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Electrochemical-Induced Transfer Hydrogenation of Imidazopyridines with Secondary Amine as Hydrogen Donor

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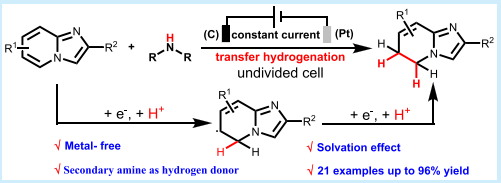
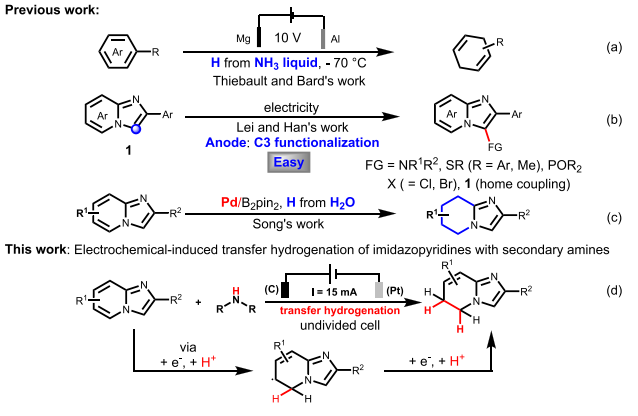
ABSTRACT: Electrochemical-induced transfer hydrogenation (TH) of N-heteroaromatic to construct biologically active functional molecule is an appealing and yet challenging task. We report herein the first selective transfer hydrogenation of imidazopyridine derivatives with secondary amines as the hydrogen donors under electrochemical conditions. The successful conversion of cathode transfer hydrogenation depends on the solvation effect. Importantly, such electrochemical-induced transfer hydrogenation can be easily amplified with excellent efficiency.



Hydrogenation is one of the most classic transformations in organic synthesis, and it has very important application prospects in the synthesis of fine chemicals and pharmaceuticals.[1] In particular, the TH strategy that attractively uses non-H_2 hydrogen donors to replace the high-pressure of H_2 gas of the direct hydrogenation has become one of the hot spots in recent years.[2] Over the past century, a large number of transition metal and organocatalysts mediated by TH have been successfully developed by using alcohol, formic acid, hydrazine, alkanes, cyclohexene, Hantzsch esters, and water as the "sacrificial" hydrogen donors.[3] However, traditional transfer hydrogenation strategies often require the participation of complex or expensive transition metal catalysts or are restricted to harsh reaction conditions. Therefore, the development of metal-free, convenient, efficient, and environmentally friendly protocols by using readily available hydrogen sources as hydrogen donors is a key scientific issue in the field of TH research. As the most abundant, piperidine as an inexpensive and readily available organic reagent often plays the role of the base and ligands in most organic reactions but has not been used as a hydrogen donor in TH under the electrochemical conditions.[4]

Electrochemistry, electrons as redox reagents, is a powerful tool for activating substrates, and a series of milestones have been achieved.[5] The elegant methods for hydrogenation of activated olefins, alkynes, and ketones with NH_3 gas, H_2O, NH_3Cl, or DMSO as hydrogen donors have been successfully achieved by an electrochemical cathode-induced transfer hydrogenation strategy.[6] However, the selective hydrogenation of aromatic compounds by electrochemical-induced transfer hydrogenation strategy has rarely been reported.[7] The first prominent protocol was Birch reduction, which employing liquid ammonia as a hydrogen source to achieve the dearomatization of aromatics under freezing conditions (Scheme 1a).[8] Recently, imidazopyridines have been selected as star molecules to easily realize a series of C3 functionalization reactions by electrochemical anodic oxidation such as amination, sulfuration, phosphorization, halogenation, and even self-coupling (Scheme1b).[9] Nevertheless, the cathodic transfer hydrogenation of imidazopyridine has not been reported.[5]

Scheme 1. Representative Reaction Examples of Imidazopyridine



The hydrogenation of N-heteroaromatics is one of the most effective protocols to access partially saturated N-heterocycles as building blocks of biologically active molecules and key intermediates in organic synthesis.[10] Consequently, many

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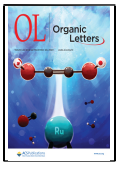

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valuable traditional methods have been established based on the transfer hydrogenation strategy.[2] For example, in 2016, palladium-catalyzed transfer hydrogenation of imidazopyridines with water as hydrogen donor was developed by Song and co-workers[11] (Scheme 1c). Despite these advances, the common drawbacks of the above-mentioned elegant approaches are bounded by the precious metal catalysts, harsh reaction conditions, and poor selectivity. Therefore, it is still an arduous task to develop a convenient and efficient strategy for the selective hydrogenation of N-heteroaromatics compounds under metal-free conditions. In the continuation of our efforts in the functionalization of the imidazopyridine,[12] here, we wish to report a metal-free selective cathode transfer hydrogenation of imidazopyridine with secondary amines as hydrogen donors in an undivided cell (Scheme 1d). Various imidazopyridine could be tolerated in the present protocol, generating the corresponding products in up to 96% yields. Noticeably, the mechanism experiments indicated that this reaction underwent the cathode-mediated radical hydrogenation reduction.

