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# Hydrosilane-Mediated Electrochemical Reduction of Amides

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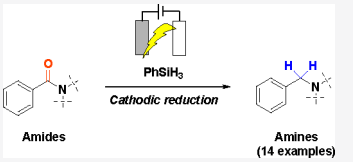
**ABSTRACT:** Electrochemical reduction of amides was achieved by using a hydrosilane without any toxic or expensive metals. The key reactive ketyl radical intermediate was generated by cathodic reduction. Continuous reaction with anodically generated silyl radicals or zinc bromide resulted in chemoselective deoxygenation to give the corresponding amines.






## INTRODUCTION

Due to the strong resonance of the N−C═O moiety, a mild reduction of amides to amines remains a simple but challenging synthetic transformation. Lithium aluminum hydride ($LiAlH_4$) and diborane ($B_2H_6$) are commonly used reductants for this type of transformation despite their flammability.[1] The development of a mild and green methodology for amide reduction is attractive as a "key green chemistry research area"; therefore, many researchers have been making an effort to develop safe methods for amide reduction.[2] For example, the reaction of a zinc hydride species with amides gives the corresponding amines with high chemoselectivity.[2a,b] Samarium iodide ($SmI_2$) generates a reactive ketyl radical species from amides under mild conditions but tends to give the corresponding alcohols via C−N bond scission.[2c] Lanthanoid-based Lewis acid catalysts have broad-scope hydrogenation activity toward amides in the presence of a stoichiometric amount of pinacolborane (Figure 1, top).[2d,e] Manganese has also been employed as a Lewis acid in the presence of mild reductants such as pinacolborane or hydrosilane.[2f] Furthermore, hydrosilanes can be used as reductants under basic conditions, and they are therefore versatile mild reductants that can be used under both acidic and basic conditions.[2g,h] However, there are no reports of amide reduction using only hydrosilanes. Therefore, we focused on an electrochemical methodology to generate a reactive intermediate to harness hydrosilanes as stand-alone reductants without any rare metal- or borate-based activators (Figure 1, bottom).

Redox-based methodologies have enabled various molecular transformations via unique reactive intermediates.[3] Photo- or electrochemically initiated single-electron transfer (SET) produces radical ion species that can be used for both oxidation and reduction reactions. In particular, electrochemical reactions have a wide potential window, so various substrates can be activated by electrodes. Previously, electrochemical amide reduction was reported using a Hg cathode or strong acidic conditions;[4a] however, heavy metal-based electrode materials should be avoided due to their high toxicity. To optimize these classical conditions, Waldvogel and co-workers established Pb cathode-mediated deoxygenation of amides with minimum corrosion of Pb.[4b,c] From these perspectives, we challenged ourselves to develop an electro-

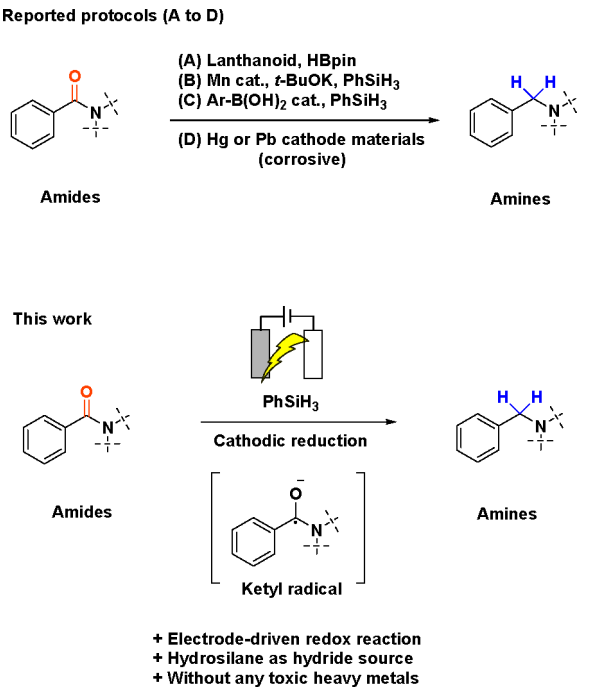



**Figure 1.** Reported tactics for amide reduction.

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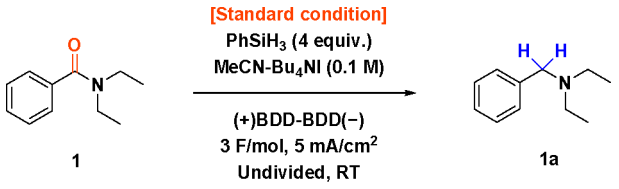
chemical reduction method for amides by using hydrosilanes as reductants without any corrosive heavy metal cathodes.

## RESULTS AND DISCUSSION

First, we explored suitable conditions for amide reduction using compound **1** as a model substrate (Table 1). Electrolysis

**Table 1. Optimization of Electrochemical Reduction**[a]



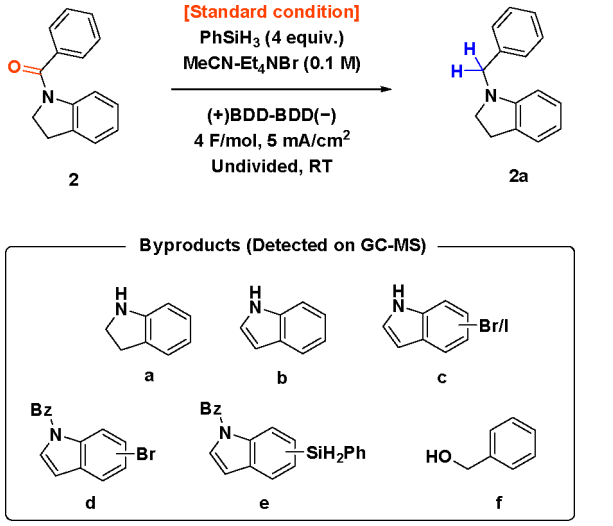

| entry | deviation from the standard condition | yield[b] (%) |
|---|---|---|
| 1 | none | 53 |
| 2 | divided cell (in cathode chamber) | 47 |
| 3 | $Ph_2SiH_2$ instead of $PhSiH_3$ | 22 |
| 4 | $(EtO)_3SiH$ instead of $PhSiH_3$ | 0 |
| 5 | $Et_3SiCl$ instead of $PhSiH_3$ | 0 |
| 6 | 4 F/mol, $Bu_4NI$ (0.1 M) | 61 |
| 7 | 4 F/mol, $Bu_4NBr$ (0.1 M) | 83 |
| 8 | 4 F/mol, $Bu_4NCl$ (0.1 M) | 51 |
| 9 | 4 F/mol, $LiClO_4$ (0.1 M) | trace |
| 10 | 4 F/mol, $NH_4I$ (0.1 M) | 0 |
| 11 | $Me_4NI$ (0.1 M) | trace |
| 12 | $Me_4NBr$ (0.1 M) | trace |
| 13 | $Et_4NI$ (0.1 M) | 51 |
| 14 | $Et_4NBr$ (0.1 M) | 82 |
| 15 | 5 F/mol, $Et_4NBr$ (0.1 M) | 95 |
| 16 | (+)GC-GC(−) | 72 |
| 17 | (+)Pt−Pt(−) | 41 |
| 18 | $H_2$ bubbling without $PhSiH_3$ | 0 |
| 19 | without electrolysis | NR |

[a]All reactions were carried out on a 0.5 mmol scale of benzamide. [b]Determined by $^1H$ NMR by using benzaldehyde as an internal standard.

by boron-doped diamond (BDD) electrodes[5] in the presence of phenylsilane gave the product in moderate yield (entry 1). A control experiment using a divided cell indicated that the reaction was initiated by cathodic reduction (entry 2). Other hydrosilane sources did not improve the yield (entries 3−5). We found that employing $Bu_4NBr$ as the electrolyte and increasing the electrical current gave a yield better than that obtained using iodine or chlorine (entries 6−8). However, $Bu_4NBr$ was difficult to remove, so further optimization was required. The Lewis acid lithium perchlorate also gave a poor yield (entry 9). Next, we changed the alkyl chain length in the ammonium cation moiety and found that $Et_4NBr$ was a suitable electrolyte (entries 10−15). BDD electrodes gave a better yield than glassy carbon (GC) or platinum (Pt), but we found that hydrosilane and an electrical current were necessary for the reaction (entries 16−19).

