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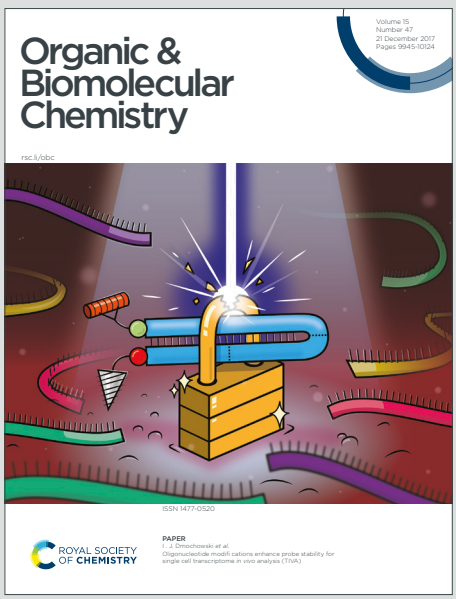

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Direct Electrochemical Reductive Amination between Aldehydes and Amines with H/D-donor Solvent

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A novel electrochemical synthesis protocol has been achieved for reductive amination between aldehydes and amines in undivided cells at room temperature. Under metal-free and external-reductant-free electrolysis conditions, various important secondary amine products are obtained in moderate to high yields. Deuterium-labeling experiments have demonstrated that low-toxicity DMSO acts both as a solvent and a H-donor in the reaction. On this basis, various deuterium-labeled products with good to excellent D-incorporation have been synthesized by using DMSO-d_6 as a solvent. Furthermore, molecule with GR-antagonistic activity has been synthesized through further sulfonylation.

Introduction

Amines are an essential class of bioactive chemicals, existing in a myriad of natural products, agrochemicals and pharmaceuticals,[1] such as anti-parkinson's disease drugs (**A**-**B**), anti-chagas disease drug (**C**), antihistamines for the treatment of rhinitis (**D**-**E**) and so on (Figure 1). Multiple synthetic methods have been established for the construction and functionalization of amines,[2] and reductive amination is considered to be one of the most versatile and efficient means.[1f] For efficient and highly selective reductive amination, great efforts had been made to find a suitable reductant (Scheme 1, a-d). Since the mid-20th century, Borch et al. had applied the stoichiometric amounts of $NaBH_4$ and $NaBH_3CN$ as strong reductants for reductive amination.[3] Later, the more stable hydrosilanes gradually became effective reductants,[4] and their application in reductive amination usually required high temperatures without the need for inert atmosphere and dry solvents. In response to the call for green chemistry,[5] molecular hydrogen had been widely utilized as a reductant in recent years for transition-metal-catalyzed or lewis pair-catalyzed reductive amination studies,[6,7] which generally required high-pressure hydrogen. Simultaneously, several examples of Rh-catalyzed reductive amination of aldehydes with CO as a reductant had also been achieved.[8] For the development of greener and sustainable methods for the synthesis of secondary amines, researchers are turning to metal-free catalytic systems that uses simple and mild reaction conditions, cheap and readily available reaction materials and low-toxicity solvents, which is extremely challenging.

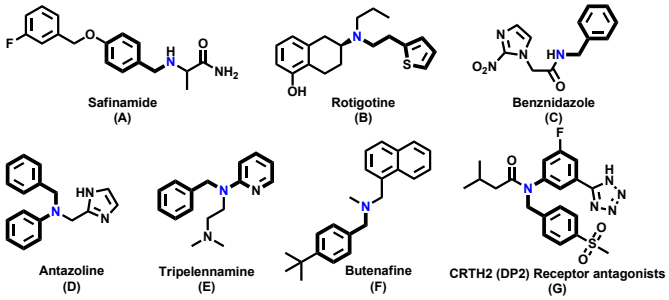

Figure 1. Selected bioactive molecules containing amines.

