Letter

Facilitating Ir-Catalyzed C-H Alkynylation with Electrochemistry: Anodic Oxidation Induced Reductive Elimination

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Facilitating Ir-Catalyzed C-H Alkynylation with Electrochemistry: Anodic Oxidation Induced Reductive Elimination

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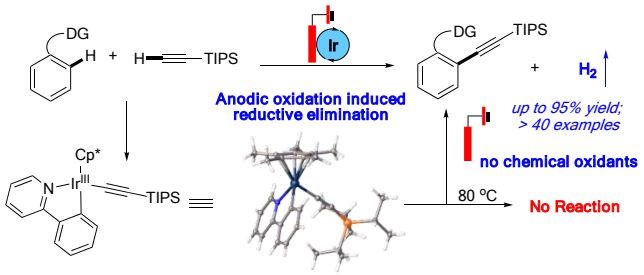
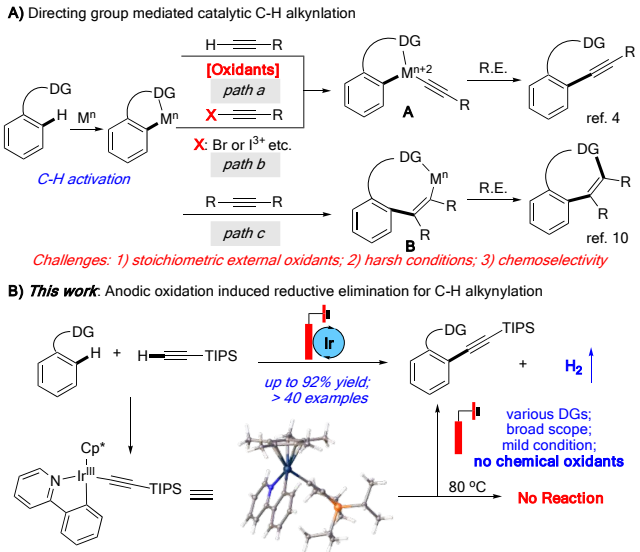
KEYWORDS C-H activation, alkynylation, electrochemistry, iridium, anodic oxidation



ABSTRACT: An electrochemical approach in promoting directed C-H alkynylation with terminal alkyne via iridium catalysis is reported. This work employed anodic oxidation of Ir(III) intermediate (characterized by X-ray crystallography) to promote reductive elimination, giving the desired coupling products in good yields (up to 95%) without the addition of any other external oxidants. This transformation is suitable for various directing groups with H_2 as the only by-product, which warrants a high atom economy and practical oxidative C-C bond formation under mild conditions.

The past two decades have witnessed the fast-growing of transition-metal catalyzed C-H functionalization, which is a highly efficient approach for complex molecule synthesis through direct C-C and C-X bond formation.[1] Among the reported works, directing group strategy has played a crucial role due to the *"site-selectivity"* when installing new functional moieties.[2] Our group has focused on developing new synthetic methodology with a particular interest in transformations involving alkynes.[3] The metal-catalyzed C-H alkynylation is an efficient strategy to install the alkyne functional group through C-C bond construction.[4] Currently, two major approaches in promoting oxidative C-H alkynylation are A) coupling with terminal alkyne using external chemical oxidants (*path a*), such as $Cu(OAc)_2$, AgOAc, and ect.[5,6] B) adopting redox-active alkynes as both reactant and oxidant (*path b*), such as ethynylbenziodoxolone reagent (EBX) or alkynyl bromide[7] (**Scheme 1A**). Despite great progress, there are still limitations for practical use in organic synthesis. Therefore, developing alternative methods to achieve C-H alkynylation with terminal alkyne practically and effectively is highly desirable.



