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Electroreductive 4-Pyridylation of Electron-deficient Alkenes with Assistance of $Ni(acac)_2$

Sheng Zhang,* Lijun Li, Xinru Li, Junqi Zhang, Kun Xu,* Guigen Li, and Michael Findlater*

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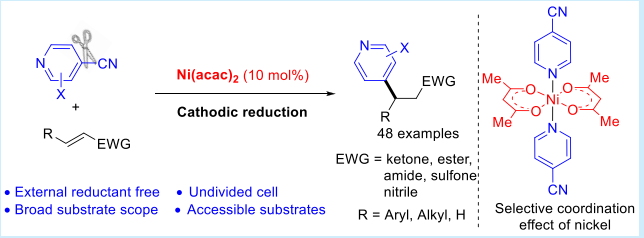
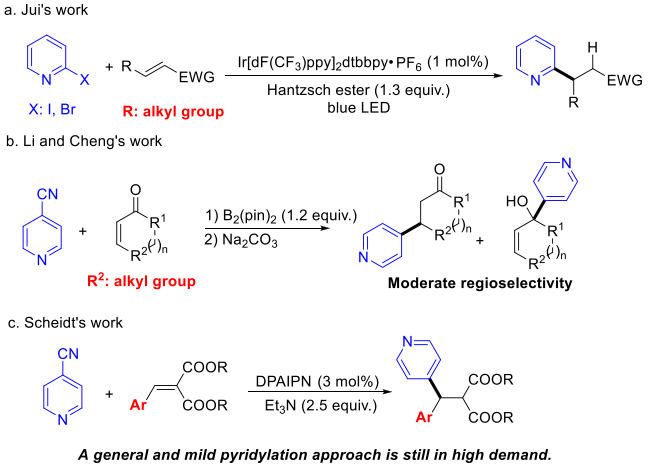
ABSTRACT: An electroreductive 4-pyridylation of activated alkenes was developed in an undivided cell with the assistance of $Ni(acac)_2$ (acac = acetylacetone). This novel protocol is compatible with a broad range of electron-poor alkenes, which are commonly regarded as challenging substrates in the previous conventional approaches. Moreover, a series of cyclic voltammetric experiments were conducted to reveal the unique role of $Ni(acac)_2$ differentiating reduction process of reaction partners.



Pyridine is one of the most important heterocycles and exists, in some form, in more than 60 United States Food and Drug Administration (U.S. FDA) approved pharmaceuticals.[1] Moreover, it is also a versatile building block in the synthesis of chiral ligands applied in asymmetric catalysis.[2] Consequently, considerable effort has been devoted to the synthesis of pyridines.[3] Specifically, pyridylation of electron-deficient alkenes has emerged as an efficient approach toward the synthesis of pyridine derivatives inspired by the pioneering work of Inoue and MacMillan.[4,5] For example, an elegant photocatalytic system was reported in a radical conjugate addition of nitrogen heterocycles by Jui and co-workers (Scheme 1a).[5a] However, this approach was limited to aliphatic electron-poor alkenes. Li and Cheng subsequently disclosed a novel pyridine-boryl radical strategy in the reaction with α,β-unsaturated ketones (Scheme 1b).[5b] Although impressive, neither the regioselectivity nor the substrate scope of this methodology was fully developed. Very recently, Scheidt described an impressive advance in reductive pyridylation of arylidene malonates, in which aliphatic substrates proved to be unsuitable (Scheme 1c).[5c] Taken together, a general and mild pyridylation approach is still in high demand.

Scheme 1. Conventional Pyridylation Approaches of Electron-deficient Alkenes



A general and mild pyridylation approach is still in high demand.

