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Direct *ortho*-Selective C−H Functionalization of Carboxybenzyl-Protected Arylalkylamines via Ir(III)-Catalyzed C−H Activation

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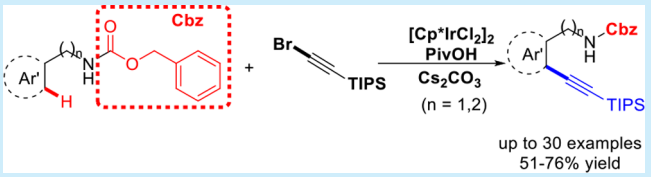
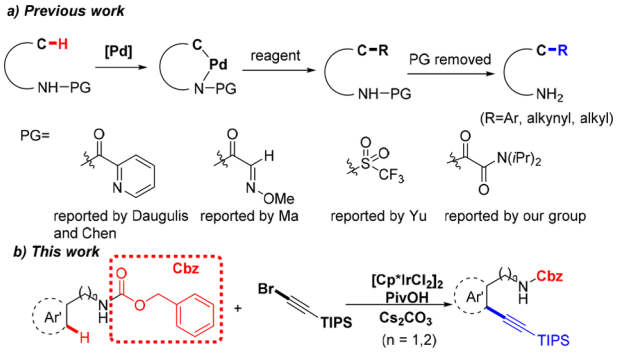
Supporting Information

ABSTRACT: A convenient and practical approach to synthesize *ortho*-alkynylated arylalkylamines through *ortho*-selective C−H functionalization has been developed using Cbz-amide as the directing group and Ir(III) as the catalyst. Various substrates were well tolerated, affording the corresponding products in moderate to good yields. Moreover, preliminary mechanistic study revealed the role of the amide as the coordination center to cooperate with the Ir(III) complex during C−H activation. Development of this Cbz-amide-promoted C_{Ar}−H functionalization offers a practical approach with potential applications in organic synthesis.



Arylalkylamines are very significant molecular scaffolds in synthetic chemistry, due to their prevalence in biologically active compounds, natural products, and approved drugs.[1] In this context, various approaches to construct the arylalkylamine derivatives have been extensively studied in the past decades.[2,3] One of the most efficient strategies is the transition-metal-catalyzed direct C−H functionalization of arylalkylamines because the prefunctionalization of the substrate could be avoided.[3] Further, the research groups of Daugulis,[4] Chen,[5] and Ma[6] have developed diverse N,N-bidentate directing groups to assist the site-selective C−H functionalization reactions (Scheme 1a). Yu and co-workers have demonstrated the

Scheme 1. Protecting-Group-Directed C−H Functionalization



efficiency of trifluoromethanesulfonamide as a directing group in combination with N-protected amino acid ligands.[7,8] In addition, our group has previously reported that oxalyl amide is an effective N,O-bidentate directing group in assisting the remote C−H functionalization of amines.[9] Even though these methods have greatly enriched the approaches to functionalize arylalkylamines, the additional steps required for installing and removing the directing groups have limited their further application in synthetic chemistry. Recently, an in situ directing strategy, which can avoid the prefunctionalization and deprotection steps, has provided a straight route to access functionalized amines.[10] However, these reactions usually required further treatment with di-*tert*-butyl dicarbonate (Boc_2O) or 2,2,2-trifluoroacetic anhydride to facilitate the isolation or further transformation.

On the other hand, the use of benzyl chloroformate (Cbz-Cl) as the protecting group is one of the common and convenient strategies to protect active amine groups in the construction of complex synthetic molecules.[11] Consequently, the development of Cbz-amide-assisted C−H functionalization reactions is of great significance in synthetic chemistry. So far, there have been no reports on the utility of Cbz-amide as a directing group to assist C−H functionalizations. Although the Pd(II) catalyst displayed excellent catalytic ability in promoting the C−H activation reactions, there are only a few examples of using simple amide directly as the substrate for the C−H functionalization reaction. It is probable that the strong coordination ability of the amide suppresses the C−H activation step. Recently, significant developments have been achieved in the Ir(III)-catalyzed C−H functionalizations, thus greatly enriching the substrate scope and the type of reactions.[12−14] In 2013, Chang and co-workers developed an Ir(III)-catalyzed C−H amidation of benzamide employing acyl azides as the nitrogen source.[15] Inspired by this result, we speculated that Cbz-amide could be used as the coordination center in assisting C−H activations in combination with an Ir(III) catalyst.

