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Iridium-Catalyzed, Weakly Coordination-Assisted *Ortho*-Alkynylation of (Hetero)aromatic Carboxylic Acids without Cyclization

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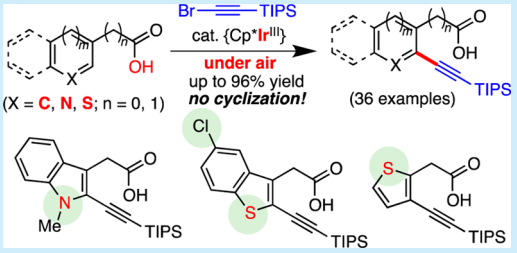
Supporting Information

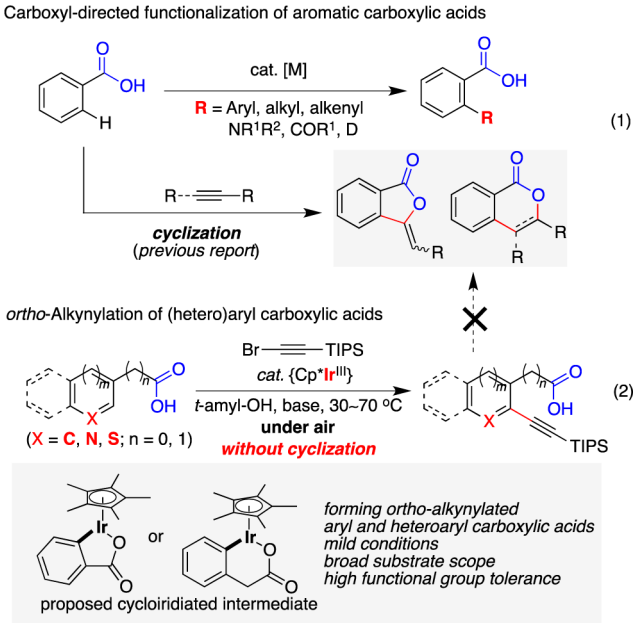
ABSTRACT: It is reported a weakly coordination-assisted alkynylation of aryl and heteroaryl carboxylic acids with iridium catalysis. The reaction is catalyzed by [{Cp*IrCl$_2$}$_2$] complex without cyclization, forming *ortho*-alkynylated aryl and heteroaryl carboxylic acids, and features high functional group tolerance and broad substrate scope under an air atmosphere. 2-(Hetero)aryl-substituted acetic acids were amenable to the alkynylation by forming an unusual six-membered ring cycloiridiated intermediate.



Aromatic alkynes are versatile building blocks in synthetic chemistry and have been widely used in the preparation of common chemicals and pharmaceutical and material molecules.[1] The development of efficient methods to the buildup of these fundamentally important motifs has attracted broad synthetic interest. Common approaches that were used to form aromatic alkynes traditionally involve the Sonogashira cross-coupling using reactive aromatic halides.[2] Recently, introducing directing groups as auxiliaries for transition-metal catalysis has led to many breakthroughs in synthetic chemistry,[3] remarkably revolutionizing the manner in the creation of appealing molecules by the functionalization of unreactive chemical bonds.[4] Carboxyls are synthetically valuable functional groups that are readily amenable to transform to the relative C−C, C−O, and C−N bonds by the corresponding decarboxylative cross-coupling reactions.[5] However, the weakly σ-coordination ability of carboxyl groups causes them difficulty in the direction of transition metals to approach and break one regiospecific chemical bond. On the other hand, the reactivity of the resulting cyclometalated intermediates toward further transformation may be lowered. Methods for the arylation,[6] alkylation,[7] alkenylation,[8,9] amination,[10] acylation,[11] annulation,[8,12] and deuteration[13] have been developed using carboxyl directing groups (Scheme 1, eq 1). However, to our knowledge, there is no report of an alkynylation reaction that was directed by a weak coordination carboxyl functionality, although approaches mediated by a strong coordination directing group have been described.[14−21] The obstacle may arise from the easy addition of the carboxyl across the alkyne via a cyclization, which causes the *ortho*-alkynylation of aromatic carboxylic acid suffering from a selectivity issue.[8]

