem. Soc. Rev.* **2009**, *38*, 606−631. (f) Bode, J. W. Emerging Methods in Amide- and Peptide-Bond Formation. *Curr. Opin. Drug Discovery Devel.* **2006**, *9*, 765−775.

(7) (a) Ociepa, M.; Wierzba, A. J.; Turkowska, J.; Gryko, D. Polarity-Reversal Strategy for the Functionalization of Electrophilic Strained Molecules via Light-Driven Cobalt Catalysis. *J. Am. Chem. Soc.* **2020**, *142*, 5355−5361. (b) Shimakoshi, H.; Hisaeda, Y. Electrochemistry and Catalytic Properties of Vitamin B$_{12}$ Derivatives in Nonaqueous Media. *Current Opinion in Electrochem.* **2018**, *8*, 24−30.

(8) (a) Zhang, L.; Hu, X. Nickel Catalysis Enables Convergent Paired Electrolysis for Direct Arylation of Benzylic C-H Bonds. *Chem. Sci.* **2020**, *11*, 10786−10791. (b) Wu, T.; Nguyen, B. H.; Daugherty, M. C.; Moeller, K. D. Paired Electrochemical Reactions and the On-Site Generation of a Chemical Reagent. *Angew. Chem., Int. Ed.* **2019**, *58*, 3562−3565. (c) Hilt, G. Basic Strategies and Types of Applications in Organic Electrochemistry. *ChemElectroChem* **2020**, *7*, 395−405. (d) Liang, Y.; Lin, F.; Adeli, Y.; Jin, R.; Jiao, N. Efficient Electrocatalysis for the Preparation of (Hetero)aryl Chlorides and Vinyl Chloride with 1,2-Dichloroethane. *Angew. Chem., Int. Ed.* **2019**, *58*, 4566−4570. (e) Ma, Y.; Yao, X.; Zhang, L.; Ni, P.; Cheng, R.; Ye, J. Direct Arylation of α-Amino C(sp^3)-H Bonds by Convergent Paired Electrolysis. *Angew. Chem., Int. Ed.* **2019**, *58*, 16548−16552. (f) Jiang, Y.-y.; Dou, G.-y.; Zhang, L.-s.; Xu, K.; Little, R. D.; Zeng, C.-c. Electrochemical Cross-Coupling of C(sp^2)-H with Aryldiazonium Salts via a Paired Electrolysis: an Alternative to Visible Light Photoredox-Based Approach. *Adv. Synth. Catal.* **2019**, *361*, 5170−5175. (g) Llorente, M. J.; Nguyen, B. H.; Kubiak, C. P.; Moeller, K. D. Paired Electrolysis in the Simultaneous Production of Synthetic Intermediates and Substrates. *J. Am. Chem. Soc.* **2016**, *138*, 15110−15113. (h) Paddon, C. A.; Atobe, M.; Fuchigami, T.; He, P.; Watts, P.; Haswell, S. J.; Pritchard, G. J.; Bull, S. D.; Marken, F. Towards Paired and Coupled Electrode Reactions for Clean Organic Microreactor Electrosyntheses. *J. Appl. Electrochem.* **2006**, *36*, 617−634.

(9) The photoduet reactions for the synthesis of an amide that were catalyzed by the B$_{12}$ complex of immobilized titanium oxide were also reported by our group. (a) Shimakoshi, H.; Hisaeda, Y. Oxygen-Controlled Catalysis by Vitamin B$_{12}$-TiO$_2$: Formation of Esters and Amides from Trichlorinated Organic Compounds by Photoirradiation. *Angew. Chem., Int. Ed.* **2015**, *54*, 15439−15443. (b) Shichijo, K.; Fujitsuka, M.; Hisaeda, Y.; Shimakoshi, H. Visible Light-Driven Photocatalytic Duet Reaction Catalyzed by the B$_{12}$-Rhodium-Titanium Oxide Hybrid Catalyst. *J. Organomet. Chem.* **2020**, *907*, 121058−121062.

(10) (a) Hu, J.; Wang, J.; Nguyen, T. H.; Zheng, N. The Chemistry of Amine Radical Cations Produced by Visible Light Photoredox Catalysis. *Beilstein J. Org. Chem.* **2013**, *9*, 1977−2001. (b) DeLaive, P. J.; Foreman, T. K.; Giannotti, C.; Whitten, D. G. Photoinduced Electron Transfer Reactions of Transition-Metal Complexes with Amines. Mechanistic Studies of Alternate Pathways to Back Electron Transfer. *J. Am. Chem. Soc.* **1980**, *102*, 5627−5631.