However, we quickly discovered that the optimized conditions could not be applied to indoline derivatives, presumably due to the instability of benzylindoline under these oxidative conditions.[6] The standard conditions gave poor yields and multiple byproducts due to the high reactivity of the electron-rich indoline ring (Table 2, entry 1, compounds **a**−**f**), and a lower temperature did not improve the yield (entries 2

**Table 2. Further Optimization Using an Indoline Substrate**[a]




| entry | deviation from the standard condition | yield[b] (%) |
|---|---|---|
| 1 | none | 16 |
| 2 | 0 °C | 10 |
| 3 | −40 °C | trace |
| 4 | (+)Al-BDD(−) | 32 |
| 5 | (+)Zn-BDD(−) | 34 |
| 6 | (+)Zn-BDD(−), Ar bubbling | 63 |
| 7 | entry 6 and 7 F/mol | 83 |
| 8 | entry 6 and 9 F/mol | 42 |
| 9 | entry 7, $Et_3SiH$ instead of $PhSiH_3$ | 3 |
| 10 | entry 7, PMHS instead of $PhSiH_3$ | 5 |
| 11 | entry 7, (+)Zn-GC(−) | 79 |
| 12 | entry 7, divided cell (in the cathode chamber) | trace |
| 13 | entry 7, $Bu_4NClO_4$ (0.1 M) | 65 |

[a]All reactions were carried out on a 0.5 mmol scale. PMHS represents polymethylhydrosiloxane. [b]Determined by $^1H$ NMR by using benzaldehyde as an internal standard.

and 3). These results indicated that the anodically generated halonium ions derived from the electrolyte inhibit the desired reaction pathways. Therefore, we used sacrificial electrodes (Al and Zn), and the yield was increased (entries 4−8). Other hydrosilanes still gave poor yields (entries 9 and 10), and BDD remained the best cathode material (entry 11). In the case of compound **2**, electrochemical reduction did not occur in a divided cell (entry 12), and we considered that compounds **1** and **2** were reduced through different reaction pathways. Finally, we found that amide reduction also occurred using a $Bu_4NClO_4$ electrolyte, so that a halogen source was not necessary under sacrificial anode conditions (entry 13).

Next, we performed a mechanistic study. The reduction wave for compound **2** was observed at −2.35 V, but *N*-acetyl indoline was not reduced under the same conditions (Figure 2A). This indicated that the benzoyl group has a crucial role in enhancing electrochemical amide reduction. A cyclic voltammogram for phenylsilane and $Et_4NBr$ indicated that oxidation of bromine first occurred using a BDD anode (Figure 2B). Furthermore, a catalytic current associated with phenylsilane was observed in the presence of $Et_4NBr$.

Control experiments were also performed (Scheme 1). An electrolyzed solution of phenylsilane has no reductive activity toward compound **2**, and we considered that the organometallic reductant ($ZnH_2$) was not generated *in situ* using a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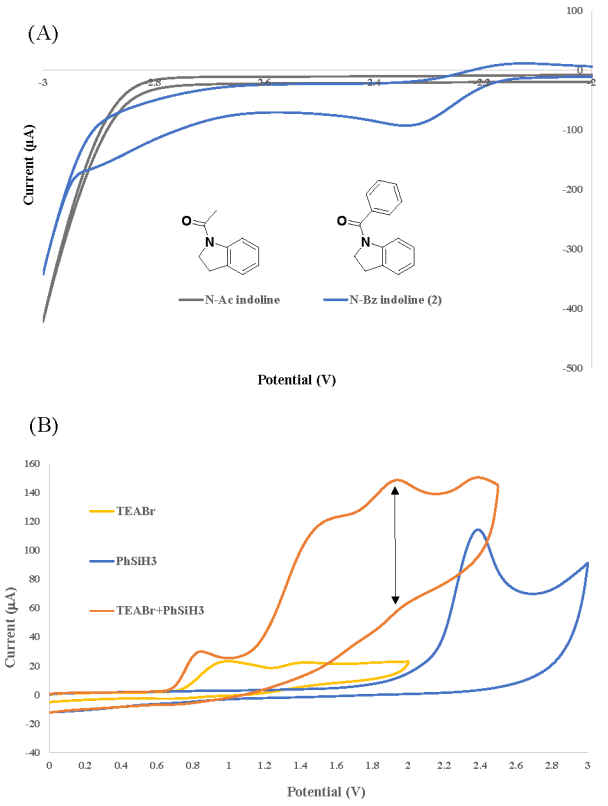
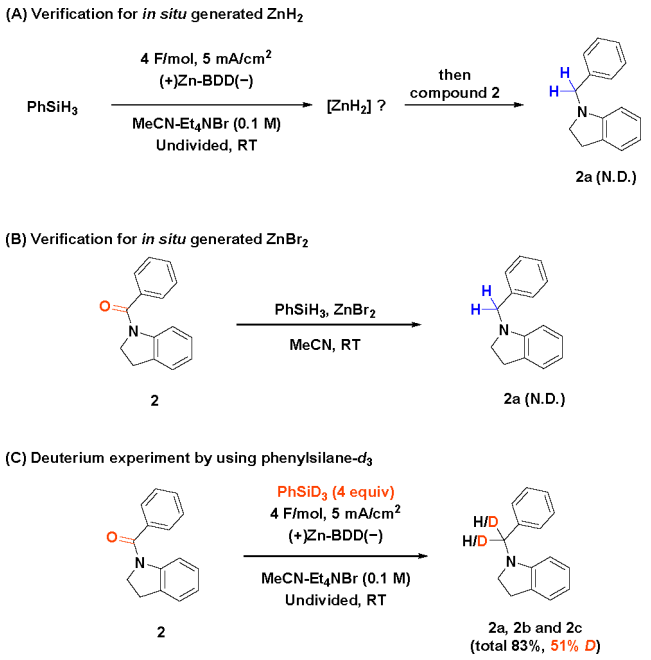



**Figure 2.** (A) Cyclic voltammogram for each compound (2 mM) in 0.05 M MeCN/$Bu_4NClO_4$. (B) Catalytic current for phenylsilane in the presence of $Et_4NBr$ (each at 2 mM).

### Scheme 1. Control Experiments




zinc anode (Scheme 1A). The combination of phenylsilane and $ZnBr_2$ also produced no reaction, so $ZnBr_2$ was not directly involved in the reduction process (Scheme 1B). Phenylsilane-$d_3$ gave deuterated benzylamine **2b** (monodeuterated) and **2c** (dideuterated), indicating that hydrosilane acts as a main hydride source under these electrochemical conditions (Scheme 1C).