Herein, we report the first weak coordination-assisted *ortho*-alkynylation of aryl and heteroaryl carboxylic acids with iridium catalysis.[22] Carboxyl groups in both aromatic and heteroaromatic carboxylic acids were able to direct iridium in the cleavage of aromatic C−H bonds and the formation of *ortho*-alkynylated aryl and heteroaryl carboxylic acids under an air atmosphere (Scheme 1, eq 2). The competitive cyclization by the addition of the carboxyl across the alkyne did not occur under catalytic conditions. While unusual six-membered ring cycloiridiated intermediates can be accessed in the realization of the *ortho*-alkynylation of 2-(hetero)aryl-substituted acetic acids.

Scheme 1. Carboxyl-Directed Functionalization of Aromatic Carboxylic Acids



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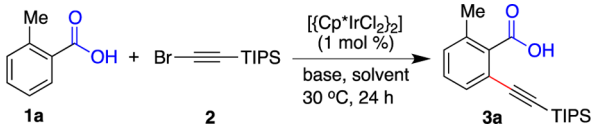
We commenced our studies by choosing the reaction of 2-methylbenzoic acid (**1a**) with (bromoethynyl)triisopropylsilane (**2**) as a model for optimizing catalytic conditions (Table 1).

Table 1. Exploring the Effect of Base and Solvent on the Alkynylation of Benzoic Acid[a]



1a 2 3a

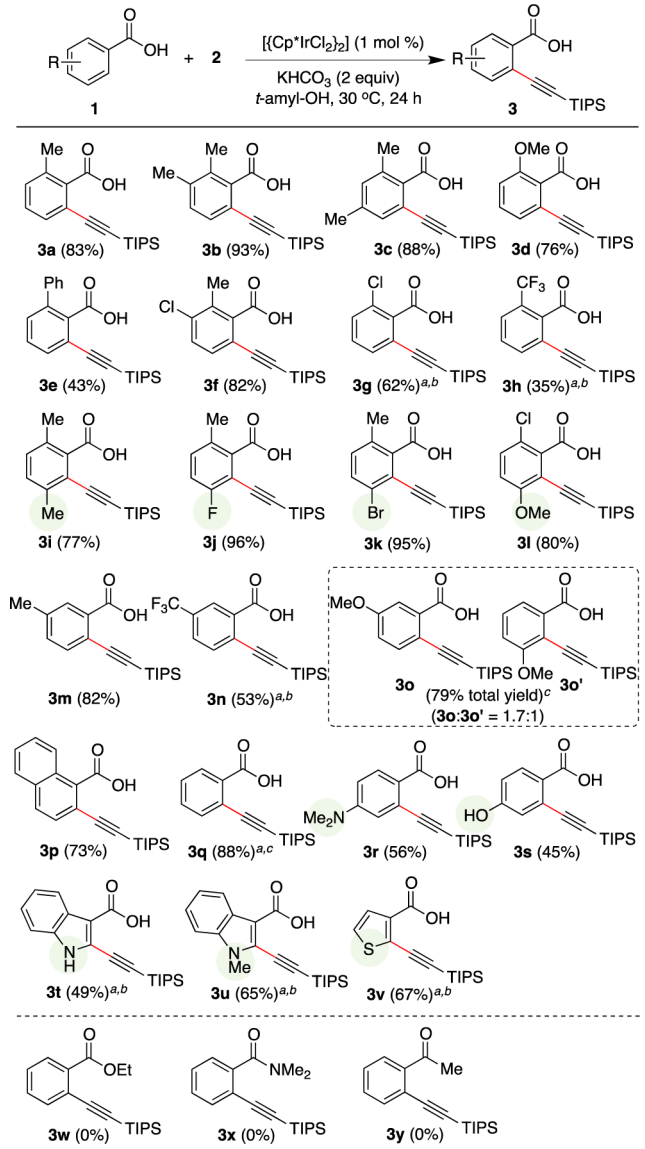
entry	base	solvent	yield of **3a** (%)
1	$KHCO_3$	DMF	nd[b]
2	$KHCO_3$	DCE	nd[b]
3	$KHCO_3$	DCM	82
4	$KHCO_3$	toluene	85
5	$KHCO_3$	1,4-dioxane	71
6	$KHCO_3$	CH_3CN	78
7	$KHCO_3$	*t*-amyl-OH	92 (83)[c]
8	none	*t*-amyl-OH	nd[b]
9	K_2CO_3	*t*-amyl-OH	trace
10	Na_2CO_3	*t*-amyl-OH	nd[b]
11	K_3PO_4	*t*-amyl-OH	trace
12	K_2HPO_4	*t*-amyl-OH	83
13	KOAc	*t*-amyl-OH	81
14	CsOAc	*t*-amyl-OH	77
15[d]	$KHCO_3$	*t*-amyl-OH	nd[b]