Herein, we report the first example of the Ir(III) complex as an efficient catalyst in promoting C−H activation of Cbz-

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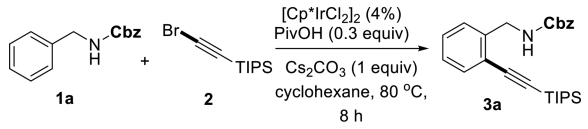
protected arylalkylamines (Scheme 1b). These Ir(III)-catalyzed Cbz-amide-assisted *ortho*-selective C−H alkynylation reactions yielded the corresponding alkynylated products in moderate to good yields. Further, preliminary mechanistic studies have exposed that the amide is the coordination center to assist the Ir(III) complex in C−H activation.

At the outset of our study, the alkynylation of Cbz-protected benzylamine was set as the model reaction. Accordingly, the Cbz-protected benzylamine **1a** was treated with bromoalkyne **2** in the presence of $[Cp^*Ir(III)Cl_2]_2$, Cs_2CO_3, and pivalic acid in cyclohexane at 80 °C for 8 h. We were delighted to find that an excellent isolated yield of *ortho*-alkynylated **3a** was obtained (Table 1, entry 1). Further screening revealed that when

Table 1. Optimization of the Reaction Conditions[a]



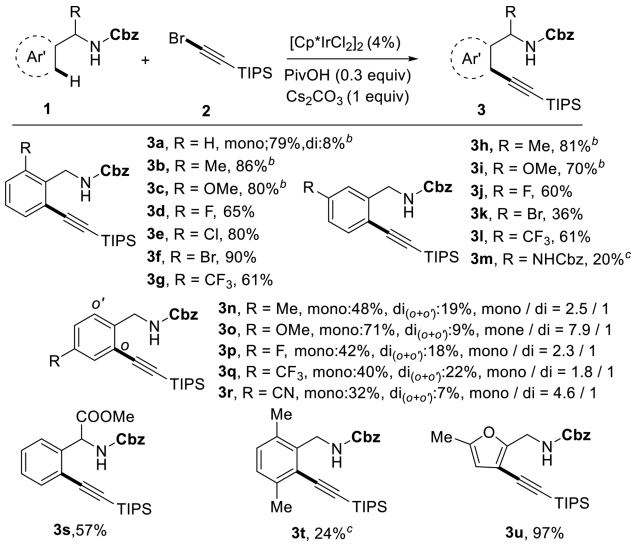
entry	various from the "standard" conditions[a]	yield of **3a** (%)
1		82(79[b])
2	$[Cp^*RhCl_2]_2$ instead of $[Cp^*IrCl_2]_2$	45
3	$Pd(OAc)_2$ instead of $[Cp^*IrCl_2]_2$	0
4	no $[Cp^*IrCl_2]_2$	0
5	no Cs_2CO_3	0
6	no PivOH	17
7	DCE as solvent	31
8	toluene as solvent	54
9	DMF as solvent	trace
10	Ag_2CO_3 instead of Cs_2CO_3	0
11	K_2CO_3 instead of Cs_2CO_3	46
12	CsOAc instead of Cs_2CO_3	8
13	60 °C	51

[a]Reaction conditions: **1a** (0.2 mmol), **2** (0.3 mmol), catalyst (4 mol %), additive (0.3 equiv), base (1 equiv) in solvent (1 mL) at 80 °C for 8 h under air in a sealed tube. Yields were based on GC analysis using tridecane as an internal standard. [b]Isolated yield of monoalkynylated product.

$[Cp^*Ir(III)Cl_2]_2$ was replaced by $[Cp^*Rh(III)Cl_2]_2$, a dramatically decreased yield of **3a** was obtained (entry 2). As expected, there was no yield of the alkynylated product **3a** when $Pd(OAc)_2$ was used as the catalyst, along with the starting material being completely recovered (entry 3). Several other solvents such as DCE, toluene, and DMF were screened, which all afforded decreased yields of the product (entries 7−9). Particularly, Cs_2CO_3 was crucial for the reaction; the yields decreased dramatically when the bases such as CsOAc or K_2CO_3 were used instead of Cs_2CO_3 (entries 11 and 12). The addition of pivalic acid was essential for this reaction for promoting C−H activation.[16]

With the optimized reaction conditions in hand, we proceeded to investigate the substrate scope to illustrate the versatility of this Cbz-enabled *ortho*-selective C−H alkynylation protocol (Scheme 2). In general, Cbz-protected benzylamines substituted with both electron-deficient and electron-rich functional groups performed well under the optimized reaction conditions, affording the corresponding products in moderate to excellent yields. A wide variety of functional groups such as Me, MeO, F, Cl, Br, CF_3, CN, and CO_2Me were all tolerated in this Cbz-assisted C−H alkynylation reaction. The *ortho*-alkynylation of substrates, in which the *meta*-position was