Synthetic electrochemistry offers an appealing alternative to traditional redox transformations.[6] With precise manipulation of redox potential, organic molecules may selectively lose or gain electrons over the surface of electrodes. The past decade has witnessed a renaissance in electrochemistry, particularly in the area of anodic oxidation transformations.[6−11] Tremendous progress in C−H oxidation,[7] C−H functionalization,[8] oxidative coupling,[9] olefin functionalization,[10] and oxidative decarboxylation[11] has been achieved. In contrast, electroreduction, which commonly requires divided cells, has received far less attention and largely lagged behind.[12−16] Recently, a remarkable breakthrough in the electrochemical Birch reduction was demonstrated by Baran and co-workers (Scheme 2a).[13] Ye reported an electrochemical arylation of an α-amino sp^3 C−H through a convergent paired electrolysis approach (Scheme 2b).[14] Very recently, reductive cross-coupling reactions of halides were unveiled independently by the Reisman and Mei groups (Scheme 2c).[15] Finally, Lehnherr and Rovis developed a novel reductive pyridylation of imines

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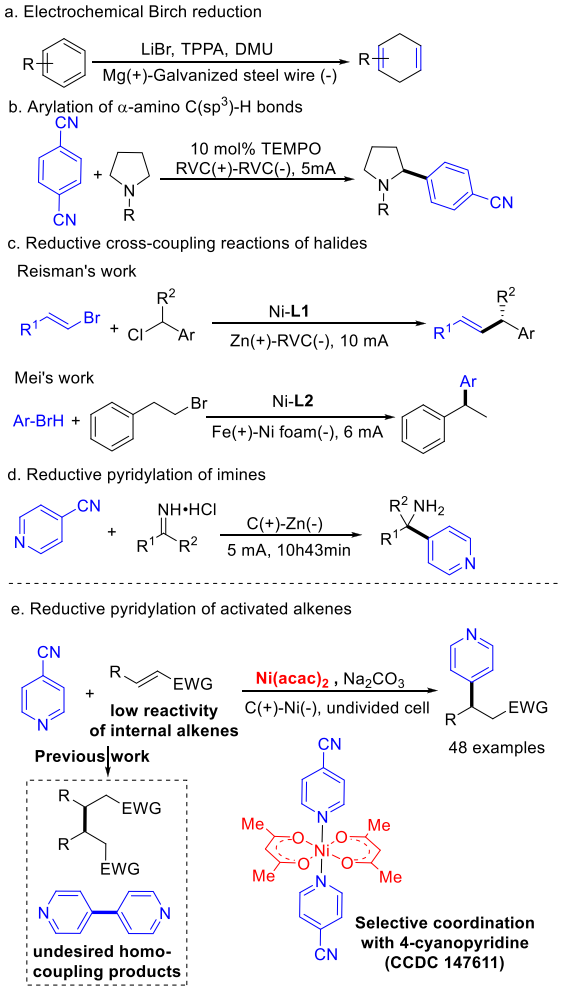
Scheme 2. Electroreductive Transformations

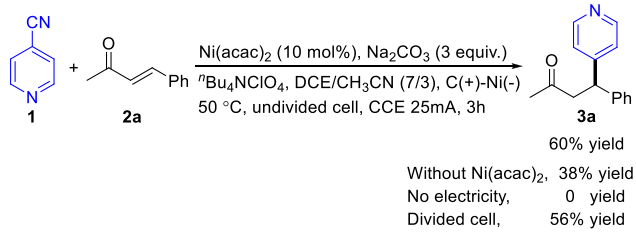


through a proton-coupled electron transfer process (Scheme 2d).[16]

To the best of our knowledge, electroreductive pyridylation of electron-deficient alkenes has never been well-developed.[17] There are two main issues hampering development of the transformation (Scheme 2e): (a) uncontrollable homocoupling reaction of alkene or pyridine precursors, due to the similar reductive potential of the reactants;[18] (b) low reactivity of internal alkenes.[17] Inspired by our previous work on nickel-catalyzed 1,4-hydroboration of *N*-heteroarenes[19a] and related work of Dunstan,[19b] we envisaged that nickel salt might selectively complex with 4-cyanopyridine, thereby differentiating the reductive potentials of the reaction partners (Scheme 2e). Thus, as part of our ongoing work in transition-metal catalysis and synthetic electrochemistry,[20] nickel-assisted electroreductive pyridylation is reported herein. This novel protocol was readily compatible with a broad range of electron-poor alkenes, including α,β-unsaturated ketone, ester, amide, nitrile, and sulfone. This novel electrochemical approach provided a complementary access to pyridines, which are challenging for conventional approaches.[5]