On the basis of these results, a plausible mechanism is proposed as shown in Figure 3A. Using a BDD anode, the anodically generated bromine radicals couple with phenylsilane and produce HBr and a silyl radical species via a hydrogen atom transfer (HAT) pathway.[7] The resulting silyl radicals react with cathodically generated ketyl radicals **B** to form alkoxide **C**, which is immediately converted into carbanion **D** by [1,2]-Brook rearrangement via pentavalent silicate.[8] These anions are oxidized to form iminium cations **E** at the anode, which are then reduced to **F** by intramolecularly tethered hydrosilyl groups. Successive elimination and reduction processes give the desired benzylamine **H** through a whole "oxidative reduction" pathway. In our screening for counteranions for the supporting electrolyte (Table 1, entries 6−8), the yield with bromine was better than that with iodine or chlorine. The bond dissociation energy for HBr (366 kJ/mol) is close to that for the Si−H bond of phenylsilane (374 kJ/mol).[9] On the contrary, the energy gaps of HI (298 kJ/mol) and HCl (431 kJ/mol) are smaller or larger than those of HBr and phenylsilane. The more reactive Cl radical would cause undesired overreaction, and therefore, we considered that the energetic similarity between the bromine radical species and phenylsilane is suitable for silyl radical generation during the HAT event. The reaction in the divided cell (anode chamber) gave a trace yield, presumably due to inhibition of cathodic reduction, decreasing the population of bromine radical species. Thus, regeneration of HBr to bromine anions in the undivided cell system is desirable.

For a Zn sacrificial anode, the reaction is initiated by the same radical anion species **J** (Figure 3B). As shown in Figure 3A, the benzoyl moiety is necessary for the radical anion species to be generated. Therefore, we considered that the radical anions are initially localized at the phenyl moieties of the benzoyl groups, and intramolecular SET gives ketyl radical **K**. On the anode side, erosive zinc ions are trapped by Br anions to produce Lewis acid $ZnBr_2$ *in situ*. Reaction with **K** gives benzyl radicals **L**. Zinc ions also act as one-electron oxidizers for **L**, and the resulting iminium cations **M** are then reduced by phenylsilane. The participation of the lone pair on nitrogen gives iminium cations **O** from hemiaminal **N**, and subsequent reduction gives benzylamine **P**. We considered that the formation of the zinc complex plays a crucial role in this elimination process to enhance the leaving ability of oxygen. The p$K_a$ value for the conjugate acid of compound **2a** is thought to be lower than that for **1a** (9.48 in water)[10] because the lone pair of the nitrogen is delocalized on the indoline ring due to resonance, and thus, the lone pair participation in **2** cannot occur as easily. The deuterated compound was generated in a 51% ratio in the control experiment (Scheme 1C), and this indicated that the Hofmann elimination of the electrolyte by cathodic reduction ($Et_4N^+$ to $Et_3N$ + ethylene + $^1/_2H_2$) and continuous hydrogen insertion into iminium cation intermediate **M** or **O** also contributed to this amide reduction process.

Finally, we demonstrated the scope of our electrochemical amide reduction (Table 3). Model substrates **1** and **2** gave good isolated yields (compounds **1a** and **2a**, respectively). Electron-donating groups (alkyl, methoxy, and methylenedioxy) on the benzoyl moiety were tolerated despite the instability of the resulting electron-rich benzyl moiety toward acidic or oxidative conditions (compounds **3**−**5**). Alkyl sulfide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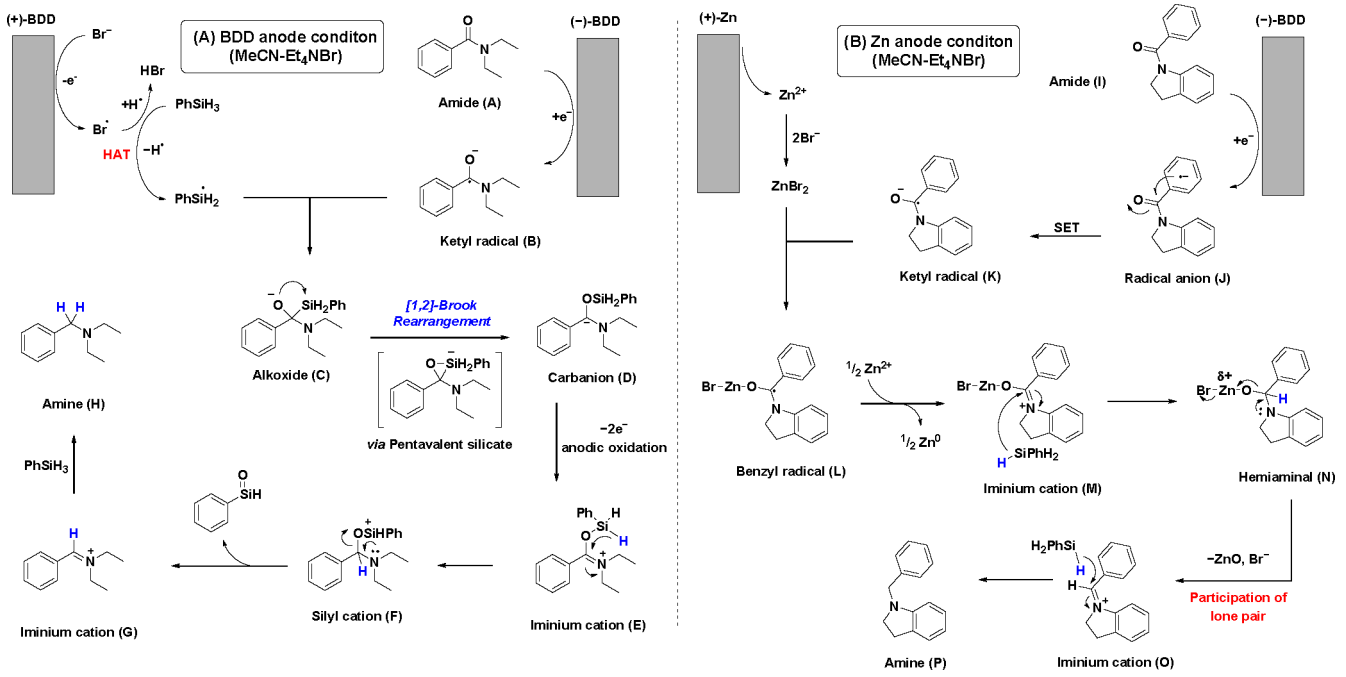
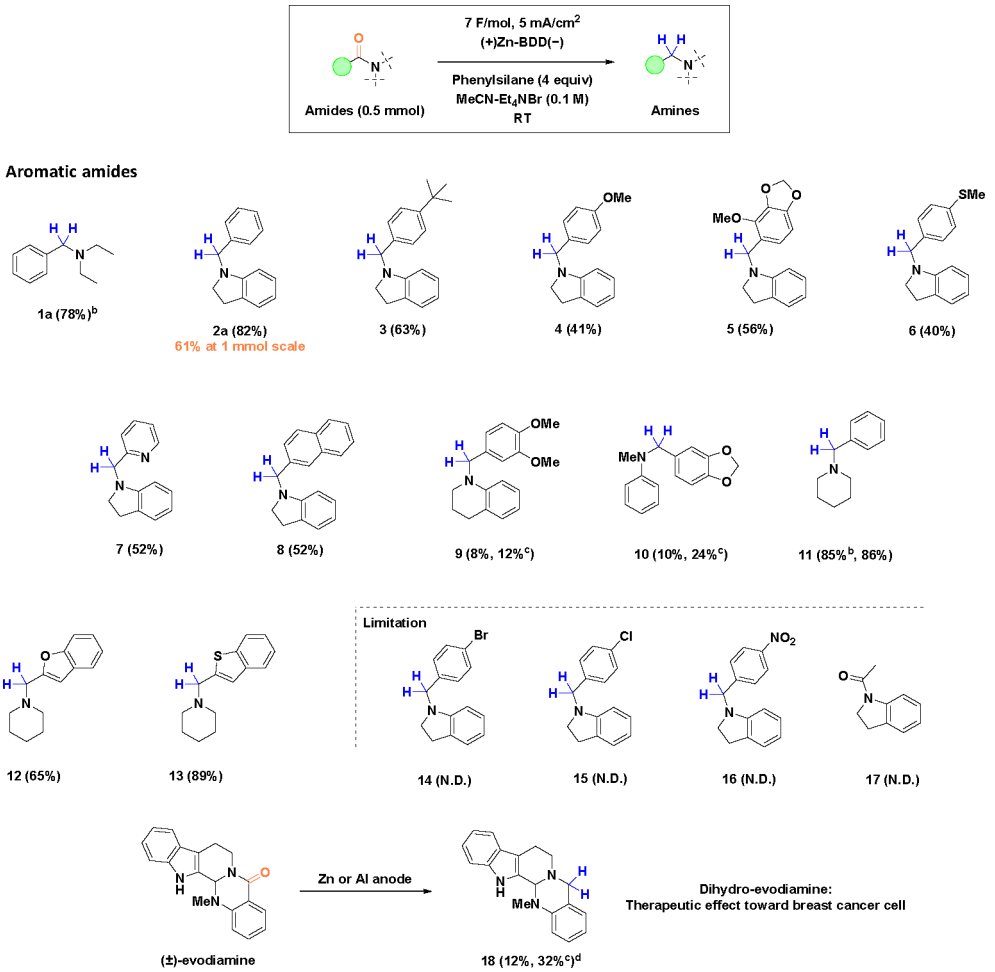