Scheme 2. C(sp^2)−H Alkynylation of Benzylamine Derivatives[a]



[a]Reaction conditions: **1a** (0.2 mmol), **2** (0.3 mmol), catalyst (4 mol %), additive (0.3 equiv), base (1 equiv) in cyclohexane (1 mL) at 80 °C for 12 h under air in a sealed tube; isolated yields. [b]For 8 h. [c]At 100 °C, 24 h.

substituted with MeO, Me, F, and CF_3 selectively took place at the less sterically hindered position, providing the corresponding products in good yields (**3h**−**3l**).

Particularly, the amide group was also tolerated in this protocol, affording the alkynylated product in synthetically acceptable yield (**3m**). The *para*-substituted Cbz-protected benzylamine afforded a mixture of both mono- and dialkynylated products in good yields, which were easily separated by silica gel chromatography (**3n**−**3r**). The 2,5-dimethyl-substituted benzylamine was also compatible in this reaction, giving the alkynylated product in a lower yield due to the steric effect (**3t**). In addition, the heterocyclic furan also performed well, affording the alkynylated product in excellent yield (**3u**).

Encouraged by the promoting effect of the Cbz-amide with Ir(III) as the catalyst, we next explored whether the alkynylation could be achieved with the Cbz-protected arylethylamines. To our great delight, the *ortho*-alkynylations have proceeded well by a slight modification of the reaction conditions (Scheme 3). An elevated temperature of 100 °C was essential for the reactions to proceed. It is worth noting that the reaction might undergo a six-membered cyclometalation, which is unusual in the Ir(III)-catalyzed C−H functionalization reactions. Interestingly, *para*-substituted substrates only provided the monoalkynylated products in good yields, whereas the dialkynylated products were observed in trace amounts. This might be due to the weak cooperating effect of the triple bond of the substrate with the Ir(III) catalyst, which hindered the highly unstable six-membered complex formation during the catalytic cycle.

Next, we demonstrated the synthetic utility of this Cbz-amide-assisted C−H alkynylation reaction. First, gram-scale reactions were effortlessly achieved, affording the corresponding products in good yields (Scheme 4). Second, selective cleavage of the protecting group (i.e., TIPS) could be accomplished by carrying out the typical deprotection reaction procedure under mild reaction conditions.[17] Herein, a valuable

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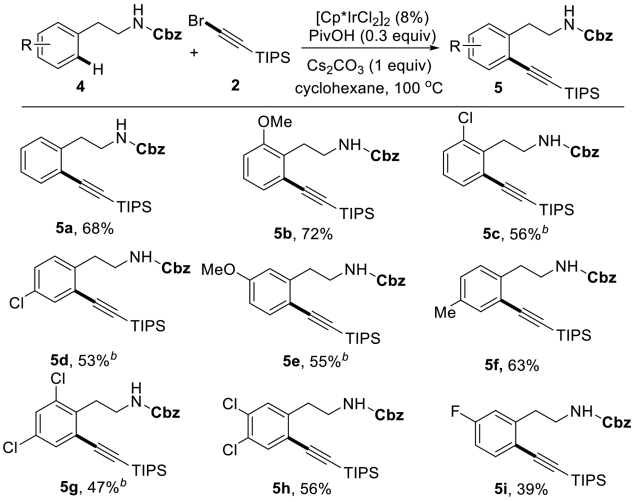
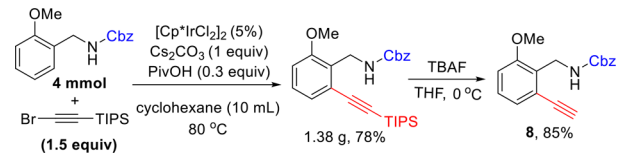
Scheme 3. C(sp^2)−H Alkynylation of Phenylethylamine Derivatives[a]



[a]Reaction conditions: **1a** (0.2 mmol), **2** (0.4 mmol), catalyst (8 mol %), additive (0.3 equiv), base (1 equiv) in cyclohexane (0.5 mL) at 100 °C for 24 h under air in a sealed tube, isolated yields. [b]**2** (0.4 mmol), $[Cp^*Ir(III)Cl_2]_2$ (10 mol %), 48 h.