Initially, benzalacetone **2a** was chosen as a model electron-poor alkene, which has received far less attention,[5] with 4-cyanopyridine as a reaction partner in an undivided cell (Scheme 3). Under direct electrolysis, the optimal result of the reaction between **1** and **2a** was observed (60% yield) with the employment of $Ni(acac)_2$ (10 mol %) (acac = acetylacetone)

Scheme 3. Optimization of Reaction Conditions



as metal additive, Na_2CO_3 (3 equiv) as base, $^nBu_4NClO_4$ as electrolyte, a mixed solution of dichloroethane (DCE)/CH_3CN (7/3 mL) as solvent, and graphite rod and nickel plate as anode and cathode, respectively (for details of optimization, see Supporting Information). Removal of metal additive led to diminished yields, which suggests it plays a critical role in the reaction. Without electricity, the above reaction ceased, and no product was detected. When we performed the reaction in the cathode part of a divided cell, an almost same yield (56%) was observed. These results suggested this reaction did proceed through an electroreductive pathway.

Having identified the optimal reaction conditions, the scope of enones amenable to this method was then evaluated (Scheme 4). A broad range of enones bearing electron-donating and -withdrawing groups were investigated (**3b**−**3j**), and the corresponding products were obtained with moderate yields (27−65% yields). Specifically, the pinacolatoboron (BPin)-substituent, which could allow for later functionalization, proved to be amenable to the reaction conditions, albeit with a lower yield (**3j**). The reaction was readily scaled up to 5 g scale, and the desired pyridylation product **3a** (5.7 g) was accessed in synthetically useful yield (51%). Substituents at the 2- or 3-positions were tolerated, including methyl, choro, and trifluoromethyl, affording the products in 32−59% yields (**3k**−**3n**). Remarkably, fused and hetero rings proceeded smoothly in the reaction furnishing the expected pyridylation products with moderate efficiency (**3o**−**3p**). This protocol was compatible with multiple substitution patterns, although the products were obtained in decreased yields (**3q**−**3s**). Notably, varying the R^1 group of **2** to cyclopropyl, adamantyl, or phenyl has a little effect on the reaction efficiency (**3t**−**3v**). Additionally, aliphatic enones can be successfully employed in the reductive pyridylation affording the products albeit with slightly diminished yields (**3w**−**3y**). Cyclic enones were further explored, and corresponding products were obtained with maintained yields (**3z**−**3ab**). To our delight, chromone underwent the electroreductive pridylation to furnish product **3ac** in low yield, which can serve as a synthetic precursor for selective σ_1 receptor antagonist.[21] To further expand the substrate scope, various cyano-pyridines were examined under optimal conditions. It was found that the substituent and the position of the cyano group significantly affected the reaction performance (**3ad**−**3ag**). Neither 2-cyano nor 3-cyano pyridine (**3ad**−**3ae**) was tolerated in the reaction; besides, 4-cyano-2-fluoropyridine failed to afford the desired product. These results might be attributed to the weaker coordination between the substrates with $Ni(acac)_2$ owing to the steric effects of substituents. In contrast, 4-cyano-3-fluoropyridine proceeded smoothly in the reaction giving a sterically hindered product **3ag** with lower yield.

