ACS Catalysis

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Mild and Efficient Ir(III)-Catalyzed Direct C−H Alkynylation of *N*-Phenoxyacetamides with Terminal Alkyne

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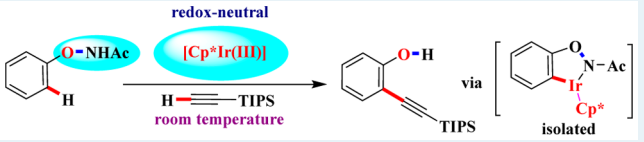
Supporting Information

ABSTRACT: Ir(III)-catalyzed direct C−H alkynylation of arenes has been developed using commercially available TIPS-acetylene as an efficient alkynylating reagent, where O-NHAc was employed as an autocleavable oxidizing-directing group (ODG^{auto}), thus giving rise to *ortho*-alkynylated phenols under mild reaction conditions in a highly efficient and redox-neutral manner. The reaction proceeded with high regioselectivity and broad substrate/functional group (FG) tolerance. The synthetic application of the products has been briefly exemplified. Preliminary mechanistic studies have been conducted, and a five-membered iridacycle has also been identified as a key intermediate.



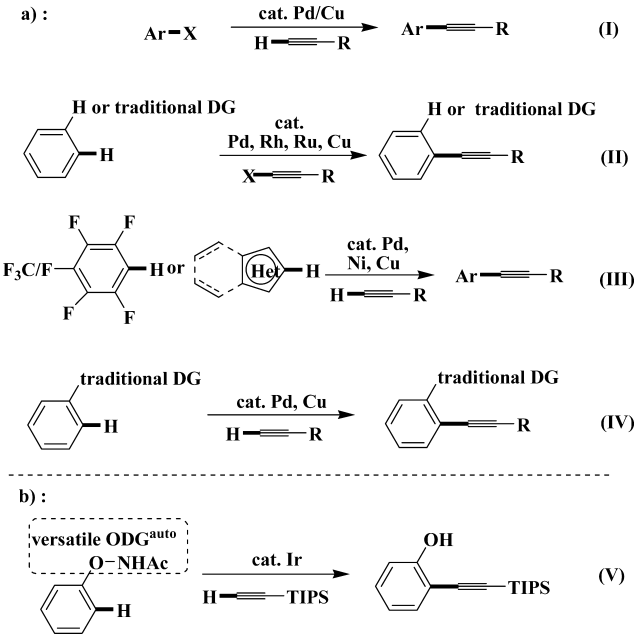
KEYWORDS: *Ir(III), C−H alkynylation, N-phenoxyacetamides, TIPS-acetylene, reaction mechanism*

Alkynylated arenes represent one of the most versatile structural motifs that are widely found in pharmaceuticals, organic materials, and natural products.[1] Besides, they are of great importance as synthetic intermediates and building blocks.[2] In particular, the unparalleled applications of alkynes in click chemistry further highlighted their values.[3] Consequently, the development of efficient synthetic methods to rapidly construct this privileged motif has attracted increasing interest. In the past decade, several versatile alkynylation systems have been successfully developed by using the preactivated aryl halides (Sonogashira reaction, Scheme 1a-I)[4] or prefunctonalized alkynyl source as coupling partners such as alkynyl halides and benziodoxolone-based hypervalent iodine reagents (Scheme 1a-II).[5]

Despite these advances, it would be ideal to take advantage of ubiquitous terminal alkynes as the alkynylating reagent, which should lead to a straightforward and atom-economy procedure. In this context, a few seminal examples has been reported by following Pd-, Ni-, and Cu-catalyzed C−H activation systems.[6] Unfortunately, these alkynylation reactions are only limited to specific substrates such as highly electron-poor arenes (Scheme 1a-III) and/or the requirement of a traditional directing group (DG) (Scheme 1a-IV), which to some extent limited their synthetic applications. Thus, it is still highly desirable to develop general and efficient alkynylation systems to broaden the current limited scope with respect to both the catalyst and the substrate.