Scheme 1. Electrochemical approach for catalytic C-H alkynylation

Over the past several years, electrochemical anodic oxidation has emerged as an attractive strategy in chemical synthesis.[8] One great advantage of anodic oxidation is the controllable cell

potential (E_{cell}), which enables challenging oxidation of transition metal cations to their higher oxidation states without external oxidants.[9] Although tremendous progress has been reported over the past several years, achieving practical conditions and good functional group compatibility are challenging for some transformations. For example, it has been reported that alkyne could react with corresponding metallacycle through migratory insertion, giving annulation products under electrochemical conditions (pathway c). [10,11] Thus, developing a new effective strategy for C-H alkynylation will reveal critical mechanistic insights and provide a new method for this important chemical transformation. Herein, we report the electrochemical promoted iridium catalyzed C-H alkynylation through anodic oxidation induced reductive elimination (**Scheme 1B**). This strategy allows directed C-H alkynylation under mild conditions using terminal alkyne without external chemical oxidants.

Our interest in exploring this basic and challenging transformation under electrochemical conditions was originated from some pioneering works in literature. Li and coworkers reported Rh(III) and Ir(III) catalyzed C-H alkynylation using EBX as both reactant and oxidant. The mild reaction condition suggested a feasible C-H activation step with Rh(III) and Ir(III) complexes, though the atom economy of this transformation is poor.[12] Recently, Xu and coworkers confirmed the rapid C-H activation with Rh(III) complexes and applied it to directed C-P bond formation under electrochemical oxidation conditions (**Figure 1A**).[13] Inspired by these works, we set our goal to explore if this chemistry could be extended to the challenging C-H alkynylation, especially avoiding the potential competing alkyne annulation.

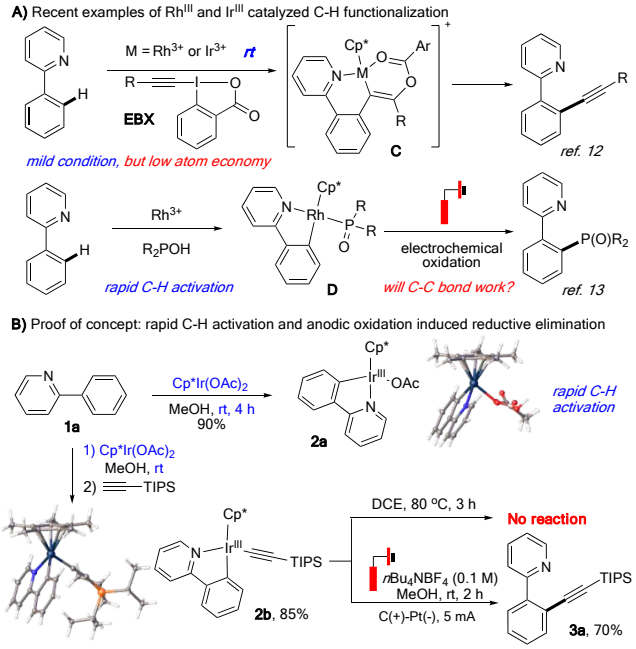
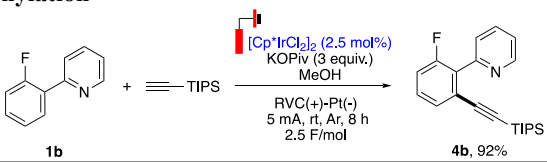


Figure 1. Proof of anodic oxidation promoted C-H alkynylation.

To start our investigation, we first explored the reaction between **1a** and Rh(III) or Ir(III) complexes with or without the presence of alkynes. Air stable Cp*Ir(III) complexes **2a** was obtained from directed C-H activation of **1a**, and the complex **2b** was formed by the addition of alkyne to **2a** (**Figure 1B**). Structures of these complexes are unambiguously confirmed by X-ray single-crystal analysis. Notably, both C-H activation and alkyne addition processes were achieved at room temperature, highlighting the efficiency of Ir(III) complexes in promoting these transformations. To the best of our knowledge, this is the first example of achieving iridium-acetylene complex through directed C-H activation.