[a]Reaction conditions: **1a** (0.1 mmol), **2** (0.15 mmol), base (0.2 mmol), $[\{Cp^*IrCl_2\}_2]$ (0.001 mmol), solvent (0.5 mL), 30 °C, 24 h, under air. [b]Yield was determined by HPLC analysis using acetophenone as internal standard. [c]Isolated yield in parentheses. [d]Without $[\{Cp^*IrCl_2\}_2]$ complex.

Using a commercially available iridium complex of $[\{Cp^*IrCl_2\}_2]$ (with 1 mol % loading) under an air atmosphere, the alkynylation of the *ortho*-C−H bond did not proceed in the solvents *N*,*N*-dimethylformamide (DMF) and dichloroethane (DCE) (entries 1 and 2). To our delight, formation of the *ortho*-alkynylated benzoic acid **3a** was observed in dichloromethane (DCM) (entry 3). *tert*-Amyl alcohol (*tert*-amyl-OH) allowed the reaction to proceed effectively, leading to **3a** in 92% yield (entry 7). Notably, base plays an important role in the alkynylation. The best result was obtained in the presence of $KHCO_3$. However, other bases such as Na_2CO_3, K_2CO_3, and K_3PO_4 shut down the reaction or decreased the reaction rate (entries 9−11). Further experiments suggested that, without iridium catalyst, the alkynylation did not take place (entry 15).

Having establishing the optimal conditions, the substrate scope in the carboxyl-directed alkynylation was next examined. As shown in Scheme 2, the *o*-C−H bonds on electron-rich aromatics were alkynylated effectively, the related products of **3a−d** were isolated in 76−93% yield. In contrast, introducing electron-deficient groups such as phenyl, chloride, and trifluoromethyl into the scaffolds of benzoic acids resulted in relatively low conversions (**3e−h**,**n**). Notably, steric hindrance around the *o*-C−H bonds has no effect on the alkynylation. It has been successfully applied in the synthesis of multisubstituted aromatic alkyne derivatives **3i−l**. As expected, the reaction with *meta*-substituted benzoic acids preferred to occur at a less hindered *ortho*-position (**3m**,**n**), whereas the regioselectively was forfeited using electron-rich 3-methoxybenzoic acid, leading to a mixed regioisomer (**3o**,**o′**). A broad range of functional groups, including fluoride, chloride, bromide, alkyoxyl, amino, and

Scheme 2. Iridium-Catalyzed *Ortho*-Alkynylation of Aromatic and (Hetero)aromatic Carboxylic Acids[*,a]



[*]Reaction conditions: **1** (0.2 mmol), **2** (0.3 mmol), $KHCO_3$ (0.4 mmol), $[\{Cp^*IrCl_2\}_2]$ (0.002 mmol), *t*-amyl-OH (1 mL), 30 °C, 24 h, under air. Isolated yields. [a]50 °C. [b]$[\{Cp^*IrCl_2\}_2]$ (0.004 mmol). [c]**2** (0.4 mmol) was used. The ratio of regioisomer was determined by ^1H NMR analysis.

hydroxyl, were well tolerated by the catalytic system. Encouragingly, heteroaromatic carboxylic acids containing indolyl and thienyl scaffolds were amenable to the alkynylation (**3t−v**). However, no expected alkynylated compounds were detected when aromatic ester, amide, and ketone (**3w−y**) were used. These results exclude the feasibility of the direction of iridium by the relative carbonyl groups.