**Figure 3.** Plausible reaction mechanism using (A) a BDD anode and (B) a Zn anode.

## Table 3. Substrate Scope of Amide Reduction[a]




[a]All reactions were performed on a 0.5 mmol scale, and yields were determined by isolated weights. [b]BDD electrodes were used as the anode and cathode. [c]An Al anode was used instead of a Zn anode. [d]NMP (1 mL) was used as the co-solvent.



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and highly electron-withdrawing pyridine-tethered substrates also gave the desired products (compounds **6** and **7**). The $\pi$-extended naphthyl moiety was tolerated (compound **8**). Ring-expanded or aniline-tethered amides gave poor yields due to the weak basicity of nitrogen atoms and the resulting competitive debenzylation (compounds **9** and **10**). We considered more Lewis acidic $AlBr_3$ would assist in deoxygenation events (intermediate **N** to **O**). As we expected, an Al anode improves the yield. An aliphatic amide, piperidine, could be reduced (compound **11**), and electron-rich heterocycles (benzofuran and benzothiophene) were tolerated (compounds **12** and **13**). Unfortunately, halogen and nitro substituents were reduced to corresponding benzoyl or *p*-aminobenzoyl groups (compounds **14**–**16**). As we expected on the basis of a cyclic voltammetry analysis, *N*-acetyl indoline also gave no desired product (compound **17**). The reaction was applied to the natural alkaloid (±)-evodiamine, and the desired product was obtained despite the presence of multiple unstable electron-withdrawing benzylic aminal moieties (compound **18**). In this case, an Al anode also gave relatively good yield compared with that seen with Zn. The cytotoxic activity of the resulting dihydro-evodiamine toward breast cancer cells is stronger than that of the parent compound;[11] thus, our electrochemical methodology demonstrated access to this pharmaceutically relevant molecule.

## CONCLUSION

We developed an electrochemical method for the amide reduction reaction. Electrochemically activated substrates were reacted with a hydrosilane, and the corresponding amines were obtained without any expensive catalysts or toxic heavy metals. This study provides novel insights for sustainable amide reduction methodologies.

## EXPERIMENTAL SECTION

**General Information.** All reactions were performed under an argon atmosphere, unless otherwise noted. $^1$H and $^{13}$C NMR spectra were recorded in $CDCl_3$ and DMSO-$d_6$ by using a JEOL ECA-600 spectrometer ($^1$H, 600 MHz; $^{13}$C, 151 MHz) or JEOL ECA-400 spectrometer ($^1$H, 400 MHz; $^{13}$C, 100 MHz). Tetramethylsilane ($^1$H NMR, $\delta$ 0.00), $CDCl_3$ ($^1$H NMR, $\delta$ 7.26; $^{13}$C NMR, $\delta$ 77.16), DMSO ($^1$H NMR, $\delta$ 2.50; $^{13}$C NMR, $\delta$ 39.52), and $CH_3NO_2$ ($^1$H NMR, $\delta$ 4.34) were used as internal standards. Mass spectra were recorded on a JEOL JMS T-100LP mass spectrometer. Cyclic voltammetry was carried out on an ALS electrochemical analyzer 611 DN. The oxidation potential was measured with a glassy carbon rod as the anode, a platinum wire as the cathode, and Ag/AgCl as the reference electrode. The melting point was measured by SMP10 (Stuart Equipment). Merck precoated silica gel $F_{254}$ plates (thickness of 0.25 mm) were used for thin-layer chromatography (TLC). All materials were obtained from TCI Fine Chemicals, Wako Pure Chemical Industries, Kanto Chemical, and Sigma-Aldrich and used without purification. *N*,*N*-Diethylbenzamide (**1**) and 1-benzoylpiperidine (**S11**) were purchased from TCI.

**Electrochemical Reduction.** *Method A*. A solution of a substrate (0.5 mmol), phenylsilane (2 mmol), and $Et_4NBr$ (210 mg, 1 mmol) in MeCN (10 mL) was equipped with a zinc plate anode (40 mm × 20 mm) and a boron-doped diamond (BDD) plate cathode (80 mm × 20 mm). The cathode surface area in the solution phase was 20 mm × 20 mm (4 $cm^2$), and the current was 20 mA. Thus, the current density was estimated to be 5 mA/$cm^2$. After being exposed to 7 F/mol (337.75 C) of electricity by current potential (5 mA/$cm^2$), to the reaction mixture was added saturated aqueous $NaHCO_3$, and the precipitate was removed by Celite pad filtration. The Celite cake was washed with EtOAc, and the filtrate was washed with brine. The organic layer was dried over anhydrous $Na_2SO_4$ and concentrated in vacuo. The resulting crude product was purified by silica gel column chromatography.

*Method B*. Compounds **1**, **2**, and **S3**–**S13** were used as substrates. The zinc anode (0.2 mm thickness) was replaced with the BDD anode, and the procedure described for method A was used.

**Indolin-1-yl(phenyl)methanone (2).** To a solution of indoline (1.12 mL, 10 mmol) in $CH_2Cl_2/H_2O$ [50 mL, 4:1 (v/v)] were added $NaHCO_3$ (2.52 g, 30 mmol) and benzoyl chloride (1.73 mL, 15 mmol), and the mixture was vigorously stirred at rt for 2.5 h. To the resulting mixture was added $H_2O$, and the mixture was extracted with $CH_2Cl_2$ (3 × 15 mL). The organic layer was washed three times with aqueous 1 M HCl and dried over anhydrous $Na_2SO_4$. After concentration in vacuo, the crude product was recrystallized from 3:1 hexane/EtOAc, and 1.54 g of the title compound was obtained as a brown needle crystal (6.91 mmol, 69%): $^1$H NMR (600 MHz, $CDCl_3$) $\delta$ 8.23–7.42 (7H, m, Ar), 7.22–7.21 (1H, d, Ar, $J$ = 7.56 Hz), 7.03 (1H, s, br, Ar), 4.08 (2H, s, br, H-2), 3.14–3.11 (2H, t, H-1, $J$ = 8.94 Hz, 17.2 Hz). This is a known compound.[12a]