Table 1. Screening conditions for Ir-catalyzed C-H alkynylation[a,b]



Entry	variation from "standard conditions"	conv.	yield
1	none	100%	95% (92%)[c]
2	under air	85%	75%
3	C as anode	74%	65%
4	C as cathode	20%	18%
5	KOAc	95%	88%
6	$NaOPiv{\cdot}H_2O$	40%	35%
7	$Cp^*Ir(DMSO)Cl_2$ 5%	100%	90%
8	$Cp^*Ir(DMSO)(OAc)_2$ 5%	100%	89%
9	$[Cp^*RhCl_2]_2$	40%	35%
10	EtOH	45%	30%
11	CF_3CH_2OH	20%	10%
12	3 mA (1.7-1.8 V)	80%	75%
13	7 mA (3.0-3.3 V)	100%	80%
14	constant V at 2.5 V	68%	64%
15	no Ir	-	n.r.
16	no current	-	n.r.
17	IKA ElectroSyn 2.0	100%	91%
18	$Cp^*Rh(OAc)_2$ 5% , KPF_6 1 eq.	50%	45%
19	other metals, Pd, Cu, Ni, Au	<20%	<10%

[a] Conditions: **1b** (0.30 mmol), alkyne (0.45 mmol), Ir cat. (2.5 mol%), base (0.90 mmol in MeOH (5.0 mL). [b] ^{19}F NMR yields using benzotrifluoride as an internal standard. [c] Isolated yield.

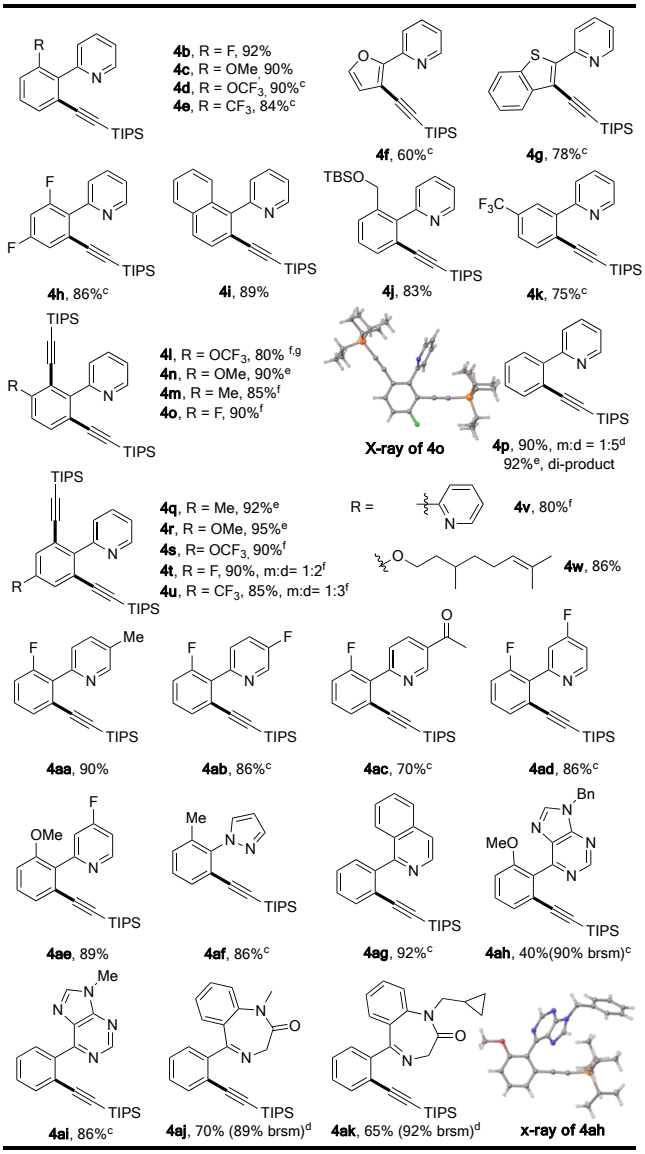
With the C-H activation and alkyne addition structures confirmed, we explored the condition of C-C bond forming step for reductive elimination. Interestingly, Ir(III) complex **2b** remained unreactive in DCE at 80 °C for 3 h, indicating that reductive elimination of **2b** to Ir(I) is challenging, likely due to a high kinetic barrier.[14] Inspired by Chang and coworkers' pioneering work on studying oxidatively induced reductive elimination for Ir-catalyzed C-H arylation,[15] we wondered whether anodic oxidation could assistant this process.[16] Complex **2b** was charged into a typical electrochemical condition (nBu_4NBF_4 as electrolyte in MeOH, constant current at 5 mA, undivided cell). The corresponding C-H alkynylation product **3a** was obtained in 70% yield. This result is promising because it suggests that electrochemical anodic oxidation induced reductive elimination is the key to overcome the energy barrier associated with Ir(III) complexes in C-C reductive elimination process. It is worth noticing that no alkyne annulation product was observed, suggesting the excellent chemoselectivity via Ir-acetylene complex **2b** under the electrochemical approach. This also highlighted the distinctive process of this transformation from previously reported