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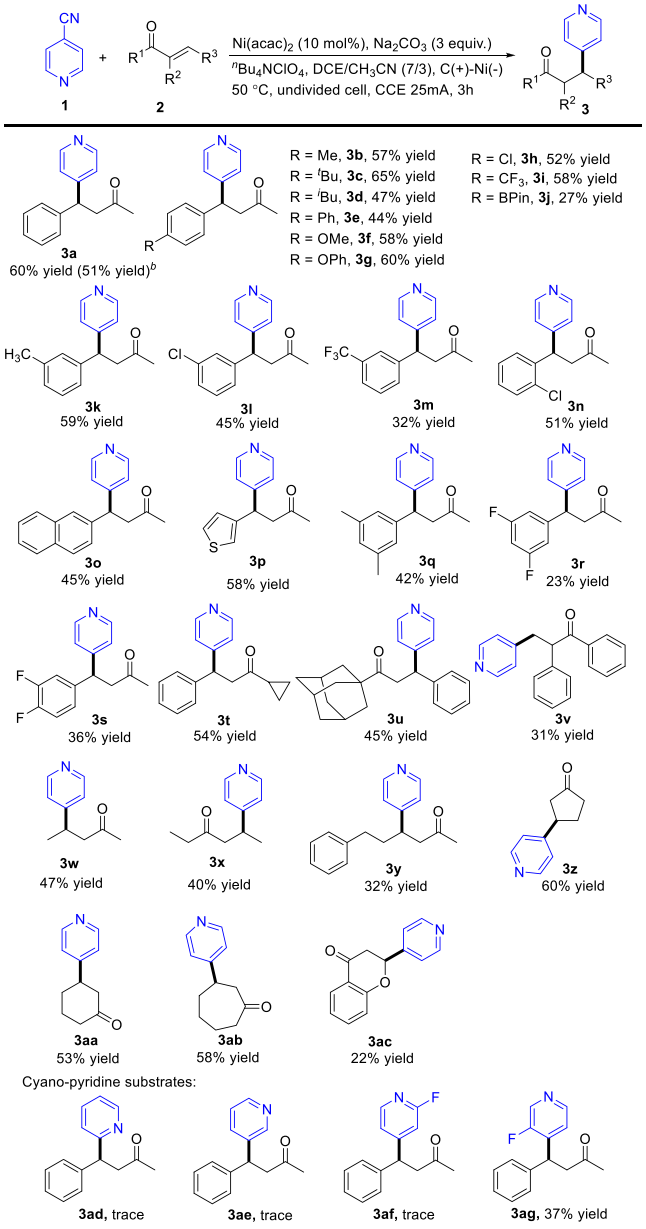
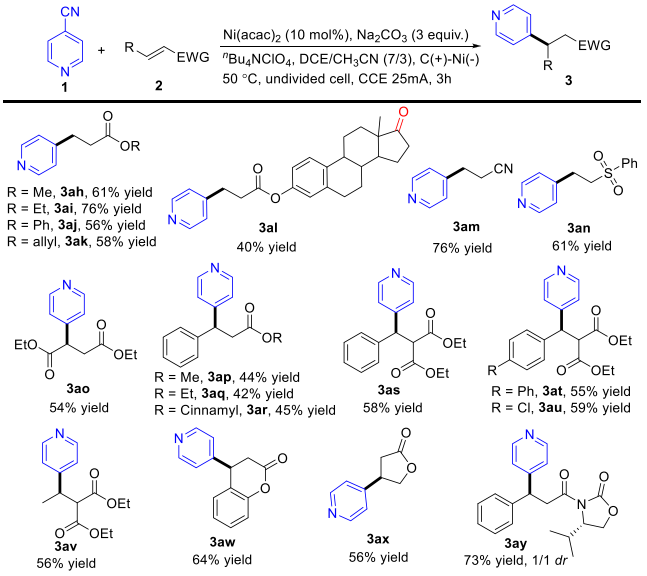
Scheme 4. Evaluation of Enone and Cyano Pyridine Scope[a]



[a]Reaction conditions: undivided cell, graphite rod (0.6 × 10 cm), Ni plate (1.8 × 1.5 cm^2, J = 9.3 $mA{\cdot}cm^{-2}$), **1** (1 mmol), **2** (3 mmol), $Ni(acac)_2$ (0.1 mmol), Na_2CO_3 (3 mmol), $^nBu_4NClO_4$ (1 mmol), DCE/CH_3CN (7/3 mL, v/v), 50 °C, 3 h. [b]Gram-scale reaction: **1** (50 mmol), **2a** (150 mmol).