**[4-(*tert*-Butyl)phenyl](indolin-1-yl)methanone (S3).** To a suspension of 4-*tert*-butylbenzoic acid (534.7 mg, 3 mmol) in $CH_2Cl_2$ (10 mL) were added indoline (224 $\mu$L, 2 mmol), $NEt_3$ (836 $\mu$L, 6 mmol), HOBt (324 mg, 2.4 mmol), EDCI·HCl (460 mg, 2.4 mmol), and DMAP (24.4 mg, 0.2 mmol), and the mixture was stirred at rt for 12 h. The reaction was quenched with saturated aqueous $NaHCO_3$, and the mixture extracted with EtOAc (3 × 15 mL). The organic layer was washed with saturated aqueous $NaHCO_3$ and aqueous 1 M HCl and dried over anhydrous $Na_2SO_4$. After concentration in vacuo, the resulting residue was recrystallized from hexane, and 290 mg of the title compound was obtained as a white solid (1.04 mmol, 52%): $^1$H NMR (600 MHz, DMSO-$d_6$, 80 °C) $\delta$ 7.70 (1H, s, br, Ar), 7.51 (4H, m, Ar), 7.27–7.25 (1H, d, Ar, $J$ = 7.56 Hz), 7.15–7.12 (1H, t, Ar, $J$ = 7.56, 15.8 Hz), 7.03–7.01 (1H, t, Ar, $J$ = 7.56, 14.4 Hz), 4.03–4.01 (2H, t, H-2, $J_{2-1}$ = 8.25 Hz, $J_{gem}$ = 16.5 Hz), 3.14–3.07 (2H, m, H-1, overlapped with residual solvent peak), 1.34 (9H, s, $C(C\underline{H}_3)_3$); $^{13}$C{$^1$H} NMR (151 MHz, DMSO-$d_6$, 80 °C) $\delta$ 167.8, 152.5, 142.5, 134.0, 132.2, 126.4, 126.3, 124.7, 124.5, 123.1, 116.0, 49.9, 34.2, 30.6, 27.3; HRMS (ESI) $m/z$ [M + Na]$^+$ calcd for $C_{19}H_{21}NNaO^+$ 302.1515, found 302.1502; mp 104 °C.

**Indolin-1-yl(4-methoxyphenyl)methanone (S4).** To a solution of indoline (336 $\mu$L, 3 mmol) in pyridine (30 mL) was added 4-methoxybenzoyl chloride (614 mg, 3.6 mmol), and the mixture was stirred at rt for 13 h. To the reaction mixture was added aqueous 1 M HCl, and the mixture was extracted with EtOAc (3 × 15 mL). The organic layer was washed with aqueous 1 M HCl and saturated aqueous $NaHCO_3$ and dried over anhydrous $Na_2SO_4$. After concentration in vacuo, recrystallization from 5:1 hexanes/EtOAc gave 497.3 mg of the title compound as a white solid (1.96 mmol, 65%): $^1$H NMR (600 MHz, $CDCl_3$) $\delta$ 7.56 (2H, m, Ar), 7.22–6.93 (6H, m, Ar), 4.14–4.11 (2H, t, H-2, $J$ = 8.25 Hz), 3.87 (3H, s, -OC$\underline{H}_3$), 3.13–3.10 (2H, t, H-1, $J$ = 8.25 Hz). This is a known compound.[12b]

**Indolin-1-yl(4-methoxybenzo[*d*][1,3]dioxol-5-yl)methanone (S5).** This compound was synthesized in our previous study.[12c]

**Indolin-1-yl[4-(methylthio)phenyl]methanone (S6).** To a suspension of 4-methylthiobenzoic acid (505 mg, 3 mmol) and DMF (3 drops) in toluene (30 mL) was added $SOCl_2$ at 0 °C. After the mixture was stirred at rt for 16 h, the solvent was removed in vacuo, and the resulting residue was dissolved in pyridine (30 mL). To the solution was added indoline (504 $\mu$L, 4.5 mmol), and the mixture was stirred at rt for 3 h. The reaction was quenched with aqueous 1 M HCl, and the mixture was extracted with EtOAc (3 × 20 mL). The organic layer was washed with aqueous 1 M HCl and saturated aqueous $NaHCO_3$ and dried over anhydrous $Na_2SO_4$. After concentration in vacuo, recrystallization from hexanes/EtOAc gave 590.7 mg of the title compound as a colorless solid (2.19 mmol, 73%): $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.76–7.49 (2H, m, Ar), 7.29–7.0 (6H, m, Ar, overlapped with residual solvent), 4.11 (2H, m, H-2), 3.14–3.10 (2H, t, H-1, $J$ = 8.24, 8.0 Hz), 2.53 (3H, s, -$SCH_3$); $^{13}$C{$^1$H} NMR (151 MHz, $CDCl_3$) $\delta$ 168.6, 142.8, 142.2, 133.2, 128.0, 127.4, 125.7, 125.1, 124.0, 117.1, 50.8, 28.3, 15.3; HRMS (ESI)


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$m/z$ [M + Na]$^+$ calcd for $C_{16}H_{15}NNaOS^+$ 292.0772, found 292.0750; mp 134 °C.

**Indolin-1-yl(pyridin-2-yl)methanone (S7).** The same reaction procedure that was used for **S3** was used for 2-picolinic acid and indoline (without the 1 M HCl wash). Purification by silica gel column chromatography (2:1 hexanes/EtOAc) gave 408.6 mg of the title compound as a purple amorphous solid (1.82 mmol, 91%): $^1$H NMR (600 MHz, $CDCl_3$, 50 °C) $\delta$ 8.67−8.66 (1H, d, Ar, $J$ = 4.81 Hz), 8.32 (1H, s, br, Ar), 7.94−7.91 (2H, m, Ar), 7.462−7.457 (1H, m, Ar), 7.23−7.22 (1H, m, Ar, overlapped with residual solvent), 7.07 (1H, s, br, Ar), 4.37−4.34 (2H, t, H-2, $J$ = 8.94, 8.59 Hz), 3.18−3.16 (2H, t, H-1, $J$ = 8.94, 8.59 Hz). This is a known compound.[12d]

**Indolin-1-yl(naphthalen-2-yl)methanone (S8).** The same reaction procedure that was used for compound **S6** was used for 2-naphthoic acid and indoline. Recrystallization from hexanes/EtOAc gave 624.1 mg of the title compound as colorless crystals (2.28 mmol, 76%): $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.07 (1H, s, Ar), 7.93−7.89 (4H, m, Ar), 7.64−7.52 (4H, m, Ar), 7.24−7.22 (1H, m, Ar), 7.03 (1H, s, br, Ar), 4.16 (2H, s, br, H-2), 3.17−3.13 (2H, t, H-1, $J$ = 8.24 Hz); $^{13}$C{$^1$H} NMR (151 MHz, $CDCl_3$) $\delta$ 169.1, 142.8, 134.4, 134.2, 132.9, 128.8, 128.6, 128.0, 127.5, 126.9, 125.1, 124.4, 124.1, 117.6, 50.8, 28.3; HRMS (ESI) $m/z$ [M + Na]$^+$ calcd for $C_{19}H_{15}NNaO^+$ 296.1051, found 296.1022; mp 149 °C.