electrochemical prompted C-H annulations, in which anodic oxidation facilitates the product dissociation from the Ir complex to reenter the catalytic cycle.[10a,17] Encouraged by these results, we explored catalytic reaction under the electrochemical settings using Cp*Ir(III) complex as the catalyst. The optimal condition of the reaction is revealed with 2.5% $[Cp^*IrCl_2]_2$, 3 eq. of KOPiv as both base and electrolyte in MeOH under Ar. Some variations to the optimal condition were revealed in **Table 1**.

The reaction was performed using RVC as anode and Pt as cathode under constant current at 5 mA for 8 h at room temperature, giving the desired product **4b** in 92% isolated yield (entry 1). Conducting the reaction under air led to lower conversion associated with Ir catalyst decomposition, likely caused by the reaction with the O_2 reduction products (peroxide radicals) on the cathode. Also, C-H methoxylation product was detected as a major side product, while no diyne product (Hay-Glaser type product) was observed. Lower conversion and yields were also observed when switching the electrodes to other materials. Comparing with the C anode, the porous nature of RVC anode with a larger surface area will greatly increase the efficiency to Ir(III) oxidation (entry 3), which is likely to be the turnover limiting step in the catalytic cycle. The Pt cathode works much better than C cathode (entry 4), due to a better ability in H_2 evolution process on the cathode surface. Switching KOPiv to KOAc provided a similar result. However, NaOPiv gave a significantly lower conversion, due to both poor solubility and low conductivity. Both $Cp^*Ir(DMSO)Cl_2$ and $Cp^*Ir(DMSO)OAc_2$ are suitable catalysts for this transformation (entries 7 and 8). Rh complex was also tested for this C-C forming transformation under the optimal conditions, giving much lower conversion and yield (entry 9). Notably, MeOH as solvent is critical for this reaction. The combination of other alcohols (CF_3CHOH and EtOH) with KOPiv resulted in much lower conversion and yields due to the observed reduce of conductivity. Under the optimal conditions (constant 5 mA current), the overall potential was maintained between 2.0-2.8 V depending on different substrates. Reducing the current to 3 mA caused poor conversion (not high enough potential for the sufficient oxidation). In contrast, raising the current to 7 mA also led to reduced yield of **4b** to 80%, though with 100% **3a** conversion (~3.0 V). In absence of either Ir catalyst or current, no reaction occurred as expected (entry 15 and 16). Under the optimal condition of Rh catalyzed C-H phosphorylation, the reaction cannot reach the completion (entry 18). Other metal ions, including Au(I), Cu(II), Ni(II), and Pd(II), all failed to produce the desired product **4b** with metal reduction observed on the cathode. No metal reduction was found on the cathode when using Cp*Ir(III) or Cp*Rh(III). These results confirmed the stability and high reduction potential of these piano-stool conformation d^9 metal complexes. Other alkynes evaluated were unsuccessful under this condition (see SI). With the optimal condition revealed, we tested C-H alkynylation with various N-based directing groups, as shown in **Table 2**.