Electrochemical synthesis is recognized as an environmentally friendly and sustainable synthesis tool that has received much attention in recent years.[9] A range of redox reactions can be achieved by efficiently utilizing energy to activate the substrate on the electrode surface.[10] On the cathode surface, electrons can be an ideal alternative to reductants for a range of reduction reactions to achieve more efficient synthesis of organic molecules.[11] So far, a number of electrochemical hydrogenations have been reported, wherein the constantly exploration of low-cost, safe and conveniently stored hydrogen sources is still of great concern.[12] As a common and inexpensive solvent, DMSO can act as a H-donor for organic reactions in the presence of a base, while converting to a stable DMSO free radical.[13] Moreover, DMSO is considered compatible with multiple electrochemical reactions.[14] To develop more hydrogenation reactions, herein, we propose a room-temperature electrochemical reductive amination of aldehydes and amines. The reaction is conducted under metal-free and external-reductant-free conditions with low-toxicity DMSO/DMSO-d_6 as a H/D-donor solvent for the synthesis of a series of secondary amines and deuterium-labeled secondary amines (Scheme 1, e).

Scheme 1. Reductive amination between aldehydes and amines with different reductants.

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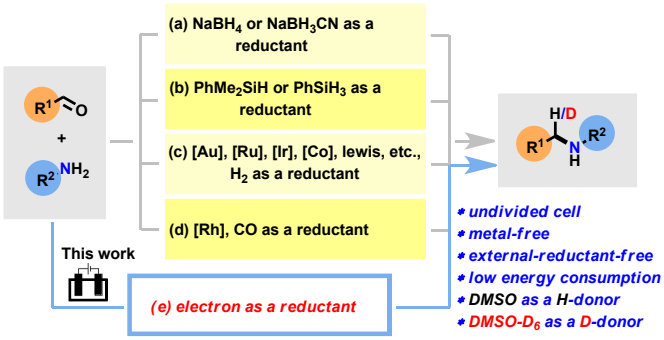
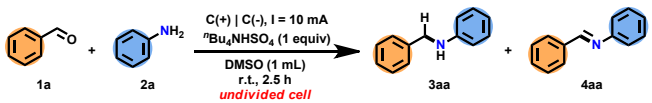


Results and discussion

To achieve this electrochemical reductive amination, benzaldehyde (**1a**) and aniline (**2a**) were selected as model substrates for condition optimization (Table 1). The reaction was initially electrolyzed in an undivided cell equipped with a graphite anode and a graphite cathode using $^{n}Bu_4NHSO_4$ in DMSO as electrolyte under a constant current of 10 mA. Satisfyingly, the initial attempt went smoothly, delivering the desired product (**3aa**) in excellent yield (>98%) (entry 1). Changing electrolyte concentration by increasing the amount of DMSO or increasing the amount of electrolyte could result in a decrease in the yield of **3aa** (entries 2-3), which indicated that appropriate electrolyte concentration was required for effective reductive amination. According to the subsequent solvent screening, other solvents, such as MeOH, MeCN and DMF, were considered unsuitable for this reaction (entries 4-6). When $NaHSO_4$ was used instead of $^{n}Bu_4NHSO_4$, no desired product was detected, but the imine (**4aa**) was formed in a yield of 36% (entry 7). The addition of HOAc (acetic acid) did not show an improvement in the yield (entry 8). As the current was gradually reduced, a gradually decreasing yield was obtained (entries 9-10). The reaction did not give **3aa** without electricity, but delivered imine product (**4aa**) in 88% yield (entry 11). Replacing the graphite cathode with a platinum plate resulted in a low yield (entry 12). Additionally, no expected product was obtained in the absence of $^{n}Bu_4NHSO_4$ (entry 13).

Table 1. Optimization of reaction conditions. [a]