**[3,4-Dihydroquinolin-1(2*H*)-yl](3,4-dimethoxyphenyl)-methanone (S9).** To a solution of 1,2,3,4-tetrahydroisoquinoline (266 $\mu$L) in pyridine (10 mL) were added 3,4-dimethoxybenzoyl chloride (480 mg, 2.4 mmol) and DMAP (24.4 mg, 0.2 mmol), and the mixture was stirred at rt for 14 h. The reaction was quenched with 1 M HCl, and the mixture was extracted with EtOAc (3 × 15 mL). The organic layer was washed with aqueous 1 M HCl and saturated aqueous $NaHCO_3$ and dried over $Na_2SO_4$. The resulting crude product was purified by amino silica gel column chromatography (NH form, 2:1 to 3:2 hexanes/EtOAc), and 591.3 mg of the title compound was obtained as a white solid (1.99 mmol, 99.5%): $^1$H NMR (600 MHz, $CDCl_3$) $\delta$ 7.15−7.14 (1H, d, Ar, $J$ = 6.87 Hz), 7.0−6.97 (1H, t, Ar, $J$ = 7.56, 15.1 Hz), 6.93−6.92 (2H, m, Ar), 6.89−6.87 (1H, t, Ar, $J$ = 7.56, 15.1 Hz), 6.71−6.68 (1H, t, Ar, $J$ = 8.25, 7.90 Hz), 3.92−3.90 (2H, t, H-3, $J$ = 6.87, 13.8 Hz), 3.86 (3H, s, -OC$\underline{H}_3$), 3.72 (3H, s, -OC$\underline{H}_3$), 2.84−2.82 (2H, t, H-1, $J$ = 6.87, 13.1 Hz), 2.07−2.03 (2H, quin, H-2, $J$ = 6.87, 6.53 Hz). This is a known compound.[12e]

***N*-Methyl-*N*-phenylbenzo[*d*][1,3]dioxole-5-carboxamide (S10).** To a solution of *N*-methylaniline (1.08 mL, 10 mmol) in $CH_2Cl_2$ (50 mL) were added $NEt_3$ (4.18 mL, 30 mmol) and piperonyloyl chloride (1.85 g, 10 mmol), and the mixture was stirred at rt for 16 h. The resulting mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with $CH_2Cl_2$ (3 × 20 mL). The organic layer was washed twice with aqueous 1 M HCl and dried over anhydrous $Na_2SO_4$. After concentration in vacuo, the resulting crude product was purified by silica gel column chromatography (1:1 hexanes/EtOAc), and 2.48 g of the title compound was obtained as a yellow oil (9.7 mmol, 97%): $^1$H NMR (600 MHz, $CDCl_3$) $\delta$ 7.27−7.26 (2H, m, Ar), 7.17−7.15 (1H, t, Ar, $J$ = 7.56, 15.1 Hz), 7.05−7.04 (2H, m, Ar), 6.83−6.81 (2H, m, Ar), 6.58−6.56 (1H, d, Ar, $J$ = 8.25 Hz), 5.90 (2H, s, -OC$\underline{H}_2$O-), 3.47 (3H, s, -NC$\underline{H}_3$). This is a known compound.[12f]

**Benzofuran-2-yl(piperidin-1-yl)methanone (S12).** The same reaction procedure that was used for **S3** was used for benzofuran-2-carboxylic acid and piperidine. Silica gel chromatography (2:1 to 1:1 hexanes/EtOAc) gave 631.3 mg of the titled compound as a white solid (2.8 mmol, 92%): $^1$H NMR (DMSO-$d_6$, 600 MHz) $\delta$ 7.73 (1H, d, Ar, $J$ = 7.56 Hz), 7.65 (1H, d, Ar, $J$ = 8.25 Hz), 7.45−7.42 (1H, m, Ar), 7.30−7.35 (2H, m, Ar), 3.64 (4H, m, br, H-2, H-6), 1.67−1.64 (2H, m, H-4), 1.59−1.55 (4H, m, H-3, H-5). This is a known compound.[12g]

**Benzo[*b*]thiophen-2-yl(piperidin-1-yl)methanone (S13).** The same reaction procedure that was used for **S3** was used for benzo[*b*]thiophen-2-carboxylic acid and piperidine. Recrystallization from hexanes/EtOAc gave 434.5 mg of the title compound as a white solid (1.8 mmol, 59%): $^1$H NMR ($CDCl_3$, 600 MHz) $\delta$ 7.85 (1H, m, Ar), 7.82−7.79 (1H, m, Ar), 7.45 (1H, s, Ar), 7.39 (2H, m, Ar), 3.69 (4H, m, br, H-2, H-6), 1.74−1.65 (6H, m, H-3, H-4, H-5); $^{13}$C{$^1$H} NMR ($CDCl_3$, 151 MHz) $\delta$ 163.7, 140.0, 138.7, 137.2, 125.5, 124.7, 124.5, 124.4, 122.3, 48.8, 44.0, 26.3, 24.6; HRMS (ESI) $m/z$ [M + H]$^+$ calcd for $C_{14}H_{16}NOS^+$ 246.0953, found 246.0973; mp 127 °C.

***N*-Benzyl-*N*-ethylethanamine (1a).** Method A was used for compound **1**, and purification by silica gel column chromatography (1:1 hexanes/EtOAc) gave 63.7 mg of the title compound as a colorless oil (0.39 mmol, 78%): $^1$H NMR (600 MHz, $CDCl_3$) $\delta$ 7.34−7.29 (4H, m, Ar), 7.24−7.22 (1H, m, Ar), 3.56 (2H, s, -NC$\underline{H}_2$Ar), 2.54−2.50 (4H, q, -NC$\underline{H}_2$CH$_3$ × 2, $J$ = 6.87, 7.22 Hz), 1.05−1.03 (6H, t, -NCH$_2$C$\underline{H}_3$ × 2, $J$ = 6.87, 7.22 Hz). This is a known compound.[12h]

**1-Benzylindoline (2a).** Method B was used for compound **2**, and purification by silica gel column chromatography (12:1 hexanes/EtOAc) gave 85.8 mg of the title compound as a brown oil (0.41 mmol, 82%). The 1 mmol scale reaction was carried out in 20 mL of MeCN/$Et_4NBr$ (0.1 M) by using the same electrochemical condition, and 128.7 mg of the title compound was obtained (0.61 mmol, 61%): $^1$H NMR (600 MHz, $CDCl_3$) $\delta$ 7.37−7.32 (4H, m, Ar), 7.28−7.27 (1H, m, Ar), 7.10−7.09 (1H, d, Ar, $J$ = 6.87 Hz), 7.07−7.04 (1H, t, Ar, $J$ = 8.25, 7.90 Hz), 6.68−6.65 (1H, t, Ar, $J$ = 7.56 Hz), 6.52−6.50 (1H, d, Ar, $J$ = 8.25 Hz), 4.25 (2H, s, -NC$\underline{H}_2$Ar), 3.33−3.30 (2H, t, H-2, $J$ = 8.25, 8.59 Hz), 2.99−2.96 (2H, t, H-1, $J$ = 8.25, 8.59 Hz). This is a known compound.[12i]

**1-[4-(*tert*-Butyl)benzyl]indoline (3).** Method B was used for compound **S3**, and purification by silica gel column chromatography (30:1 to 20:1 hexanes/EtOAc) gave 85.3 mg of the title compound as a colorless oil (0.32 mmol, 63%): $^1$H NMR ($CDCl_3$, 600 MHz) $\delta$ 7.35 (2H, d, Ar, $J$ = 8.16 Hz), 7.29 (2H, d, Ar, $J$ = 8.16 Hz), 7.03−7.12 (2H, m, Ar), 6.66 (1H, t, Ar, $J$ = 7.3 Hz), 6.53 (1H, d, Ar, $J$ = 7.8 Hz, 1H), 4.22 (2H, s, -ArC$\underline{H}_2$N-), 3.30 (2H, t, -NC$\underline{H}_2$CH$_2$-, $J$ = 8.25 Hz), 2.96 (2H, t, -CH$_2$C$\underline{H}_2$Ar-, $J$ = 8.25 Hz), 1.32 (9H, s, -ArC(C$\underline{H}_3$)$_3$); $^{13}$C{$^1$H} NMR ($CDCl_3$, 151 MHz) $\delta$ 152.6, 150.0, 135.4, 130.0, 127.6, 127.3, 125.4, 124.5, 117.5, 107.0, 53.5, 53.2, 34.5, 31.4, 28.5; HRMS (ESI) $m/z$ [M + Na]$^+$ calcd for $C_{19}H_{23}NNa^+$ 288.1728, found 288.1729.