7-Methyl-2-phenylimidazo[1,2-*a*]pyridine (**1b**) was chosen as the model reaction substrate, in which reduction potentials were reviewed by cyclic voltammetry (CV) experiments. The electrode potential of **1b** (−0.78 V and −2.09 V vs Ag/AgCl) was not observed with basic CH_3CN or THF solution, indicating that the reducing abilities of these single solvents might be poor. In contrast, the adoption of a mixed solvent of CH_3CN/THF (9:1) showed the obvious reduction potential and current, which reveals that this electrochemical system should present grisly the reduction ability. At the same time, other mixed solvent systems were investigated, and the results confirm that the CH_3CN/THF system can enjoy the strongest reducing ability (Figure 1).

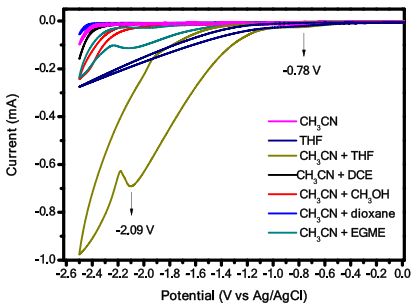
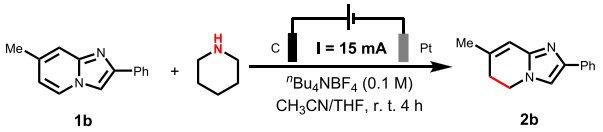


Figure 1. Cyclic voltammograms at glass carbon as work electrode, Pt (1 × 1 cm^2) as counter electrode in 0.1 M nBu_4NBF_4 with different solvent under N_2, **1b** (0.25 mM), the mixed solvent of CH_3CN/others (v = 9:1), scan rate 100 mV/s.

As a proof of concept, a pilot electrochemical-induced transfer hydrogenation of **1b** was performed in an undivided cell with pyrrolidine as the hydrogen donor under ambient temperature with the mixed solvent of CH_3CN/THF (9:1). The desired product **2b** was produced in an 88% yield (Table S1, entry 1). The formation of **2b** was suppressed by performing the reaction at other solvents (Table S1, entries 2−8). These experimental results further confirmed that the mixture of CH_3CN/THF should possess a strong reducing ability for the imidazopyridine derivatives under the electrochemical conditions. Subsequently, the performances of electrochemical-induced transfer hydrogenations with other typical amines instead of pyrrolidine as hydrogen donors were investigated. The experimental results are summarized in Scheme S1, showing that many types of secondary amines could be used as the hydrogen donors, among which piperidine as the optimal choice with the desired product yields up to 92%. To better explain that the aliphatic cyclic secondary amine has a better conversion to the transfer hydrogenation of imidazopyridine, the electrochemical reduction behavior between the secondary amine and **1i** was selected and the CV experiment was used to conduct a detailed study. As shown in Figure S6, the results show that the reduction potential of **1i** was decreased in the presence of THF, piperidine, and tetrahydropyrrole. Therefore, the aliphatic cyclic secondary amines are a better sacrificial reductant choice in the transfer hydrogenation of imidazopyridine compared with other secondary amines.

Assuredly, the control experiments confirmed that electricity and piperidine should play a key role in the transfer hydrogenation of imidazopyridine (Table 1, entries 2 and 3).

Table 1. Optimization of Transfer Hydrogenation[a]



entry	variation of standard conditions	yield[b] (%)
1	none	92
2	without electricity	n. d.
3	without piperidine	n. d.
4	10 mA instead of 15 mA, 3 h	67
5	20 mA instead of 15 mA, 3 h	70
6	$LiClO_4$ instead of nBu_4NBF_4	55
7	nBu_4NClO_4 instead of nBu_4NBF_4	52
8	nBu_4NPF_6 instead of nBu_4NBF_4	83
9	Pt as anode and carbon as cathode	trace
10	Ni (−) instead of Pt (−)	trace

[a]Standard conditions: carbon rod (d: 6 mm) as anode, Pt (1 × 1 cm^2) as cathode, I = 15 mA, **1b** (0.25 mmol), piperidine (0.75 mmol), $^nBu_4NBF_4$ (4.0 equiv), CH_3CN/THF (10.0 mL, V = 9:1), r. t., N_2, 4 h. n. d. = not detected. [b]Isolated yields.