Because of the relative instability of six-membered ring cyclometalated intermediates compared to five-membered ring ones, the functionalization of C−H bond aromatic carboxylic acids via a six-membered ring cyclometalated species has rarely been achieved.[6f,12,13,23] The success in developing the *ortho*-alkynylation of benzoic acids stimulated us to explore the reaction with 2-phenylacetic acids. Gratifyingly, an increase of the amount of $[\{Cp^*IrCl_2\}_2]$ to 2.5 mol % allowed the reaction

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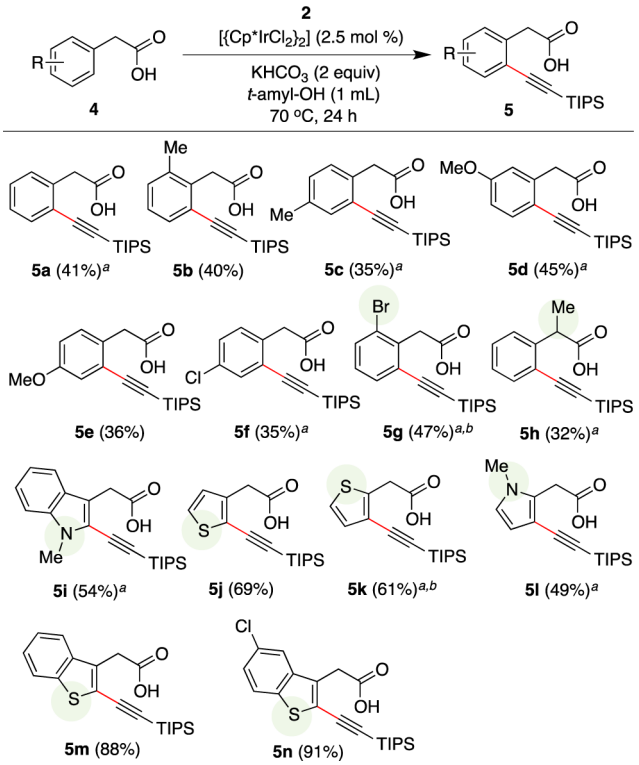
to occur smoothly at elevated temperature, forming the compound **5a** in moderate yield (Scheme 3). Both electron-

Scheme 3. Iridium-Catalyzed *Ortho*-Alkynylation of Aromatic and (Hetero)aromatic Acetic Acids*[a]

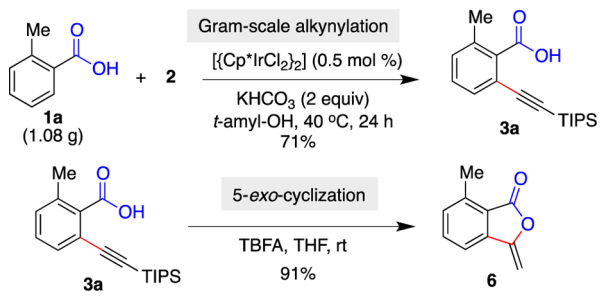


*The reaction was performed on a 0.2 mmol scale at 70 °C for 24 h under air. Isolated yields were given. [a]90 °C. [b][{Cp*IrCl$_2$}$_2$] (5 mol %).

rich and electron-deficient aromatics on the scaffolds of acetic acids can be alkynylated smoothly (**5b–g**). In addition, 2-phenylpropanoic acid was also suitable for the transformation (**5h**). Interestingly, carboxyl was able to direct iridium to activate the *o*-C–H bonds in heterocycles of indole, thiophene, pyrrole, and benzo[*b*]thiophene, leading to the formation of the alkynylated heteroaryl acetic aids **5i–n** in moderate to excellent yields.