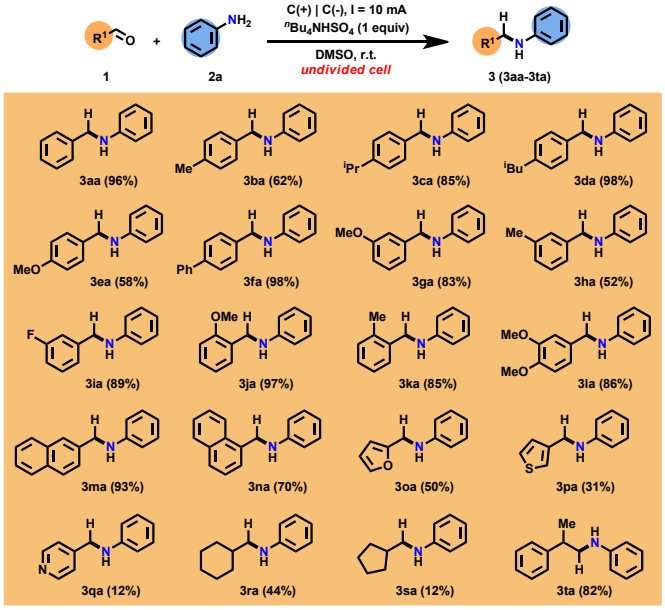


Entry	Variation from standard conditions	Yield (%)	
		3aa	4aa
1	***none***	***>98***	***0***
2	DMSO (2.5 mL) as solvent	81	12
3	$^{n}Bu_4NHSO_4$ (2 equiv) was used	67	<5
4	MeOH (1 mL) as solvent	18	<5
5	MeCN (1 mL) as solvent	8	0
6	DMF (1 mL) as solvent	36	0
7	$NaHSO_4$ instead of $^{n}Bu_4NHSO_4$	0	36
8	HOAc (1 equiv) was added	95	<5
9	8 mA instead of 10mA	86	12
10	5 mA instead of 10mA	80	17
11	No electricity	0	88
12	C(+) | Pt(-)	11	<5
13	Without $^{n}Bu_4NHSO_4$	0	<5

[a] Reaction conditions: undivided cell, graphite anode, graphite cathode, constant current = 10 mA, **1a** (0.1 mmol), **2a** (0.12 mmol), electrolyte, solvent, air, 2.5 h. Yield determined by GC analysis with *n*-dodecane as the internal standard.

With the optimized conditions established, the electrochemical reductive amination of aldehydes **1a**-**1t** was subsequently examined with aniline (**2a**) (Table 2). To our satisfaction, aldehyde substrates (**1b**-**1l**) bearing methyl (Me), isopropyl (^{i}Pr), *tert*-butyl (^{t}Bu), methoxy (MeO), phenyl (Ph) or fluorine (F) on the phenyl ring could undergo the reaction smoothly, and the reaction delivered the corresponding products (**3aa**-**3la**) in moderate to excellent yields. Among them, aldehydes containing a methyl group at the *para*- or *meta*-position of benzene ring gave lower yields (**3ba** and **3ha**). It was noteworthy that the use of 2-substituted aldehydes allowed the reaction to proceed smoothly (**3ja**-**3ka**), demonstrating that the steric hindrance of the 2-position did not affect the substrate reactivity. Naphthaldehyde substrates could transfer to the corresponding products **3ma**-**3na** in 93% and 70% isolated yield, respectively. Aldehydes containing heterocycles such as furan, thiophene and pyridine appeared to be easily oxidized and decomposed at the anode, resulting in a lower yield of the products (**3oa**-**3qa**). Moreover, reductive amination of cyclic aliphatic aldehydes could also be performed (**3ra**-**3sa**), where the yield of the more stable cyclohexanecarboxaldehyde (44%) was superior to that of cyclopentanecarbaldehyde (12%). Finally, the reaction of 2-phenylpropionaldehyde was found to be feasible with aniline to afford desired product (**3ta**) in 82% yield.

Table 2. Scope of aldehydes. [a, b]