Increasing or decreasing the current yields of **2b** will be decreased (Table 1, entries 4 and 5). Subsequently, the reaction efficiency was decreased when the other types of electrolytes such as $LiClO_4$, $^nBu_4ClO_4$, and $^nBu_4NPF_6$ were selected as replacements for $^nBu_4NBF_4$ (Table 1, entries 6−9). Moreover, the only trace of the desired products **2b** was gained when the graphite rod (anode) or platinum (cathode) was instead of graphite rod (cathode) or Ni (cathode) (Table 1, entries 9 and 10). The data reveal that the cathode material might play a vital role in the transfer hydrogenation of imidazopyridine with piperidine as hydrogen donor. In this regard, we speculate that the surface of the platinum sheet might be more conducive to hydrogen evolution than other kinds of electrode materials.

With the optimized conditions in the hand, we investigated the substrate scope to test the utility and versatility of the electrochemical-induced transfer hydrogenation of imidazopyridines with piperidine (Scheme 2). The current protocol could tolerate a variety of electron-donating and electron-withdrawing groups at different positions of the imidazo[1,2-*a*]pyridines ring (**2a**−**2h**). Nevertheless, only a small amount of the corresponding product was generated under the

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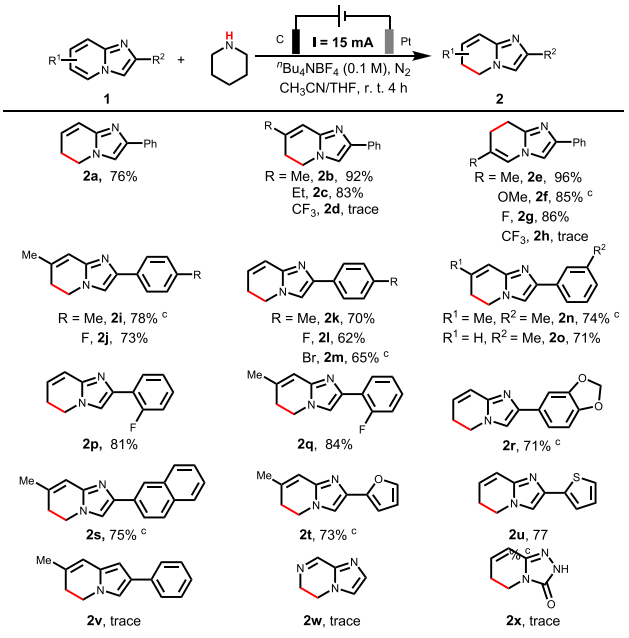
Scheme 2. Scope of Imidazopyridines[a,b]

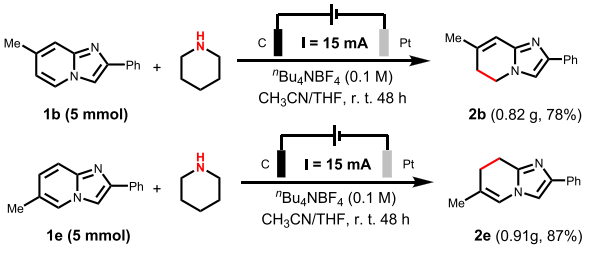


[a]Standard conditions: C anode, Pt cathode, constant current = 15 mA, **1** (0.25 mmol), piperdine (0.75 mmol), $^{n}Bu_4NBF_4$ (4 equiv), CH_3CN/THF (10.0 mL, V = 9:1), r. t., N_2, 4 h. n. d. = not detected. [b]Isolated yields. [c]Pyrrolidine instead of piperdine.

standard conditions when C-7 or C-8 positions of the imidazopyridines have a strong electro-drawing group CF_3 (**2d**, **2h**). Subsequently, the influence of the substituent at the C-2 position on the phenyl ring was also investigated under the established standard. To our delight, the electron-donating and electron-withdrawing groups at different positions of substituents on the phenyl ring could afford the corresponding transfer hydrogenation products with excellent yields (**2i**−**2q**). It should be emphasized that the C-2 substituents on the phenyl ring were not affected by the steric hindrance and electronic effects. Furthermore, the imidazo[1,2-*a*]pyridines with sterically hindered, heterocycle, or alkyl substitution can be compatible under the existing conditions (**2r**−**2v**). However, only traces of desired products were generated when 7-methyl-2-phenylindolizine, imidazo[1,2-*a*]pyrazine, and 1,2,4-triazolo [4,3-*a*]pyridin-3(2H)-one were performed at the standard conditions (**2v**−**2x**).