Recently, [Cp*TM] complexes (transition metal (TM) = Rh, Ru and Ir) have attracted particular attention and stand out as highly efficient catalysts in C−H functionalization, owing to their high activity and excellent tolerance of substrate/

Scheme 1. Transition-Metal-Catalyzed C−H Alkynylation: (a) Previous Work; (b) This Work



Received: July 23, 2015
Revised: October 14, 2015
Published: October 22, 2015

DOI: 10.1021/acscatal.5b01571
ACS Catal. 2015, 5, 6999−7003

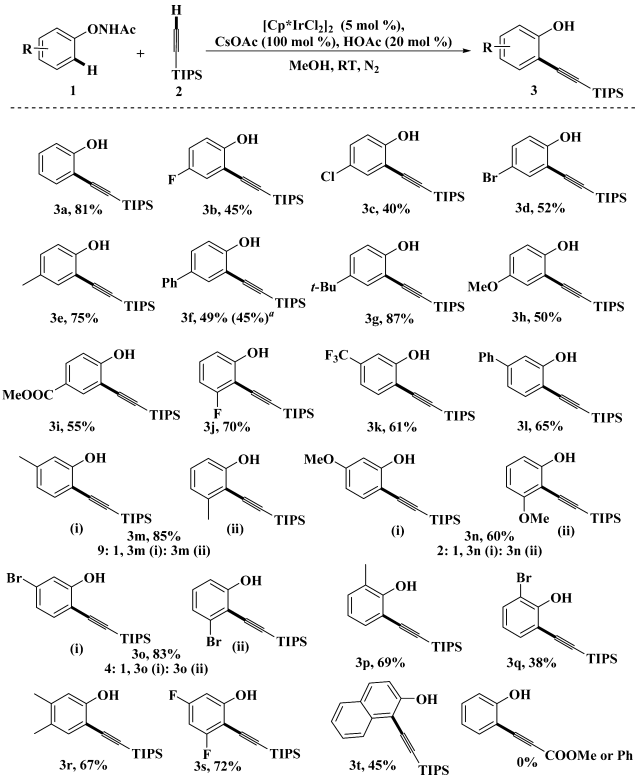
functional group (FG). A tremendously large number of key structural motifs have been efficiently constructed in a step-economical and waste-reducing fashion by employing such a C−H activation strategy.[7] In particular, since the pioneering work by the research group of Yu in Pd(II) chemistry that employed CONH-OMe group as a versatile DG for C−H activation,[8] so far several autocleavable oxidizing-directing groups (ODGs^{auto}) such as CONH−OR,[9] N−NHR[10] or O−NHAc[11] that act both as a DG and an internal oxidant have stood out from the traditional DGs. Indeed, such functionalized substrates offer three main advantages: (i) the use of ODGs is often traceless in the products, facilitating their structural diversity; (ii) the necessity of external oxidants is eliminated, avoiding stoichiometric amounts of metal wastes; (iii) the ODGs are readily autocleavable and can be incorporated into the structural backbone of the product or transformed into highly valuable FGs, expanding their synthetic potentials.

In accordance with the above information and inspired by recent advances in transition-metal-catalyzed C−H functionalization for phenol synthesis,[11b,c,g,12] we now describe a new, mild, and efficient synthesis of *ortho*-alkynylated phenols via Ir(III)-catalyzed direct C−H alkynylation of relatively inert arenes bearing an O−NHAc group, a versatile ODG^{auto} (Scheme 1b-V). The resulting products can serve as useful platforms for further synthetic transformations, including heterocycle synthesis.

Although [Cp*TM] complexes have proved highly efficient in catalytic C−H activation, alkynylation using terminal alkynes remains unreported using these catalysts. We commenced our studies with the coupling between TIPS-acetylene (**2**) and arenes bearing an ODG^{auto} (CONH−OMe, NH−NAc, N-(CH_3)−NO and O−NHAc) in MeOH using several representative [Cp*TM] (TM= Rh(III), Ru(II) and Ir(III)) catalysis (see Supporting Information). To our delight, the desired alkynylation proceeded efficiently at room temperature when $[Cp^*IrCl_2]_2$ was used as the catalyst with O−NHAc group being the ODG^{auto}, delivering *ortho*-alkynylated phenol **3a** in 68% yield. Encouraged by this finding, we next chose $[Cp^*IrCl_2]_2$ as the catalyst, as well as *N*-phenoxyacetamide **1a** (0.15 mmol) and **2** (1.5 equiv) as model substrates, and various experimental parameters were extensively investigated to define the optimal reaction conditions. A survey of solvents revealed that MeOH was the optimal solvent. The catalyst loading screening suggested that the amount of the catalyst played a key role in determining the catalytic activity for this reaction. With the introduction of both CsOAc (1.0 equiv) and HOAc (0.2 equiv) as additives, we were pleased to find that **3a** was obtained in 81% yield, suggesting that the presence of HOAc might disminish the undesired homocoupling of TIPS-acetylene substrate by inhibiting the dissociation of relatively acidic terminal proton.[6g] However, further increasing the amount of HOAc gave inferior result. In summary, we obtained the optimal conditions consisting of $[Cp^*IrCl_2]_2$ (5 mol %), CsOAc (1.0 equiv), HOAc (0.2 equiv), substrate **1a** (0.15 mol), and **2** (1.5 equiv) in MeOH (1.0 mL) at room temperature.

