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Electrochemical cross-dehydrogenative coupling of *N*-aryl-tetrahydroisoquinolines with phosphites and indole

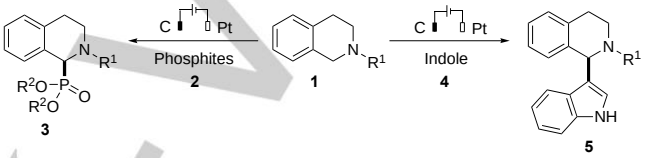
Wenxia Xie,[a] Nian Liu,[a] Bowen Gong,[a] Shulin Ning,[a] Xin Che,[a] Lili Cui*[b] and Jinbao Xiang*[a]

Abstract: A metal- and reagent-free, electrochemical cross-dehydrogenative coupling reaction of *N*-aryl-tetrahydroisoquinolines with phosphites and indole is developed. This method provides an environmentally benign and simple approach for the construction of C−P and C−C bonds from moderate to high yields with wide tolerance of functional groups.

Introduction

With increased consciousness of the chemical process impacting on environmental, to develop clean and sustainable synthetic methodology has been paid much attentions.[1] It is accepted that electrochemical synthesis is sustainable and eco-friendly in comparison with the conventional redox processes, because electrons are employed as reagents without the existance of transition-metal catalysts or toxic oxidants.[2] Recently, several important milestones in electrochemical synthesis have been accomplished,[3] such as the cation-pool method,[4] N−N bond formation,[5] allylic oxidation,[6] cross/homo-coupling,[7] and amination.[8]

Direct formation of C–P and C–C bonds by oxidative cross-dehydrogenative coupling (CDC) reaction is an attractive research area in organic synthesis,[9]since pre-functionalized precursors is not required in CDC methods, which are atom economical and environmentally benign.[10] Among all of substrates which can be used for C–P and C–C coupling reactions using CDC, tetrahydroisoquinoline is the most interesting ones attributed to its prevalence and abundance in natural products.[10c,11] Most of the CDC reactions unavoidably have to use transition-metal catalysts (Cu,[9,12] Mo,[13] Au,[14] and so on.[15]) or stoichiometric non-metal oxidants (DDQ,[16] TBHP,[17] DEAD,[18] and so on.[19]), which would produce undesired waste. Moreover, visible-light-mediated phosphorylation and indolation of *N*-aryl-tetrahydroisoquinolines, under the assistance of expensive Ir(III)-[20] and Ru(II)-based catalysts[21] and Eosin Y[22], are also reported.[23] More recently, Prabhu's group synthsized α-aminophosphonate via CDC reaction employing air as the oxidant in DCE under reflux for 48 hours.[24] Suib's group reported the CDC reaction of tetrahydroisoquinolines with indoles using a heterogeneous mesoporous manganese oxide catalyst at 100 °C.[25] However, these reported procedures have the disadvantages of complicated procedure, harsh reaction condition, and non-environmental friendliness. Inspired by the seminal example of electrochemical CDC reaction involving a two-step synthesis protocol in a divided cell by Li and co-workers,[26] It is envisioned that aminophosphonates **3** and compounds **5** can be readily prepared from tetrahydroisoquinoline **1** and nucleophile **2** or **4** via a one-pot direct electrochemical oxidative C–P and C–C bonds formation in an undivided cell (Scheme 1). Herein, the details on these studies are exhibited.

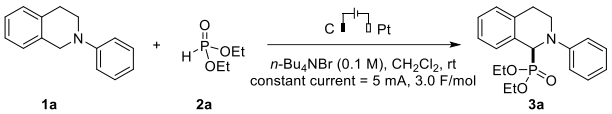


Scheme 1. One-pot Oxidant-free Dehydrogenative C–P and C–C Bonds Formation.

Results and Discussion

The optimized reaction conditions for the CDC reaction of *N*-phenyltetrahydroisoquinoline **1a** with diethyl phosphite **2a** is first identified, which involved constant-current electrolysis employing a graphite rod as anode and and Pt plate as cathode in an undivided cell containing an electrolyte solution of *n*-Bu_4NBr in CH_2Cl_2 at room temperature (Table 1). Under these mild conditions, the desired

Table 1. Optimization of the Reaction Conditions[a]



entry	Variation from standard conditions	yield (%)[b]
1	none	83
2	Et_4NOTs instead of *n*-Bu_4NBr	49
3	*n*-Bu_4NPF_6 instead of *n*-Bu_4NBr	41
4	EtOH instead of CH_2Cl_2	58
5	CH_3CN instead of CH_2Cl_2	67
6	TsOH (0.1 equiv.) was added	66
7	DBU (0.1 equiv.) was added	61
8	no electric current	< 1

[a] Standard conditions: graphite rod anode (*d* = 5 mm), Pt plate cathode (0.5 cm × 0.5 cm), constant current = 5 mA, **1a** (0.25 mmol), **2a** (0.3 mmol), *n*-Bu_4NBr (0.5 mmol), CH_2Cl_2 (5 mL), undivided cell, room temperature, 3.0 F/mol. [b] Isolated yield.