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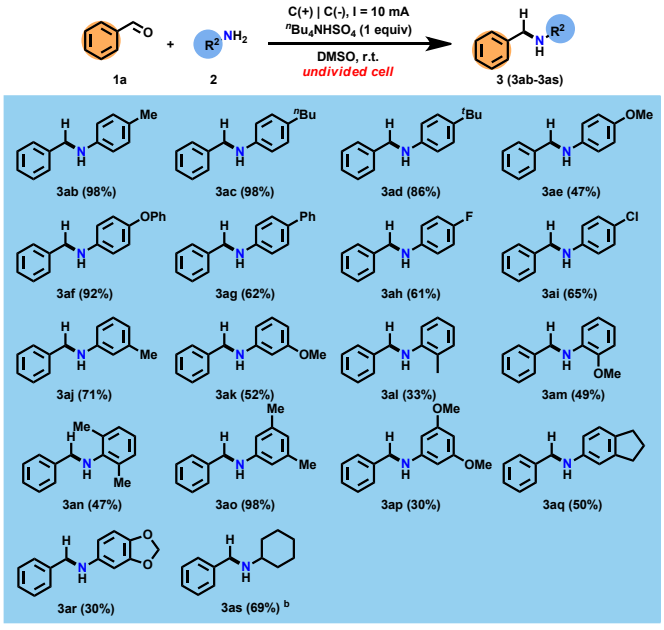
[a] Reaction conditions: graphite anode, graphite cathode, constant current = 10 mA, **1** (0.5 mmol), **2a** (0.6 mmol), $^{n}Bu_4NHSO_4$ (1 equiv), DMSO (5 mL), undivided cell, r.t., 5 h. Isolated yields.

Next, the scope of amines **2** for this electrochemical reductive amination was investigated (Table 3). Electron-rich groups (Me, ^{n}Bu, ^{t}Bu, MeO, PhO and Ph) and halogen groups (F and Cl) on the phenyl ring were well tolerated in the conversion (**3ab**-**3am**). By comparison, substrates containing a *meta*-substituent on the phenyl ring (**3aj**-**3ak**) were better converted than those containing an *ortho*-substituent (**3al**-**3am**), which might be due to steric hindrance. Moreover, a higher yield of 98% was obtained when using 3,5-dimethylaniline (**3ao**) as a substrate, while the reaction yield was lower when dimethoxy-substituted aniline (**3ap**) was used, possibly because the electron-rich substrate was prone to oxidation. 2,3-Dihydro-1*H*-inden-5-amine and benzo[*d*][1,3]dioxol-5-amine were also proved to be useful and the corresponding products (**3aq**-**3ar**) were afforded in lower yields. In addition, the reaction with 3 equivalents of cyclohexylamine delivered **3as** in an acceptable yield, suggesting that aliphatic amines were equally applicable to the reaction.

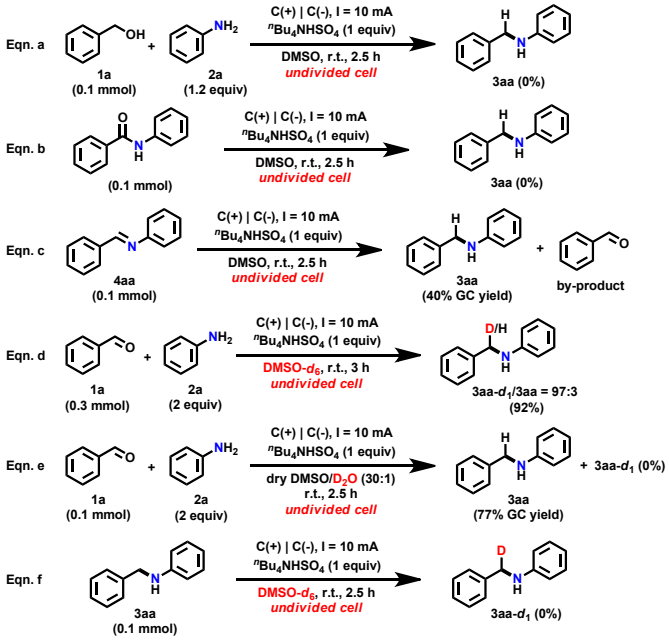
Table 3. Scope of amines. [a, b]



[a] Reaction conditions: graphite anode, graphite cathode, constant current = 10 mA, **1a** (0.5 mmol), **2** (0.6 mmol), $^{n}Bu_4NHSO_4$ (1 equiv), DMSO (5 mL), undivided cell, r.t., 5 h. Isolated yields. [b] Cyclohexylamine (3 equiv).