With the optimal catalytic system in hand, we sought to investigate the scope and limitations of *N*-phenoxyacetamide substrates. As given in Scheme 2, a great variety of substituted *N*-phenoxyacetamides reacted smoothly with TIPS-acetylene **2** to afford the corresponding *ortho*-alkynylated phenols in moderate to good isolated yields. Both electron-donating and -withdrawing groups at the *para*- (**3a**−**i** and **3r**), *meta*- (**3j**−**o** and **3r**), and *ortho*- (**3p**−**q**) position are well-tolerated.

Scheme 2. Substrate Scope of *N*-Phenoxyacetamide[b]



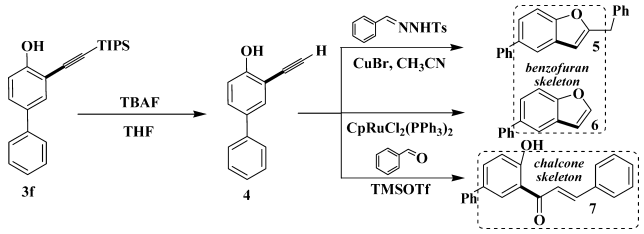
[a]Five mmol scale. [b]Reaction conditions: **1** (0.15 mmol), **2** (0.23 mmol), $[Cp^*IrCl_2]_2$ (5 mol %), CsOAc (1.0 equiv), and HOAc (0.2 equiv) in MeOH (1.0 mL) at room temperature for 12−24 h, under N_2. Isolated yields of isolated products are given.

Additionally, the reaction also showed good compatibility with a wide range of valuable FGs, including Fluoro (**3b**, **3g** and **3s**), chloro (**3c**), bromo (**3d**, **3o** and **3p**), alkyl (**3e**, **3g**, **3m** and **3p**), phenyl (**3f** and **3l**), methoxy (**3h** and **3n**), ester (**3i**), and trifluoromethyl (**3k**) substituents. Interestingly, substrates **1j**−**l** bearing fluoro, trifluoromethyl, and phenyl FGs at the *meta*-position, respectively, offered the corresponding alkynylation products **3j**−**l** with high regioselectivity and good yield. Nevertheless, the *meta*-methyl, methoxy, and bromo derivatives all gave a mixture of regioisomeric products (**i**) and (**ii**) in good to high combined yields (**i**:**ii** = 2−9:1). Taken together, these results revealed that the nature of the substituent at the *meta*-position played a vital role in determining the outcome of the reaction. Notably, polysubstituted *N*-phenoxyacetamides, such as *N*-(3,4-dimethylphenoxy)acetamide (**1r**) and *N*-(3,5-difluorophenoxy)acetamide (**1s**) are also applicable to deliver the desired products in good yields. Gratifyingly, the alkynylation reaction with **2** also tolerated the polyaromatic naphthalene substrate, producing the interesting **3t** in synthetically useful yield with excellent regioselectivity. The preparation of **3f** on a 5 mmol scale with reasonable yield further illustrated the scalability of this Ir(III)-catalyzed system. To better define the scope of this reaction, we further explored other terminal alkynes such as phenylacetylene and methyl propiolate. However, no expected coupling products were observed, indicating that the presence of a TIPS substituent was crucial for this reaction.

Importantly, the TIPS moiety, the alkyne part, and the *free*−OH in the products served as important handles for further chemical manipulation. As illustrated in Scheme 3, the

DOI: 10.1021/acscatal.5b01571
ACS Catal. 2015, 5, 6999−7003

Scheme 3. Derivatization of 3f



desilylation of **3f** was easily achieved upon treatment with TBAF to provide 3-ethynylbiphenyl-4-ol (**4**), which could be used as a useful synthon for one-pot construction of highly attractive benzofuran (**5** and **6**) and chalcone (**7**) scaffolds, two privileged core structural motifs in many biologically active compounds.[13]

We next performed a series of experimental investigations to explore the possible reaction mechanism. First, the reversibility of the C−H activation step was examined by running the reaction in deuterated methanol in the absence of **2**. As shown in Scheme 4a, after stirring at room temperature for 2 h, 98% of **1a** was recovered and no incorporation of deuterium (<5% D) was observed, revealing that the C−H bond activation process was largely irreversible.[14]