Next, we turned our attention to other electron-deficient alkenes (Scheme 5). Various acrylates were subjected to the optimized pyridylation conditions, and the products **3ah**−**3ak** were obtained with acceptable yields. It is noteworthy that an allyl group (**3ak**) was untouched during the reaction. For the case of **3al**, a product containing the estrone moiety was exclusively produced without observation of ketone pyridylation product. Subsequently, acrylonitrile (**3am**), phenyl vinyl sulfone (**3an**), and diethyl maleate (**3ao**) were also found to participate smoothly in the electroreductive pyridylation, delivering the desired products with moderate to good yields. To further expand the substrate scope, less reactive cinnamate substrates were examined, and the synthetically challenging

Scheme 5. Evaluation of Other Electron-deficient Alkenes



[a]Reaction conditions: undivided cell, graphite rod (0.6*10 cm), Ni plate (1.8 *1.5 cm^2, J = 9.3 $mA{\cdot}cm^{-2}$), **1** (1 mmol), **2** (3 mmol), $Ni(acac)_2$ (0.1 mmol), Na_2CO_3 (3 mmol), $^nBu_4NClO_4$ (1 mmol), DCE/CH_3CN (7/3 mL, v/v), 50 °C, 3 h.

products (**3ap**−**3ar**) were obtained with 42−45% yields.[5c] A variety of arylidene (**3as**−**3au**) and even alkylidene malonates (**3au**), which are often unsuccessful in photocatalyzed methods,[5c] proved to be viable substrates in this protocol. Unsaturated lactones reacted effectively with 4-cyanopyridine giving rise to the cyclic pyridylation products (**3aw**−**3ax**). In addition, a preliminary effort to achieve asymmetric induction was explored via use of a cinnamamide bearing a chiral auxiliary. Unfortunately, a mixture of diastereoisomers (*dr* 1/1) was detected in 73% yield (**3ay**), which could be easily isolated by column chromatography.

To better understand the reaction mechanism, we conducted a series of cyclic voltammetric experiments (Figure 1). First, similar reductive potentials of benzalacetone (−2.12 V) and 4-cyanopyridine (−2.33 V) were observed, although 4-cyanopyridine proved to be slightly harder to reduce than benzalacetone (Figure 1a). Second, the effect that $Ni(acac)_2$ and Na_2CO_3 exert on the reduction process was further explored (Figure 1b−e). It revealed that no significant reduction peak of $Ni(acac)_2$ or Na_2CO_3 could be detected (curve a, Figure 1b−e), which suggested they were redox-inert within the potential window under examination. Interestingly, introducing $Ni(acac)_2$ resulted in the disappearance of the reduction peak arising from 4-cyanopyridine within the potential window (curve b vs c, Figure 1b), while an increase in reductive peak current of benzalacetone was detected (curve b vs c, Figure 1c). This result indicated that metal additive $Ni(acac)_2$ dampened the reduction of 4-cyanopyridine and promoted the reduction of benzalacetone. As a result, $Ni(acac)_2$ could significantly differentiate the reduction process of the substrates, which could be attributed to the coordination between $Ni(acac)_2$ and 4-cyanopyridine.[19] By contrast, inorganic base Na_2CO_3 marginally affected the reduction of 4-cyanopyridine (curve b vs c, Figure 1d), and slightly increased peak current of benzalacetone (curve b vs c, Figure 1e). Third, the effect of $Ni(acac)_2$ was further studied by