(11) The current efficiency (CE) was determined in air for the paired electrolysis of **2** with tribenzylamine (**52**) to evaluate the how much electricity was utilized for the desired amide synthesis. To evaluate the CE for the anodic reaction, the amount of benzaldehyde (**53**) was used for the calculation since the anodic product, dibenzylamine (**54**), was consumed for the amide synthesis. *N,N*-Dibenzylbenzamide (**26**) was formed in a 50% CE from the cathodic process, while **53** was formed in an 86% yield from the anodic electrolysis as shown in Scheme S1(A) (see Figure S16 and Table S1). The difference in the CEs between the electrodes is probably due to the loss of the Co(I) active species on the cathode by autoxidation in the air. In contrast, the CEs of the cathodic and anodic reactions were 85% for **50** and **51** and 91% for **53**, and the values were almost the same for the anaerobic electrolysis under N$_2$.

(12) Murakami, Y.; Hisaeda, Y.; Fan, S.-D. Characterization of a Simple Vitamin B$_{12}$ Model Complex and Its Catalysis in Electrochemical Carbon-skeleton Rearrangement. *Chem. Lett.* **1987**, *16*, 655−658.

(13) When we used cobalt salt, Co(acac)$_2$, as a catalyst, the reaction did not proceed.

(14) Constant current electrolysis (CCE) was also applied to the paired electrolysis of **2** and **3** using the C(+)−C(−) electrode pair and catalyst **1** in CH$_3$CN. After passing the 10 mA cathodic current, an 87% yield of the desired amide **4** was obtained. Thus, the paired electrolysis should be executed in a technically easier CCE system.

(15) (a) Katz, T. M.; Miller, J. H.; Hebert, A. A. Insect Repellents: Historical Perspectives and New Developments. *J. Am. Acad. Dermatol.* **2008**, *58*, 865−871. (b) Habeck, J. C.; Diop, L.; Dickman, M. Synthesis of *N,N*-Diethyl-3-methylbenzenzamide (DEET): Two Ways to the Same Goal. *J. Chem. Educ.* **2010**, *87*, 528−529. (c) Fradin, M. S.; Day, J. F. Comparative Efficacy of Insect Repellents against Mosquito Bites. *N. Engl. J. Med.* **2002**, *347*, 13−18.

(16) Katritzky, A. R.; Wang, Z.; Slavov, S.; Tsikolia, M.; Dobchev, D.; Akhmedov, N. G.; Hall, C. D.; Bernier, U. R.; Clark, G. G.; Linthicum, K. J. Synthesis and Bioassay of Improved Mosquito Repellents Predicted from Chemical Structure. *Proc. Natl. Acad. Sci. U. S. A.* **2008**, *105*, 7359−7364.

(17) Mancuso, R.; Raut, D. S.; Ca, N. D.; Fini, F.; Carfagna, C.; Gabriele, B. Catalytic Oxidative Carbonylation of Amino Moieties to Ureas, Oxamides, 2-Oxazolidinones, and Benzoxazolones. *ChemSusChem* **2015**, *8*, 2204−2211. (b) Mitsudome, T.; Noujima, A.; Mizugaki, T.; Jitsukawa, K.; Kaneda, K. Highly Efficient Double-carbonylation of Amines to Oxamides Using Gold Nanoparticles Catalysts. *Chem. Commun.* **2012**, *48*, 11733−11735.

(18) Neta, P.; Huie, R. E.; Ross, A. B. Rate Constants for Reactions of Peroxyl Radicals in Fluid Solutions. *J. Phys. Chem. Ref. Data* **1990**, *19*, 413−513.

(19) (a) Yamazaki, S.; Tanimura, T.; Yoshida, A.; Hori, K. Reaction Mechanism of Photocatalytic Degradation of Chlorinated Ethylenes on Porous TiO$_2$ Pellets: Cl Radical-initiated Mechanism. *J. Phys. Chem. A* **2004**, *108*, 5183−5188. (b) von Sonntag, C.; Schuchmann, H.-P. The Elucidation of Peroxyl Radical Reactions in Aqueous Solution with the Help of Radiation-chemical Methods. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1229−1253. (c) Bennett, J. E.; Howard, J. A. Bimolecular Self-reaction of Peroxy Radicals. Oxygen-18 Isotope Study. *J. Am. Chem. Soc.* **1973**, *95*, 4008−4010.