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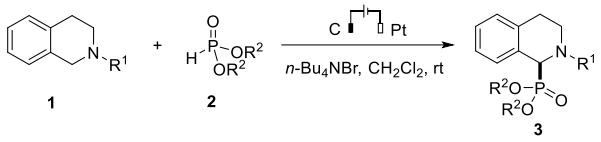
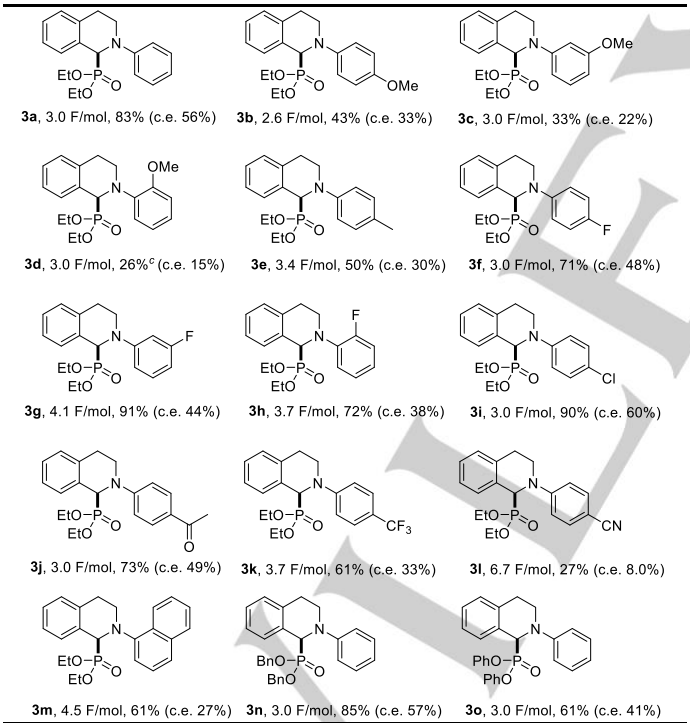
aminophosphonate **3a** was isolated in 83% yield (entry 1). In comparison, reduced yields were isolated when one of the following factors of the reaction conditions was modified: changing the electrolyte to Et_4NOTs (entry 2) or *n*-Bu_4NPF_6 (entry 3), using other organic solvents such as EtOH (entry 4) or MeCN (entry 5), or adding the catalytic *p*-toluenesulfonic acid (TsOH) (entry 6) or 1,8-diazabicyclo(5.4.0)undec-7-ene (DBU) (entry 7). A control experiment revealed that only trace of **3a** was obtained in the absence of electric current, suggesting the key role of electric energy for the reaction (entry 8).

Having optimized the reaction conditions, we next examined the scope of the CDC reaction by testing a series of tetrahydroisoquinoline substrates (Table 2). To our delight, various functional groups, including alkoxy (OMe), alkyl (Me and CF_3), halogen (F and Cl), carbonyl (COMe), and cyano substituents in the *N*-phenyl ring, were tolerated in the reaction conditions (**3a−l**). It shows that mild electron-withdrawing substituents generally offer a higher yield than strong electron-donating group (**3f−i** versus **3b-d**) or strong electron-withdrawing one (**3f−i** versus **3l**). Tetrahydroisoquinolines bearing other *N*-aryl ring including naphthalene could be accessed (**3m**). Other phosphites, such as dibenzyl phosphite and particularly diphenyl phosphite, underwent a smooth CDC reaction with *N*-phenyl-tetrahydroisoquinoline **1a**, furnishing the desired products **3n** and **3o** in good yields (85% and 61% yields, respectively, Table 2).

Table 2. Synthesis of α-Aminophosphonates **3**[a][b]