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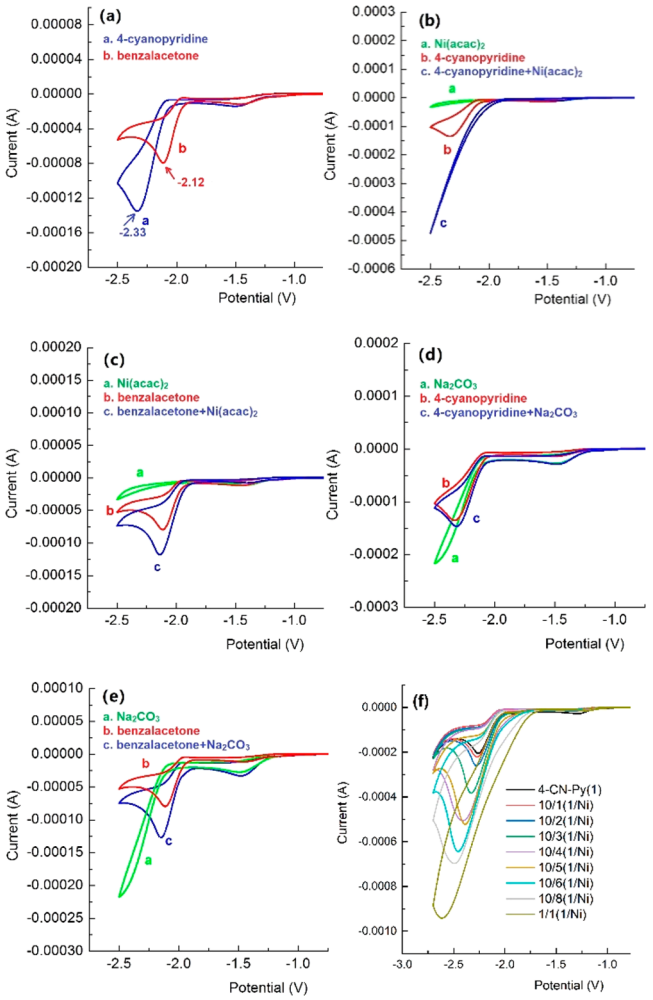

Figure 1. Cyclic voltammograms (shortcuts) of substrates in 0.1 M $^{n}Bu_4ClO_4$ (CH_3CN/DCE = 3/7), using a glassy carbon working electrode and Pt wire and $Ag/AgNO_3$ (0.1 M in CH_3CN) as counter and reference electrodes at a 100 $mV \cdot s^{-1}$ scan rate: (a) 0.5 mM **1**, 0.5 mM **2a**; (b) 0.5 mM $Ni(acac)_2$, 0.5 mM **1**; (c) 0.5 mM $Ni(acac)_2$, 0.5 mM **2a**; (d) 1.5 mM Na_2CO_3, 0.5 mM **1**; (e) 0.5 mM Na_2CO_3, 0.5 mM **2a**; (f) 0.5 mM **1**, with different ratio of $Ni(acac)_2$ (for details of CV spectra, see Supporting Information).

varying the ratio of the additive with substrate **1** (Figure 1f). As shown in Figure 1f, increasing the ratio of $Ni(acac)_2$ led to significant increase of the position (absolute value even higher than 2.6 V) of reductive peak of 4-cyanopyridine. Even though we lowered the ratio of $Ni(acac)_2$ to 10 mol %, it still made 4-cyanopyridine harder to reduce.