**1-(4-Methoxybenzyl)indoline (4).** Method B was used for compound **S4**, and purification by silica gel column chromatography (12:1 hexanes/EtOAc) gave 48.5 mg of the title compound as a colorless oil (0.2 mmol, 41%): $^1$H NMR ($CDCl_3$, 600 MHz) $\delta$ 7.28 (2H, d, Ar, $J$ = 8.25 Hz), 7.09 (1H, d, Ar, $J$ = 7.56 Hz), 7.05 (1H, t, Ar, $J$ = 7.56 Hz), 6.87 (2H, d, Ar, $J$ = 8.25 Hz), 6.66 (1H, t, Ar, $J$ = 7.56 Hz), 6.53 (1H, d, Ar, $J$ = 7.56 Hz), 4.19 (2H, s, -ArC$\underline{H}_2$N-), 3.81 (3H, s, -OCH$_3$), 3.27 (2H, t, -NC$\underline{H}_2$CH$_2$-, $J$ = 8.25 Hz), 2.95 (2H, t, -CH$_2$C$\underline{H}_2$Ar-, $J$ = 8.25 Hz). This is a known compound.[13a]

**1-[(4-Methoxybenzo[*d*][1,3]dioxol-5-yl)methyl]indoline (5).** Method B was used for compound **S5**, and purification by silica gel column chromatography (10:1 hexanes/EtOAc) gave 78.9 mg of the title compound as a colorless oil (0.28 mmol, 56%): $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 7.09−7.04 (2H, m, Ar), 6.82−6.80 (1H, d, Ar, $J$ = 8.24 Hz), 6.66−6.63 (1H, t, Ar, $J$ = 7.33 Hz), 6.57−6.54 (1H, d, Ar, $J$ = 7.79 Hz), 6.51−6.49 (1H, d, Ar, $J$ = 7.79 Hz), 4.18−4.16 (2H, m, -NHC$\underline{H}_2$Ar), 4.0 (3H, s, -OC$\underline{H}_3$), 3.37−3.33 (2H, t, H-2, $J$ = 8.24 Hz), 2.98−2.94 (2H, t, H-1, $J$ = 8.24 Hz); $^{13}$C{$^1$H} NMR (101 MHz, $CDCl_3$) $\delta$ 152.7, 148.7, 141.9, 136.7, 134.9, 130.0, 127.9, 127.4, 124.5, 123.8, 122.2, 117.4, 107.1, 102.5, 101.1, 59.8, 53.7, 48.4, 28.7; HRMS (ESI) $m/z$ [M + Na]$^+$ calcd for $C_{17}H_{17}NNaO_3^+$ 306.1101, found 306.1084.

**1-[4-(Methylthio)benzyl]indoline (6).** Method B was used for compound **S6**, and purification by silica gel chromatography (12:1 hexanes/EtOAc) gave 50.9 mg of the title compound as a colorless oil (0.20 mmol, 40%): $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 7.26−7.32 (2H, m, Ar), 7.20−7.25 (2H, m, Ar), 7.01−7.12 (2H, m, Ar), 6.64−6.70 (1H, m, Ar), 6.50 (1H, d, Ar, $J$ = 7.8 Hz), 4.20 (2H, s, -NC$\underline{H}_2$Ar), 3.29 (2H, t, H-2, $J$ = 8.24 Hz), 2.96 (2H, t, H-1, $J$ = 8.24 Hz), 2.48 (3H, s, -SC$\underline{H}_3$); $^{13}$C{$^1$H} NMR ($CDCl_3$, 101 MHz) $\delta$ 152.6, 137.1, 135.6, 130.2, 128.6, 127.4, 127.0, 124.7, 117.9, 107.2, 53.7, 53.4, 28.7,


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16.2; HRMS (ESI) $m/z$ $[M + Na]^+$ calcd for $C_{16}H_{17}NNaS^+$ 278.0974, found 278.0993.

**1-(Pyridin-2-ylmethyl)indoline (7).** Method B was used for compound **S7**, and purification by silica gel column chromatography (3:1 hexanes/EtOAc) gave 53.8 mg of the title compound as a yellow oil (0.26 mmol, 52%): $^1$H NMR ($CDCl_3$, 600 MHz) $\delta$ 8.58−8.57 (1H, d, br, $J$ = 4.81 Hz), 7.66−7.64 (1H, dt, Ar, $J$ = 1.37, 7.56 Hz), 7.42−7.41 (1H, d, Ar, $J$ = 8.25 Hz), 7.19−7.17 (1H, m, Ar), 7.12−7.11 (1H, d, Ar, $J$ = 6.87 Hz), 7.05−7.00 (1H, m, Ar), 6.71−6.64 (1H, m, Ar), 6.45−6.44 (1H, d, Ar, $J$ = 7.56 Hz), 4.40 (2H, s, -NC$\underline{H}_2$Ar), 3.56−3.43 (2H, td, H-2, $J$ = 8.25 Hz), 3.04−3.02 (2, t, H-1, $J$ = 8.25 Hz); $^{13}$C{$^1$H} NMR (151 MHz, $CDCl_3$) $\delta$ 159.0, 152.4, 149.4, 136.9, 130.0, 127.5, 127.3, 124.8, 124.6, 122.2, 121.9, 118.0, 109.6, 107.1, 55.8, 54.2, 30.0, 28.8; HRMS (ESI) $m/z$ $[M + Na]^+$ calcd for $C_{14}H_{14}N_2Na^+$ 233.1049, found 233.1068.

**1-(Naphthalen-2-ylmethyl)indoline (8).** Method B was used for compound **S8**, and purification by silica gel chromatography (12:1 hexanes/EtOAc) gave 67.7 mg of the title compound as a yellow solid (0.26 mmol, 52%): $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 7.77−7.86 (4H, m, Ar), 7.41−7.54 (3H, m, Ar), 7.02−7.15 (2H, m, Ar), 6.65−6.72 (1H, m, Ar), 6.55 (1H, d, Ar, $J$ = 7.8 Hz), 4.39 (2H, s, -NC$\underline{H}_2$Ar), 3.34 (2H, t, H-2, $J$ = 8.24 Hz), 2.99 (2H, t, H-1, $J$ = 8.24 Hz). This is a known compound.[13b]

**1-(3,4-Dimethoxybenzyl)-1,2,3,4-tetrahydroquinoline (9).** Method B was used for compound **S9** with an Al anode, and purification by silica gel column chromatography (12:1 hexanes/EtOAc) gave 34 mg of the title compound as a colorless oil (0.06 mmol, 12%): $^1$H NMR ($CDCl_3$, 600 MHz) $\delta$ 7.0−6.97 (2H, m, Ar), 6.81−6.80 (3H, m, Ar), 6.59−6.54 (2H, m, Ar), 4.41 (2H, s, -NC$\underline{H}_2$Ar), 3.86−3.84 (6H, m, -$OCH_3$ × 2), 3.34−3.32 (2H, t, H-3, $J_{3-2}$ = 6.19, 11.7 Hz), 2.82−2.80 (2H, t, H-1, $J_{1-2}$ = 6.87 Hz, $J_{gem}$ = 13.1 Hz), 2.02−1.98 (2H, quin, H-2, $J_{2-3}$ = 6.19 Hz, $J_{2-1}$ = 6.19 Hz); $^{13}$C{$^1$H} NMR (151 MHz, $CDCl_3$) $\delta$ 149.3, 148.0, 145.9, 131.5, 129.1, 127.3, 122.5, 118.7, 116.0, 111.3, 111.2, 109.9, 56.1, 56.0, 55.1, 49.8, 28.4, 22.5; HRMS (ESI) $m/z$ $[M + Na]^+$ calcd for $C_{18}H_{21}NNaO_2^+$ 306.1465, found 306.1477.