Using this newly developed electrochemical method, both electron-donating group (EDG) and electron-withdrawing group (EWG) substituted arenes worked well. Generally, EDG substituted substrates ran smoothly at room temperature, giving the desired product in excellent yields (>90%). In some cases, substrates with EWG modified aromatic rings required a high temperature (50 °C) to reach the full conversion (**4d**, **4e**). Good regioselectivity (> 10: 1) was obtained for benzene with a large

Table 2. Substrate scope for N-based heterocyclic derivatives[a,b]



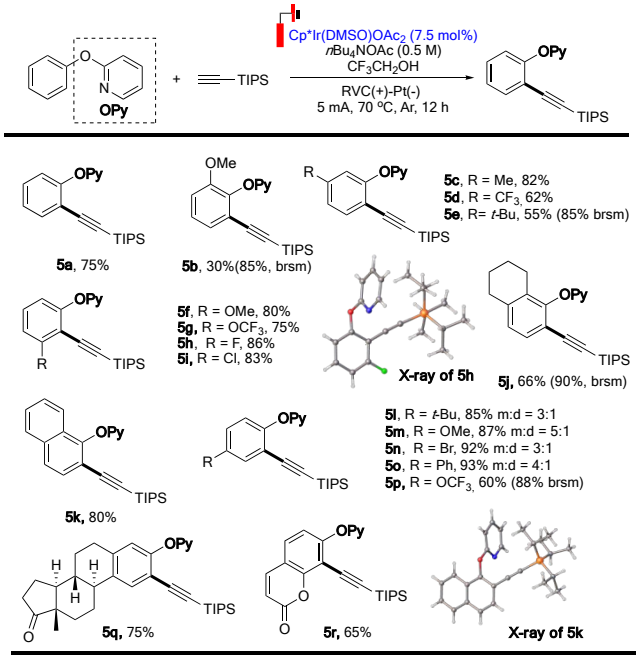
[a] General reaction conditions: substrate (0.30 mmol), alkyne (0.45 mmol), KOPiv (0.90 mmol), and $[Cp^*IrCl_2]_2$ (2.5 mol%) was added into MeOH (5.0 mL) under Ar. The mixture was performed under constant current (5.0 mA) at r.t. [b] Isolated yield. [c] at 50 °C. [d] alkyne (0.60 mmol) [e] alkyne (0.90 mmol) [f] alkyne (0.90 mmol), at 50 °C. [g] 12% mono-alkynylation product was also obtained.

meta-substituent (**4k**), and alkynylation occurred on the less hindered C-H. In other cases, the selectivity between mono- and di-alkynylation was poor (**4l-4w**). Nevertheless, complete di-alkynylation products could be achieved with good to excellent yields with an excess amount of alkyne. This strategy was also suitable for di-alkynylation for more sterically hindered meta-substituted benzene (**4l-4o**). The linkage containing functional groups, such as pyridine (**4v**) and alkene (**4w**), were also found to be compatible.

The scope of the pyridine directing group was also evaluated. Both EDG and EWG modified pyridine rings (**4aa- 4ad**) could serve as directing groups, giving the desired products in excellent yields. Pyrazole (**4af**), quinoline (**4ag**), and purine (**4ah**, **4ai**) could also be utilized as directing groups to

accomplish this transformation. Notably, the success of installing alkyne on diazepam derivatives (**4aj**, **4ak**) highlighted the potential application as late-stage functionalization of these drug molecules.

Table 3. Substrate scope for O-(2-pyridyl)phenol derivatives[a,b]



[a] General reaction conditions: substrate (0.30 mmol), alkyne (0.60 mmol), and Cp*Ir(DMSO)$(OAc)_2$ (7.5 mol%) was added into nBu$_4$NOAc (0.5 M) solution of CF_3CH_2OH (5.0 mL) under Ar. The mixture was performed under constant current (5.0 mA) at 70 °C. [b]Isolated yield.

Encouraged by the high efficiency and mild reaction conditions of this C-C bond forming transformation, we explored substrates with "removable" directing groups.[18] After several failed attempts (see SI of all tested removable directing groups), we finally discovered O-(2-pyridyl)phenol derivatives as valid substrates for this C-H alkynylation under our newly developed electrochemical conditions. Using Cp*Ir(DMSO)$(OAc)_2$ as catalyst (7.5%) and nBu$_4$NOAc (0.50 M) as the electrolyte in CF_3CH_2OH at 70 °C under constant current of 5 mA, the desired product **5a** was obtained in 75% isolated yield. With this new optimal condition, various O-(2-pyridyl)phenol derivatives were tested, as summarized in **Table 3**.