On the basis of the experimental observations, related mechanistic study, and potentiostatic electrolysis control experiments (for details, see Supporting Information),[16,18b] a plausible mechanism is proposed and is illustrated in Figure 2. At the outset, a radical anion intermediate **I** is generated by a single-electron transfer (SET) to **2a**. In the presence of Na_2CO_3, intermediate **I** tautomerizes to enolate species **II**, which is a stabilized radical with a larger conjugated system. Subsequently, the stabilized radical **II** could proceed via **path a** or **path b**. In **path a**, radical **II** undergoes a radical addition to 4-cyanopyridine with the assistance of the coordination effect of $Ni(acac)_2$ delivering adduct **III**. The resulting adduct **III** is readily reduced to carbanion **IV**. Finally, the desired product **3a** is generated via a sequential cyanide loss and protonation.

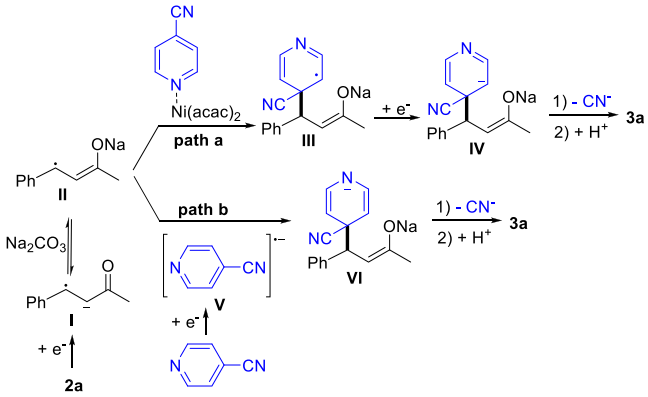

Figure 2. Proposed mechanism.

For **path b**, a radical anion **V** is in situ generated from the reaction of 4-cyanopyridine, although it is less reducible. Then a radical coupling between **II** and **V** affords adduct **VI**, which as a tautomer of **IV** produces the product **3a** via similar steps.

In conclusion, a general and efficient pyridylation of electron-deficient alkenes has been achieved via a novel electroreductive approach. This method enables a complementary approach to access pyridine derivatives, which are notoriously difficult or simply inaccessible by traditional methods. The mild conditions, ease of operation, and good scalability make this approach more appealing in synthetic applications. Moreover, the important role of $Ni(acac)_2$ differentiating two substrates is demonstrated by a series of cyclic voltammetric experiments. Further exploration of the reaction mechanism and enantioselective pyridylation is currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c01014.

Experimental details and spectra (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

Sheng Zhang − *Engineering Technology Research Center of Henan Province for Photo- and Electrochemical Catalysis, College of Chemistry and Pharmaceutical Engineering, Nanyang Normal University, Nanyang, China;* orcid.org/0000-0002-9686-3921; Email: shengzhang@nynu.edu.cn

Kun Xu − *Engineering Technology Research Center of Henan Province for Photo- and Electrochemical Catalysis, College of Chemistry and Pharmaceutical Engineering, Nanyang Normal University, Nanyang, China;* orcid.org/0000-0002-0419-8822; Email: xukun@nynu.edu.cn

Michael Findlater − *Department of Chemistry and Biochemistry, Texas Tech University, Lubbock, Texas 79423, United States;* orcid.org/0000-0003-3738-4039; Email: Michael.Findlater@ttu.edu

Authors

Lijun Li − *Engineering Technology Research Center of Henan Province for Photo- and Electrochemical Catalysis, College of Chemistry and Pharmaceutical Engineering, Nanyang Normal University, Nanyang, China*

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Xinru Li − *Engineering Technology Research Center of Henan Province for Photo- and Electrochemical Catalysis, College of Chemistry and Pharmaceutical Engineering, Nanyang Normal University, Nanyang, China*

Junqi Zhang − *Engineering Technology Research Center of Henan Province for Photo- and Electrochemical Catalysis, College of Chemistry and Pharmaceutical Engineering, Nanyang Normal University, Nanyang, China*

Guigen Li − *Department of Chemistry and Biochemistry, Texas Tech University, Lubbock, Texas 79423, United States;* orcid.org/0000-0002-9312-412X

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.0c01014

Notes

The authors declare no competing financial interest.

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