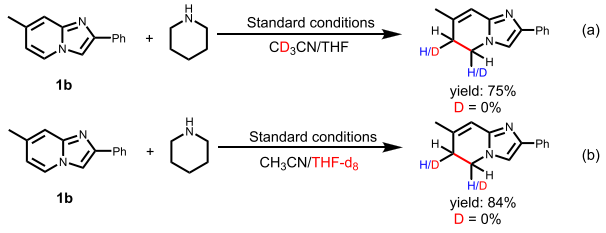
The **1b** and **1e** were selected as substrates for gram-scale experiments to investigate the superiority of the electrochemical transfer hydrogenation strategy. As shown in Scheme 3, the reaction could afford **2b** and **2e** in 78% and 87% yields, respectively. These results indicate that this electrochemical-induced selective transfer hydrogenation of imidazopyridine is a practical and effective strategy by using secondary amines as the hydrogen donor.

Scheme 3. Gram-Scale Experiments



The deuteration and control experiments were performed to further insights into the mechanism of the electrochemical-induced transfer hydrogenation of imidazopyridines with piperidine. First, the deuteration experiments were conducted to explore the source of hydrogen in the product (Scheme 4).

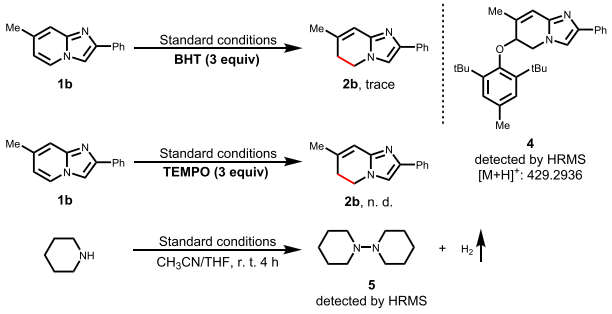
Scheme 4. Deuteration Experiments



When the CD_3CN (Scheme 4a) or THF-d_8 (Scheme 4b) were used as the solvent instead of CH_3CN or THF performed in standard conditions, the deuteration of products was not observed from the ^{1}HNMR spectra (Figures S2 and S3). These results should indirectly prove that hydrogen may be originated from piperidine.

Besides, the control experiments and CV experiments were performed to deeper understand the reaction mechanism. First, it was found that the hydrogenation reaction is tremendously repressed when in the presence of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) or 2,6-ditertbutyl-4-hydroxytoluene (BHT), which indicates that the reaction presumably adopts a radical pathway (Scheme 5). Also, intermediate **4** was detected

Scheme 5. Radical-Trapping Study



by a high-resolution mass spectrometer (HRMS) when TEMPO or BHT was loaded into the system (Figure S4). The N−N coupling of piperidine product **5** was also detected by HRMS (Figure S5) when piperidine was performed under the standard conditions and large quantities of gas released from the electrolytic cell.

On the basis of the preliminary experimental results and literature reports,[6,9,13] a reasonable mechanism was hypothesized for selective transfer hydrogenation of imidazopyridines with piperidine as the hydrogen donors (Scheme 6). Initially, the substrate **1b** underwent the one-electron reduction on the surface of the cathode Pt to generate a radical anion intermediate A. Subsequently, the radical anion intermediate **A** was attacked by H^+ to afford the radical intermediate **B**, which was then subjected to the single-electron reduction and nucleophilic attack on the cathode surface yielding the desired product **2b**. At the same time, piperidine was oxidized on the

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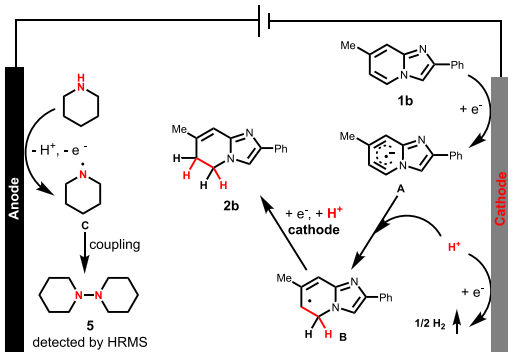
Scheme 6. Presumed Reaction Mechanism



surface of the anode to obtain intermediate **C**, which underwent the radical coupling to afford **5**.

In conclusion, the electrochemical-induced selective transfer hydrogenation of imidazopyridines by using secondary amines as the hydrogen donor has been disclosed. The successful conversion of cathode transfer hydrogenation depends on the solvation effect (CH_3CN/THF) with a strong reduction capability. The developed synthesis method successfully avoided the presence of transition metals and high-pressure hydrogen compared with the conventional N-heteroarene hydrogenation strategies. Moreover, this transfer hydrogenation synthesis method of cathode reduction can realize gram scaled up, which is favorable to practical applications. Besides, our laboratory is adopting a similar green transfer hydrogenation strategy to synthesize other biologically active compounds.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c03205.

Experimental procedures, optimization of reaction conditions, preliminary mechanistic studies, characterization data, HRMS data, NMR spectra of products (PDF)

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Notes

The authors declare no competing financial interest.

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