The scalability of this reaction was then studied. Using 0.5 mol % of iridium complex, the alkynylation of benzoic acids on a 1 g scale proceeded effectively to form **3a** in 71% yield (Scheme 4). The resulting 2-alkynylbenzoic acid can be facilely functionalized by a late-stage 5-*exo* cyclization, providing an alternative strategy

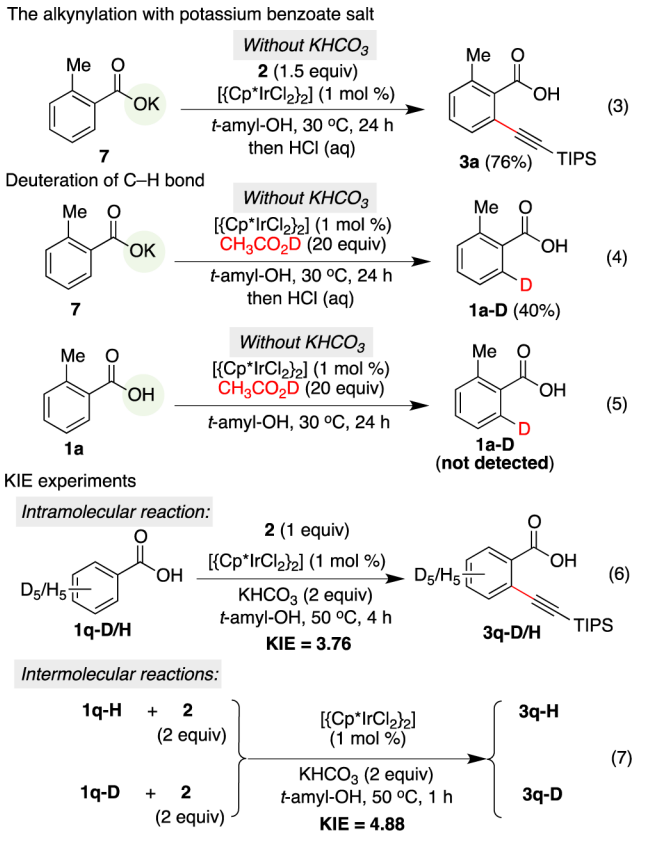
Scheme 4. Gram-Scale Reaction and Cyclization



to the preparation of biologically interesting benzofuranone motif.

To obtain mechanistic insight, we probed the role of base in the carboxyl-directed reaction. Starting from potassium benzoate, the alkynylation of C–H bond proceeded smoothly without KHCO$_3$ (Scheme 5, eq 3). Furthermore, the deuteration

Scheme 5. Mechanistic Studies



of potassium benzoate was accomplished in the absence of base (Scheme 5, eqs 4 and 5). These results suggest that KHCO$_3$ is responsible for the deprotonation of benzoic acid rather than for the assistance of cleavage of the C–H bond. Interestingly, the *o*-C–H bond in benzoic acid cannot be cleaved without base. A high kinetic isotope effect (KIE) value of 3.76 or 4.88 was obtained in either intramolecular or intermolecular reactions, indicating that the catalytic cleavage of *o*-C–H bond of benzoic acid is likely to be the rate-limiting step in the alkynylation (Scheme 5, eqs 6 and 7).

In conclusion, we have developed a weakly coordination-assisted alkynylation of aromatic and heteroaromatic carboxylic acids with iridium catalysis. The reaction was directed by a synthetically useful carboxyl functionality in featuring high functional group tolerance and broad substrate scope. The relative cyclization by the addition of a carboxyl group across the alkyne did not occur under our catalytic conditions. This reaction provides an efficient methodology for the preparation of *ortho*-alkynylated aryl and heteroaryl carboxylic acids under an air atmosphere.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00581.

Experimental procedures and characterization data for all products, including ^{1}H, ^{13}C, and ^{19}F NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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