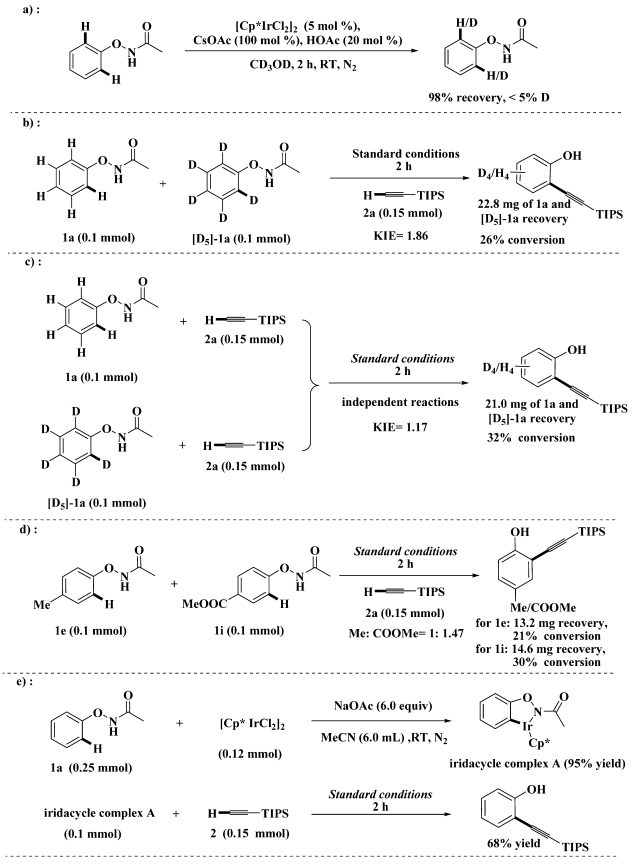
Second, the isotope-labeling experiment was carried out with [D_5]-**1a** (Scheme 4b). Treatment of **2** with an equimolar amount of **1a** and [D_5]-**1a** for 2 h under our standard conditions gave a k_H/k_D ratio of 1.86. A similar KIE value (k_H/k_D= 1.17) was also obtained from two independent, side-by-side experiments using an equimolar amount of **1a** and [D_5]-**1a** (Scheme 4c). These results indicated that the C−H bond cleavage was not involved in the turnover-limiting step of the Ir(III) cycle.[15]

Subsequently, a competitive coupling between an equimolar amount of **1e** and **1i** in the coupling with **2** was conducted to delineate the electronic preference of the reaction (Scheme 4d). The ratio of products showed that the electron-deficient **1i** was preferentially converted (**3e**/**3i** = 1:1.5), suggesting that the C−H activation process might follow a concerted metalation−deprotonation (CMD) mechanism.[16]

To gain further insights into the catalytic cycle, we further carried out the synthesis and analysis of the possible intermediate (Scheme 4e). Thus, substrate **1a** was reacted with the catalyst [Cp*$IrCl_2$]$_2$ in CH_3CN at room temperature in the presence of NaOAc, producing the five-membered iridacyclic intermediate **A** in excellent yield. Complex **A** proved to be an active catalyst for the coupling of **1a** with **2**, and **3a** was obtained in 68% isolated yield, which provided clear evidence that C−H activation was involved in the catalytic cycle.

In conclusion, we have developed a new, mild and effective Ir(III)-catalyzed system for the direct alkynylation of arenes with TIPS-acetylene using the O−NHAc group as the versatile ODG^{auto}, which enables highly efficient and redox-neutral synthesis of diverse *ortho*-alkynylated phenols with broad substrate/FG tolerance. Moreover, the synthetic utilities with regard to the TIPS moiety, the alkyne part, and the *free*−OH group of the coupled products have been demonstrated in subsequent derivatization reactions for rapid construction of biologically important benzofuran and chalcone scaffolds. Through the mechanistic studies, a key five-membered iridacycle has been established as a key intermediate. Further studies on the scope, mechanism, and application of this catalytic system are currently underway in our laboratories.

Scheme 4. Mechanistic Studies[a]



[a](a) Reversibility of the C−H activation. (b) Isotope-labeling experiment. (c) Independent kinetic isotope study. (d) Competitive experiment. (e) Reaction intermediate investigation.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.5b01571.

Experimental procedures, characterization of products, and copies of ^{1}H, ^{13}C, and ^{19}F NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors thank the Jay and Betty Van Andel Foundation, Amway (China), the Shanghai Municipal Natural Science Foundation (15ZR1447800), China, NSFC (21472186, 21525208, and 81502909), and the Chinese Postdoctoral Science Foundation (2014M560363) for financial support on this study.

DOI: 10.1021/acscatal.5b01571
ACS Catal. 2015, 5, 6999−7003

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