For these substrates with this removable directing group, the position of substituents plays a crucial role. Slightly reduced conversions were observed for substrates with ortho-substituents (**5b**, **5j**). For benzenes containing large meta-substituted groups (**5c**-**5e**), the desired alkynylation products were obtained in good yields on less hindered C-H. Interestingly, a reversed regioselectivity was obtained (**5f**-**5i**, **5r**), leading to C-H alkynylation at a more hindered C-H bond (confirmed by X-ray crystallography structure analysis). The detailed reasoning for this regioselectivity is currently under investigation. Notably, mono-alkynylation became the dominant product for para-substituted aromatic rings (**5l**-**5p**), highlighting the good chemoselectivity of this particular class of substrates. Also, bromo-group was tolerated under this condition (**5n**). Finally, substrates containing Estrone (**5q**) and Coumarin (**5r**) moieties worked well with sensitive functional groups, including ketone and α,β-unsaturated ester, which highlighted the excellent functional group tolerability and good potential for practical synthesis of this newly developed electrochemical promoted transformation.

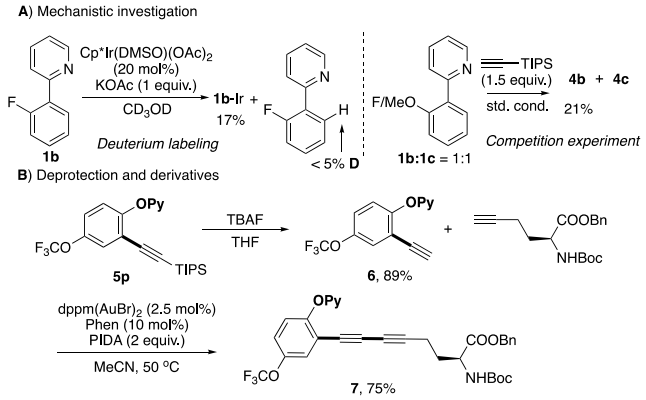


Figure 2. Competition experiment and synthetic utility.

To further explore the reaction mechanism, we first performed the deuterium labeling experiments. Unlike previously reported Rh catalysis[13], no H-D exchange was observed when mixing **1a** with Cp*Ir$(OAc)_2$ in CD_3OD. This result suggested the excellent stability of C-Ir bond, which might lead to a different reactivity between Ir and Rh metallacycle (**Figure 2A**). The competition experiment between substrates containing electron-rich and electron-deficient aromatic rings was also conducted. The electron-rich aromatic ring was more favored, suggesting an acetate-assisted C-H activation pathway (CMD, concerted metalation deprotonation), followed by the formation of a stable Ir-C bond.[19] The detailed mechanistic investigation is current undergoing in our lab and will benefit future development of new transformation. Following the literature reported protocol, the pyridine protection group could be easily removed, giving alkynyl substituted phenols.[20] To further demonstrate its synthetic utility, gold catalyzed oxidative coupling of **6** with amino acid modified alkynes was performed, providing modified amino acid derivative **7** in 75% yield (**Figure 2B**).[3b] Overall, the capability of C-H alkynylation under mild conditions with good functional group tolerability makes this electrochemical method a practical late-stage functionalization strategy for complex molecule synthesis.

In summary, we report herein Ir(III) catalyzed directed C-H alkynylation with terminal alkynes via electrochemical anodic oxidation induced reductive elimination. The desired C-C bond coupling products were successfully achieved with a broad substrate scope, excellent functional group tolerance under mild conditions. This reaction protocol not only represents a new atom economic approach to install alkyne functional group with no need of external oxidants but also offers mechanistic insights on Ir(III) promoted C-H activation, which would lead to the discovery of new synthetic utility.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.
Experimental details, NMR spectra, and details of the experiment

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Notes

The authors claim no competing financial interest.

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