(20) The formation of diethylamine (**59**) by the electrolysis of **3** was confirmed by GC. Conditions are as follows: [**3**] = 1.4×10^{-1} M, and the solvent was 5 mL of CH$_3$CN containing of 0.1 M ^{n}Bu$_4$NClO$_4$. The applied potential was −0.7 V vs. Ag/AgCl using carbon felt electrodes. During the electrolysis, a voltage of ca. +1.3 V vs. Ag/AgCl was applied to the anode that was monitored by the multimeter. See Figure S19 in the Supporting Information.

(21) Buettner, G. R. Spin Trapping: ESR Parameters of Spin Adducts. *Free Radical Biol. Med.* **1987**, *3*, 259−303.

(22) We also quantified the amount of Cl$^-$ after the paired electrolysis via a spectrophotometric determination using the mercury(II) thiocyanate method.[23] In the case of **2**, 2.93 equiv moles of Cl$^-$ were detected toward the product **4**.

(23) Florence, T. M.; Farrar, Y. J. Spectrophotometric Determination of Chloride at the Parts-per-billion Level by the Mercury(II) Thiocyanate Method. *Anal. Chim. Acta* **1971**, *54*, 373−377.

(24) (a) Murakami, Y.; Hisaeda, Y.; Kajihara, A. Hydrophobic Vitamin B$_{12}$. I. Preparation and Axial Ligation Behavior of Hydrophobic Vitamin B$_{12r}$. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 3642−3646. (b) Werthemann, L.; Keese, R.; Eschenmoser, A. Unpublished

results; see Werthemann, L. Dissertation, ETH Zürich (no. 4097); Juris Druck and Velag, Zürich, Switzerland, 1968.

(25) Murakami, Y.; Hisaeda, Y.; Fan, S.-D.; Matsuda, Y. Redox Behavior of Simple Vitamin B_{12} Model Complexes and Electrochemical Catalysis of Carbon-Skeleton Rearrangements. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 2219−2228.

(26) Saito, K.; Umi, T.; Yamada, T.; Suga, T.; Akiyama, T. Niobium(V)-catalyzed Defluorinative Triallylation of α,α,α-Trifluorotoluene Derivatives by Triple C-F Bond Activation. *Org. Biomol. Chem.* **2017**, *15*, 1767−1770.

(27) Becke, A. D. Density-functional Thermochemistry. III. The Role of Exact Exchange. *J. Chem. Phys.* **1993**, *98*, 5648−5652.

(28) Lee, C.; Yang, W.; Parr, R. G. Development of the Colle-Salvetti Correlation-energy Formula into a Functional of the Electron Density. *Phys. Rev. B: Condens. Matter Mater. Phys.* **1988**, *37*, 785−789.

(29) Hehre, W. J.; Ditchfield, R.; Pople, J. A. Self-consistent Molecular Orbital Methods. XII. Further Extensions of Gaussian-type Basis Sets for Use in Molecular Orbital Studies of Organic Molecules. *J. Chem. Phys.* **1972**, *56*, 2257−2261.

(30) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Petersson, G. A.; Nakatsuji, H.; Li, X.; Caricato, M.; Marenich, A.; Bloino, J.; Janesko, B. G.; Gomperts, R.; Mennucci, B.; Hratchian, H. P.; Ortiz, J. V.; Izmaylov, A. F.; Sonnenberg, J. L.; Williams-Young, D.; Ding, F.; Lipparini, F.; Egidi, F.; Goings, J.; Peng, B.; Petrone, A.; Henderson, T.; Ranasinghe, D.; Zakrzewski, V. G.; Gao, J.; Rega, N.; Zheng, G.; Liang, W.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Throssell, K.; Montgomery, Jr., J. A.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Keith, T.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Millam, J. M.; Klene, M.; Adamo, C.; Cammi, R.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Farkas, O.; Foresman, J. B.; Fox, D. J. *Gaussian 09*, rev. E.01; Gaussian, Inc.: Wallingford, CT, 2016.