***N*-(Benzo[*d*][1,3]dioxol-5-ylmethyl)-*N*-methylaniline (10).** Method B was used for compound **S10** with an Al anode, and purification by silica gel column chromatography (12:1 hexanes/EtOAc) gave 57.9 mg of the title compound as a colorless oil (0.12 mmol, 24%): $^1$H NMR ($CDCl_3$, 600 MHz) $\delta$ 7.23−7.21 (2H, m, Ar), 6.76−6.69 (6H, m, Ar), 5.93 (2H, s, -$OCH_2$O-), 4.43 (2H, s, -NC$\underline{H}_2$Ar), 2.98 (3H, s, -NC$\underline{H}_3$). This is a known compound.[13c]

**1-Benzylpiperidine (11).** Method B was used for *N*-benzoylpiperidine, and purification by silica gel column chromatography (2:3 hexanes/EtOAc) gave 75.8 mg of the title compound as a colorless oil (0.43 mmol, 86%). Method A gave 74.5 mg of **11** (0.425 mmol, 85%): $^1$H NMR ($CDCl_3$, 600 MHz) $\delta$ 7.45−7.23 (5H, m, Ar, overlapped with residual solvent), 3.47 (2H, s, -NC$\underline{H}_2$Ar), 2.37 (4H, s, br, H-2, H-6), 1.59−1.55 (4H, quint, H-3, H-5), 1.42 (2H, m, br, H-4). This is a known compound.[13d]

**1-(Benzofuran-2-ylmethyl)piperidine (12).** Method B was used for **S12**, and purification by silica gel column chromatography (1:1 hexanes/EtOAc) gave 70.2 mg of the title compound as a colorless oil (0.33 mmol, 65%): $^1$H NMR ($CDCl_3$, 600 MHz) $\delta$ 7.51 (1H, d, Ar, $J$ = 6.87 Hz), 7.47 (1H, d, Ar, $J$ = 8.94 Hz), 7.25−7.18 (2H, m, Ar), 6.57 (1H, s, Ar), 3.65 (2H, s, -NC$\underline{H}_2$Ar), 2.59−2.34 (4H, m, br, H-2, H-6), 1.64−1.60 (4H, quint, H-3, H-5, $J$ = 5.50 Hz), 1.53−1.34 (2H, m, br, H-4). This is a known compound.[13e]

**1-(Benzo[*b*]thiophen-2-ylmethyl)piperidine (13).** Method B was used for **S13**, and purification by silica gel column chromatography (6:1 to 4:1 hexanes/EtOAc) gave 101.6 mg of the title compound as a yellow solid (0.45 mmol, 89%): $^1$H NMR ($CDCl_3$, 600 MHz) $\delta$ 7.78 (1H, d, Ar, $J$ = 7.56 Hz), 7.67 (1H, d, Ar, $J$ = 7.56 Hz), 7.32−7.24 (2H, m, Ar), 7.12 (1H, s, Ar), 3.75 (2H, s, -NC$\underline{H}_2$Ar), 2.46 (4H, m, br, H-2, H-6), 1.62−1.59 (4H, tt, H-3, H-5, $J$ = 5.50 Hz), 1.49−1.37 (2H, m, H-4); $^{13}$C{$^1$H} NMR ($CDCl_3$, 151 MHz) $\delta$ 144.1, 140.0, 139.7, 123.9, 123.7, 123.0, 122.3, 121.9, 58.6, 54.4, 25.9, 24.3; HRMS (ESI) $m/z$ $[M + H]^+$ calcd for $C_{14}H_{18}NS^+$ 232.1160, found 232.1172; mp 68 °C.

**14-Methyl-5,7,8,13,13b,14-hexahydroindolo[2′,3′:3,4]-pyrido[2,1-*b*]quinazoline (18).** Method B was used for (±)-ebodiamine (1 mL of NMP was used as the co-solvent with 9 mL of MeCN) using an Al anode, and purification by silica gel column chromatography (4:1 hexanes/EtOAc) gave 47 mg of the title compound as a white solid (0.16 mmol, 32%): $^1$H NMR (600 MHz, DMSO-$d_6$) $\delta$ 11.1 (1H, s, -NH), 7.45−7.44 (1H, d, Ar, $J$ = 7.56 Hz), 7.35−7.33 (1H, d, Ar, $J$ = 8.25 Hz), 7.14−7.11 (1H, t, Ar, $J$ = 6.87 Hz), 7.09−7.06 (1H, t, Ar, $J$ = 7.56 Hz), 7.02−7.01 (1H, d, Ar, $J$ = 6.19 Hz), 6.99−6.97 (1H, t, Ar, $J$ = 7.56 Hz), 6.95−6.93 (1H, d, Ar, $J$ = 8.25 Hz), 6.84−6.82 (1H, t, Ar, $J$ = 6.19 Hz), 4.89 (1H, s, -NC$\underline{H}$N-), 3.93 (2H, s, -NC$\underline{H}_2$Ar), 3.27−3.24 (1H, m, -$NCH_2C\underline{H}_a$(-$\underline{H}_b$)Ar), 2.87−2.81 (1H, m, -$NCH_2CH_a$(-$\underline{H}_b$)Ar), 2.78−2.72 (2H, m, -NC$\underline{H}_2CH_2$Ar), 2.65 (3H, s, -$NCH_3$). This is a known compound.[11]

**Phenylsilane-$d_3$.** $LiAlD_4$ (1.0 g, 23.8 mmol) was placed in a flame-dried round-bottom flask to which was added dry $Et_2O$ (80 mL) at 0 °C. To the resulting suspension was added trichlorophenylsilane (2.08 mL, 13 mmol), and the mixture was refluxed for 30 h. The solvent was removed in vacuo at 0 °C, and the resulting crude was distilled under reduced pressure (1 kPa, diaphragm pump). The desired compound was collected with a cold trap (−40 °C), and residual $Et_2O$ was removed by heating in an oil bath (60 °C). Finally, 54.1 mg of the title compound was obtained as a colorless 30% $Et_2O$ solution (0.49 mmol, 4% yield, 99% D): $^1$H NMR (600 MHz, $CDCl_3$) $\delta$ 7.61−7.60 (2H, m, Ar), 7.43−7.40 (1H, m, Ar), 7.38−7.36 (2H, m, Ar). This is a known compound.[13f]

**1-(Phenylmethyl-*d*)indoline (2b) and 1-(Phenylmethyl-$d_2$)-indoline (2c).** Method B was used for compound **2** (26.8 mg, 0.12 mmol) in a MeCN/$Et_4NBr$ (0.1 M) solution (5 mL) in the presence of $PhSiD_3$ (0.49 mmol, 30% $Et_2O$ solution). Purification by silica gel column chromatography (12:1 hexanes/EtOAc) gave 21 mg of the inseparable mixture of **2b**, **2c**, and **2a** as a brown oil (0.1 mmol, total 83% yield, 51% D): $^1$H NMR (600 MHz, $CDCl_3$) $\delta$ 7.50−7.27 (5, m, Ar), 7.14−7.08 (2H, m, Ar), 6.72−6.57 (2H, m, Ar), 4.28−4.25 (0.99 H, m, -N$\underline{H}_2$Ar and -N$\underline{H}$DAr), 3.35 (2H, s, br, H-2), 2.99−2.96 (2H, t, H-1, $J$ = 8.25 Hz); HRMS (ESI) $m/z$ $[M + H]^+$ calcd for $C_{15}H_{15}DN^+$ (**2b**) 211.1346, found 211.1357; HRMS (ESI) $m/z$ $[M + H]^+$ calcd for $C_{15}H_{14}D_2N^+$ (**2c**) 212.1408, found 212.1388.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.1c00931.

Spectral data of compounds (PDF)

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### Notes

The authors declare no competing financial interest.

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