To gain mechanistic insight into this electrochemical reductive amination, some control experiments were then conducted (Scheme 2). The reaction of benzyl alcohol and aniline did not produce the desired product **3aa**, proving that benzyl alcohol was only a by-product formed in the reaction (Eqn. a). Subsequently, *N*-phenylbenzamide proved to be unable to form **3aa** in this electrochemical reduction system (Eqn. b). In order to verify whether the reaction was *via* the formation of an imine-like intermediate and further reduction to a product, we used (*E*)-*N*-benzylideneaniline (**4aa**) as a substrate to carry out the reaction (Eqn. c). Part of **4aa** in the reaction was decomposed into benzaldehyde, and 40% of **3aa** was formed, from which we speculated the reaction was *via* the formation of imine-like intermediates. In order to explore the source of hydrogen in this electrochemical reductive amination, the deuterium-labeling experiments were then conducted. Surprisingly, when performing the reaction with DMSO-d_6 as a solvent, the ratio of **3aa-d_1** and **3aa** was confirmed by ^{1}H NMR to be 97:3 among 92% isolated yield (Eqn. d), wherein **3aa-d_1** had been confirmed through NMR and HRMS analysis. Subsequently, the transformation with DMSO/D_2O (30:1) as a solvent was also performed (Eqn. e), and it was noted that no deuterated product **3aa-d_1** was detected in the reaction except that 77% of **3aa** was detected. In addition, no **3aa-d_1** was produced after the treatment of **3aa** under the conditions of using DMSO-d_6 as a solvent, which proved that no H/D exchange occurred (Eqn. f). The above experiments confirmed that one hydrogen atom in the product **3aa** was derived from the methyl hydrogen of DMSO in this electrochemical reductive amination.

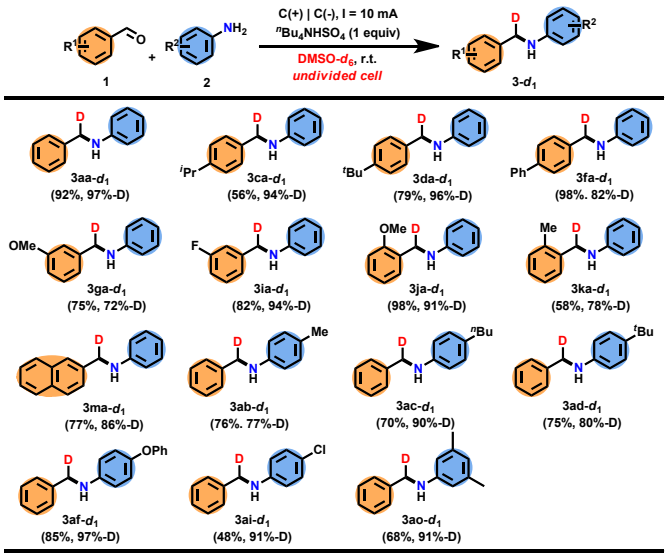
Scheme 2. Mechanistic studies.



Deuterium-labeled molecules have received significant attention from organic and medicinal chemists because of their important applications in mechanistic studies and drug modification.[15] After learning that DMSO-d_6 could provide a deuterium atom to construct various deuterium-labeled secondary amines through the formation of a C-D bond, we subsequently investigated the substrate scope for the reductive amination (Table 4). Both electron-rich groups (Me, ^{i}Pr, ^{t}Bu, MeO and Ph) and electron-poor groups (F) on the aromatic ring of aldehyde were tolerated in the transformation, and the corresponding products (**3ca-d_1**-**3ka-d_1**) were given with good to excellent D-incorporation. Among them, *p*-phenylbenzaldehyde and *o*-methoxybenzaldehyde were good substrates, and both reactions delivered the corresponding products (**3fa-d_1** and **3ja-d_1**) in 98% yields. Naphthaldehyde with a large conjugated structure could also be applied in the reaction, and **3ma-d_1** was obtained with 86% D-

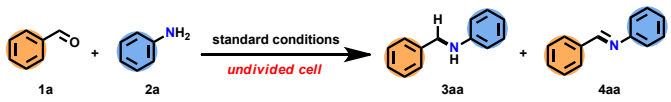
incorporation in 77% yield. Gratifyingly, the reactions of benzaldehyde and amines containing different groups (Me, ^{n}Bu, ^{t}Bu, OPh and Cl) on the aromatic ring could give products (**3ab-d_1**-**3ao-d_1**) with good to excellent D-incorporation.