(31) Zhao, Z.; Snieckus, V. Directed *ortho* Metalation-Based Methodology. Halo-, Nitroso-, and Boro-Induced *ipso*-Desilylation. Link to an *in situ* Suzuki Reaction. *Org. Lett.* **2005**, *7*, 2523−2526.

(32) Ning, X.; Lou, S.; Mao, Y.; Xu, Z.; Xu, D. Nitrate-promoted Selective C-H Fluorination of Benzamides and Benzeneacetamides. *Org. Lett.* **2018**, *20*, 2445−2448.

(33) Yates, M. H.; Kallman, N. J.; Ley, C. P.; Wei, J. N. Development of an Acyl Sulfonamide Anti-Proliferative Agent, LY573636·Na. *Org. Process Res. Dev.* **2009**, *13*, 255−262.

(34) Tian, H.; Shimakoshi, H.; Ono, T.; Hisaeda, Y. Visible Light-Driven, One-pot Amide Synthesis Catalyzed by the B_{12} Model Complex under Aerobic Conditions. *ChemPlusChem* **2019**, *84*, 237−240.

(35) Mills, R. J.; Taylor, N. J.; Snieckus, V. Directed Ortho Metalation of *N,N*-Diethylbenzamides. Silicon Protection of Ortho Sites and the *o*-Methyl Group. *J. Org. Chem.* **1989**, *54*, 4372−4385.

(36) Kumar, P. S.; Kumar, G. S.; Kumar, R. A.; Reddy, N. V.; Rajender Reddy, K. Copper-Catalyzed Oxidative Coupling of Carboxylic Acids with *N,N*-Dialkylformamides: An Approach to the Synthesis of Amides. *Eur. J. Org. Chem.* **2013**, *2013* (7), 1218−1222.

(37) Yang, J.; Xiang, D.; Zhang, R.; Zhang, N.; Liang, Y.; Dong, D. $POCl_3$-Mediated Reaction of 1-Acyl-1-carbamoyl Oximes: A New Entry to Cyanoformamides. *Org. Lett.* **2015**, *17*, 809−811.

(38) Chen, X.; Chen, T.; Li, Q.; Zhou, Y.; Han, L.; Yin, S. Copper-Catalyzed Aerobic Oxidative Inert C-C and C-N Bond Cleavage: A New Strategy for the Synthesis of Tertiary Amides. *Chem. - Eur. J.* **2014**, *20*, 12234−12238.

(39) Mane, R. S.; Sasaki, T.; Bhanage, B. M. Silica Supported Palladium-Phosphine as a Reusable Catalyst for Alkoxycarbonylation and Aminocarbonylation of Aryl and Heteroaryl Iodides. *RSC Adv.* **2015**, *5*, 94776−94785.

(40) Pathak, U.; Bhattacharyya, S.; Pandey, L. K.; Mathur, S.; Jain, R. An Easy Access to Tertiary Amides from Aldehydes and *N,N*-Dialkylchlorothiophosphoramidates. *RSC Adv.* **2014**, *4*, 3900−3903.

(41) Leggio, A.; Belsito, E.L.; Di Gioia, M.L.; Leotta, V.; Romio, E.; Siciliano, C.; Liguori, A. Silver Acetate-Assisted Formation of Amides from Acyl Chlorides. *Tetrahedron Lett.* **2015**, *56* (1), 199−202.

(42) Adeppa, K.; Rupainwar, D. C.; Misra, K. An Improved One-pot Cost-effective Synthesis of *N,N*-Disubstituted Carbamoyl Halides and Derivatives. *Can. J. Chem.* **2010**, *88*, 1277−1280.

(43) Leggio, A.; Belsito, E.L.; Di Gioia, M.L.; Leotta, V.; Romio, E.; Siciliano, C.; Liguori, A. Silver Acetate-Assisted Formation of Amides from Acyl Chlorides. *Tetrahedron Lett.* **2015**, *56* (1), 199−202.

(44) Mancuso, R.; Raut, D. S.; Ca, N. D.; Fini, F.; Carfagna, C.; Gabriele, B. Catalytic Oxidative Carbonylation of Amino Moieties to Ureas, Oxamides, 2-Oxazolidinones, and Benzoxazolones. *ChemSusChem* **2015**, *8* (13), 2204−2211.

https://doi.org/10.1021/acs.joc.1c00161
J. Org. Chem. 2021, 86, 5983−5990