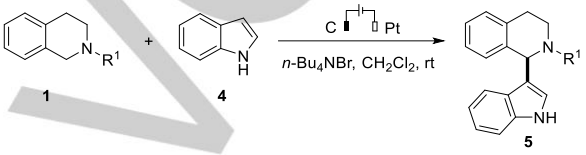


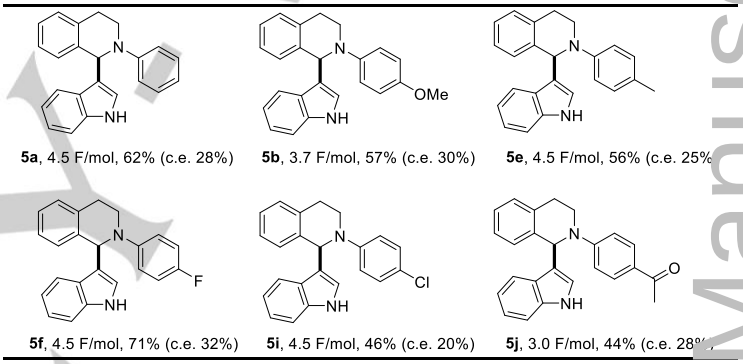


[a] Standard conditions: graphite rod anode (*d* = 5 mm), Pt plate cathode (0.5 cm × 0.5 cm), constant current = 5 mA, **1** (0.25 mmol), **2** (0.3 mmol), *n*-Bu_4NBr (0.5 mmol), CH_2Cl_2 (5 mL), undivided cell, room temperature, 3.0–6.7 F/mol. [b] Isolated yield. [c] The reaction was conducted under N_2 protection.

The success of C–P bond formation of tetrahydroisoquinoline under the above mild electrochemical conditions encouraged us to study C–C bond formation reactions. Indole, as a privileged scaffold, plays an important role in the field of drug discovery.[27] In this work, free indole could react with various tetrahydroisoquinolines to afford the desired products **5** from moderate to good yields with an exclusive regioselectivity (Table 3).

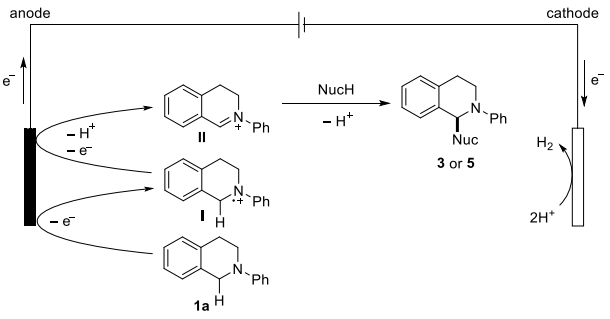
Table 3. CDC Reaction of Tetrahydroisoquinolines with Indole[a][b]





[a] Standard conditions: graphite rod anode (*d* = 5 mm), Pt plate cathode (0.5 cm × 0.5 cm), constant current = 5 mA, **1** (0.25 mmol), **4** (0.3 mmol), *n*-Bu_4NBr (0.5 mmol), CH_2Cl_2 (5 mL), undivided cell, room temperature, 3.0–4.5 F/mol. [b] Isolated yield.

Based upon careful observations and existing literature reports,[24-26] a possible mechanism for the electrochemical cross-dehydrogenative coupling reaction was proposed (Scheme 2). As a start, compound **1a** loses an electron on the anode to generate the radical cation **I**, which then loses a proton and an electron to generate the iminium-ion intermediate **II**. Finally, intermediate **II** is captured by the reactive nucleophile to afford the CDC product **3** or **5**.



Scheme 2. Proposed Reaction Mechanism.

Conclusions

In summary, we have successfully developed an electrochemical CDC reaction of *N*-aryl-tetrahydroisoquinolines with phosphites and indole using an undivided cell. This reaction could be accomplished without the use of any oxidants, catalysts or additives at room temperature. This protocol offers an alternative to conventional methods that require chemical oxidants or metal catalysts and represents an environmentally friendly tool for oxidative C–P and C–C bonds formation.

Experimental Section

A 10 mL distillation flask equipped with a magnetic stir bar was charged with phosphite **2** or indole **4** (0.3 mmol), CH_2Cl_2 (5.0 mL), compound **1** (0.25 mmol) and *n*-Bu_4NBr (0.5 mmol). The resulting suspension was stirred until complete dissolution was achieved. The flask equipped with graphite rod anode (d = 5 mm) and Pt plate cathode (0.5 cm × 0.5 cm). The reaction solution was stirred and electrolyzed at a constant current of 5 mA for corresponding time under room temperature. When the reaction was finished, the reaction mixture was diluted with CH_2Cl_2. The resulting solution was washed with water and brine, dried over Na_2SO_4, and concentrated in vacuo. Purification by flash column chromatography (ethyl acetate/petroleum ether = 5:1 or 20:1, v/v) afforded the desired product **3** or **5**.

Acknowledgments

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Keywords: Electrochemistry • Cross-dehydrogenative coupling reaction • Tetrahydroisoquinoline • Phosphite • Indole

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J.-Y. Hu, H.-Y. Yin, G.-X. Wang, Z.-S. Yang, J. Jie, K. Liu, Z.-S. Meng, Z. Zhang, H. Su, C. Shu and J.-L. Zhang, *Chem. Eur. J.*, **2016**, *22*, 9676–9686.

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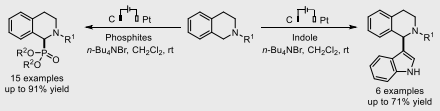

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Electrochemical CDC reaction*

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