Table 4. Deuterium-labeled substrate scope for the electrochemical reductive amination. [a, b]



[a] Reaction conditions: graphite anode, graphite cathode, constant current = 10 mA, aldehydes **1** (0.3 mmol), amines **2** (0.6 mmol), ^{n}Bu$_4$NHSO$_4$ (1 equiv), DMSO-d_6 (3 mL), undivided cell, r.t., 3 h. Isolated yields.

To gain more insight into this transformation, we monitored the electrochemical reductive amination of benzaldehyde and aniline at room temperature by GC-MS analysis, as shown in Figure 2. During the first 0.5 h, **1a** and **2a** were rapidly consumed, the concentration of **3aa** in the reaction gradually increased, and the by-product **4aa** reached the maximum at 0.29 h. Over the next period, accompanied by the continuous accumulation of **3aa**, the concentration of **4aa** gradually decreased to zero. Among them, a trace amount of benzyl alcohol was detected in the reaction. According to these interesting conversion processes, we speculated that **4aa** may be an intermediate in the reaction, and **3aa** was obtained by the reduction of **4aa**.



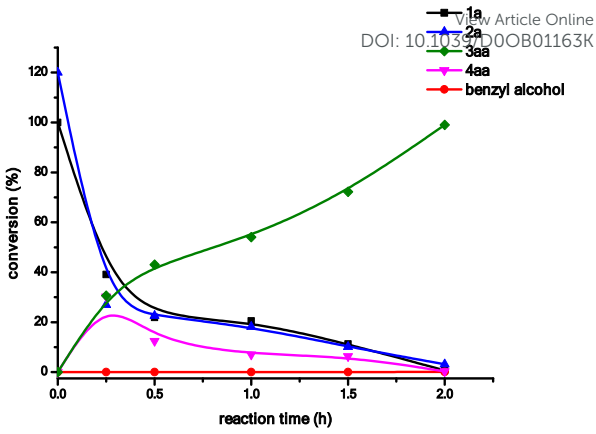
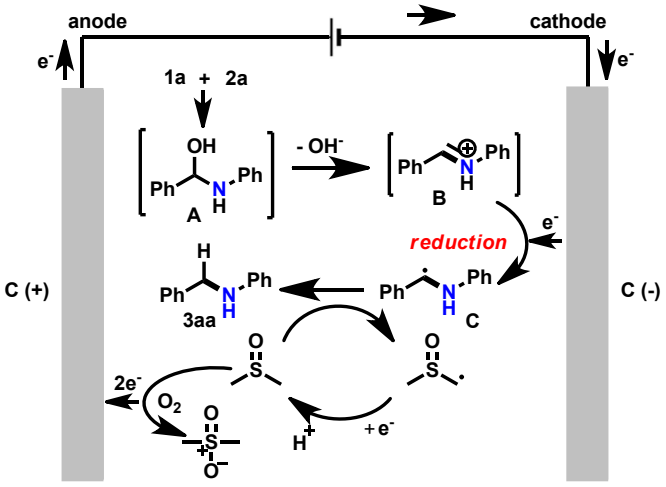


Figure 2. Sampling experiment. Standard conditions: graphite rod (ϕ 6 mm) anode, graphite rod (ϕ 6 mm) cathode, constant current = 10 mA, benzaldehyde **1a** (0.1 mmol), aniline **2a** (0.12 mmol), ^{n}Bu$_4$NHSO$_4$ (1 equiv), DMSO (1 mL), room temperature, GC yields.

Based on the above experimental results and previous reports, a plausible reaction mechanism for the formation of **3aa** in electrochemical conditions was depicted in Scheme 3. Firstly, benzaldehyde **1a** and aniline **2a** could form a phenyl(phenylamino)methanol intermediate **A**, followed by the departure of OH^- to form imine cation **B**. Subsequently, imine cation **B** obtained an electron through electrochemical reduction to form a radical intermediate **C**.[16] Then, radical Intermediate **B** abstracted a hydrogen atom from DMSO to form **3aa** and a DMSO radical,[13] which could re-form DMSO *via* reduction and protonation at the cathode. At the anode, DMSO was oxidized to provide electrons for the reduction of substrate.[17]

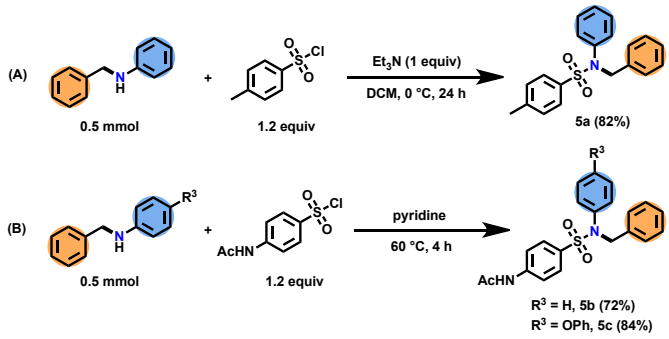
Scheme 3. Proposed mechanism.



Finally, we found the products from this electrochemical reductive amination could be applied to the synthesis of active aryl sulfonyl tertiary amine molecules (Scheme 4). The reaction of *N*-benzylaniline and 4-methylbenzenesulfonyl chloride in the presence of triethylamine could deliver the sulfonylated product **5a** in 82% isolated yield (A). Moreover, with pyridine as the solvent, the reaction of *N*-acetylsulfanilyl chloride with **3aa** or **3af** gave products

5b and **5c** in isolated yields of 72% and 84%, respectively (B). Among them, **5c** has been reported as a novel class of nonsteroidal glucocorticoid receptor (GR) modulators, which is expected to be a drug candidate for treating immune-related disorders.[18]

Scheme 4. Construction of aryl sulfonyl tertiary amine molecules from **3aa** and **3af**.



Conclusions

In conclusion, we have developed a novel electrochemical reductive amination between aldehydes and amines at room temperature. The reaction proceeds in undivided cells to deliver various important secondary amine products in moderate to high yields, some of which can be converted to molecules with GR-antagonistic activity by further sulfonylation. Interestingly, deuterium-labeling experiments have demonstrated that DMSO is not only the solvent in the reaction, but also the H-donor in the reaction, providing a hydrogen atom for the product. Based on the experiments, various deuterium-labeled secondary amines with good to excellent D-incorporation are subsequently synthesized by using DMSO-d_6 as a solvent. Compared with previous reductive amination reactions, no metal or external-reductant is required in this protocol. Furthermore, inexpensive and readily available substrates, simple and mild electrolysis conditions and low energy consumption make this transformation extremely attractive. Our further efforts are to elucidate the mechanism of this novel reaction and develop more hydrogenation and deuteration reactions by cathodic reduction.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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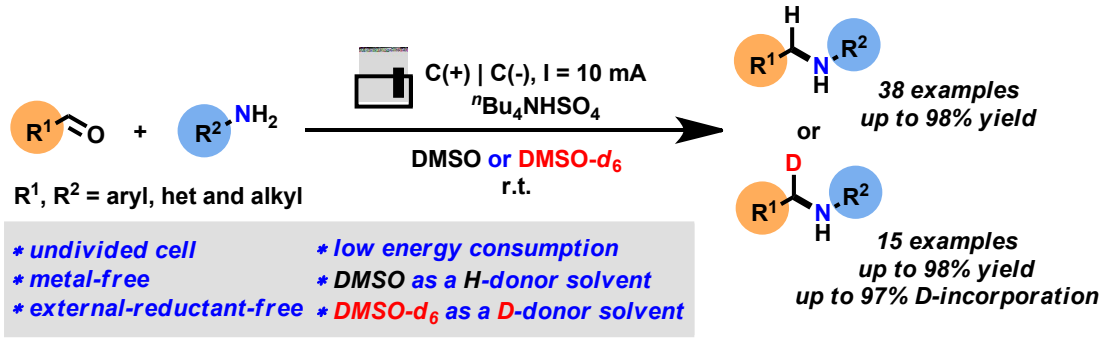

Electrochemical reductive amination of aldehydes and amines was first realized at room temperature by using DMSO/DMSO-d_6 as a H/D-donor solvent.