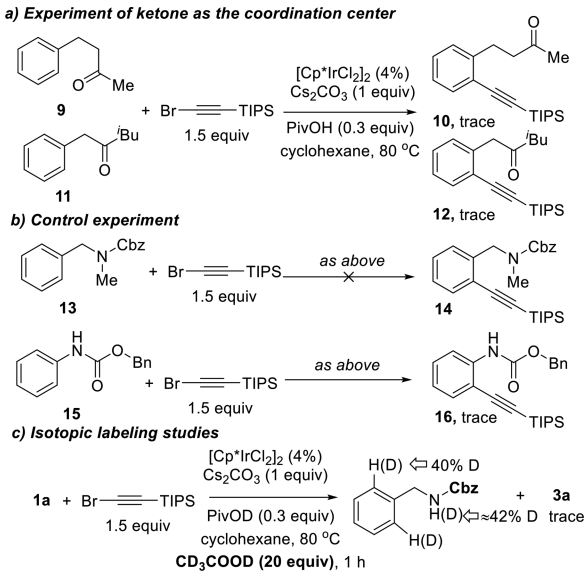
Scheme 4. Gram-Scale Reaction and Further Transformation in the Alkynylation



synthetic protocol for the synthesis of *ortho*-alkynylated benzylamines has been developed.

In order to elucidate the mechanism of this Cbz-amide-assisted Ir(III)-catalyzed C−H functionalization reactions, additional experiments were performed (Scheme 5). Initially, benzylacetone and 4-methyl-1-phenyl-2-pentanone were both

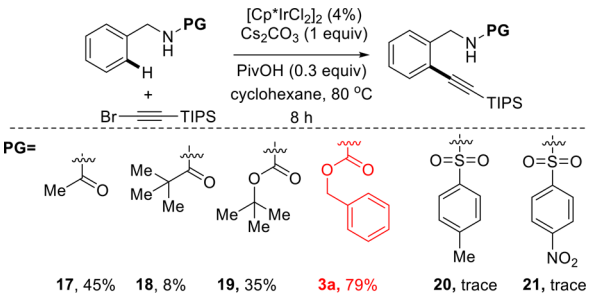
Scheme 5. Preliminary Mechanistic Study



subjected to the standard reaction conditions to explore the feasibility of the ketone as the coordination center. However, only the starting materials were recovered, without the formation of any alkynylated product (Scheme 5a). This result supports the role of the amide moiety as the coordination center, rather than the oxygen in the Cbz-protected benzylamines. Further, a control experiment was carried out by using Cbz-protected *N*-benzylmethylamine as the substrate under the standard reaction conditions (Scheme 5b). In this case, no alkynylated product was observed, and the starting material was completely recovered. This may suggest the significance of the formation of a N−Ir bond to realize the *ortho*-selective C−H functionalization. To further support this hypothesis, the Cbz-protected aniline was also investigated, but no alkynylated product was obtained under the standard reaction conditions. Subsequently, the deuteration experiment was explored by directly adding D_4-acetic acid into the reaction (Scheme 5c). The result from this experiment might suggest the formation of a N−Ir bond during the catalytic cycle.

To further understand the electronic and steric effects of the coordination center on the reaction pathway, several other protected benzylamines were subjected to the optimized reaction conditions (Scheme 6). For instance, the sterically

Scheme 6. Screening of Different Protecting Groups



hindered pivaloyl-protected substrate provided the alkynylated product in only 8% yield, whereas the less sterically hindered acetyl- or Boc-protected substrates afforded comparatively higher yields. In contrast, both the *p*-toluenesulfonyl and *p*-nitrobenzenesulfonyl were ineffective as directing groups for this reaction. It is likely that the electron-deficient protecting groups reduced the electron-donating effect of the N atom, resulting in its weak coordinating ability with the Ir(III) catalyst. Unfortunately, all of these substrates only afforded poorer yields, compared to that of Cbz-protected benzylamines. Even though the clear reason for the optimum performance of the Cbz-protected benzylamines in these C−H alkynylation reactions is not well understood, we might speculate that the phenyl ring may form weak coordination with the active Ir(III) catalyst.

Based on the experimental results and previous reports,[18,19] a probable catalytic cycle was proposed for this Cbz-amide-assisted C−H alkynylation reaction, as shown in Scheme 7. Initially, the dimeric precursor $[Cp^*Ir(III)Cl_2]_2$ was converted into the complex **I** with the assistance of Cs_2CO_3 and substrate **1a**. Subsequently, the cyclometalated Ir(III) complex was generated with the aid of the proton shuttle PivO− additive, followed by oxidation and reductive elimination, affording the complex **IV**, which would then produce the complex **I** by reacting with substrate **1a** and Cs_2CO_3.

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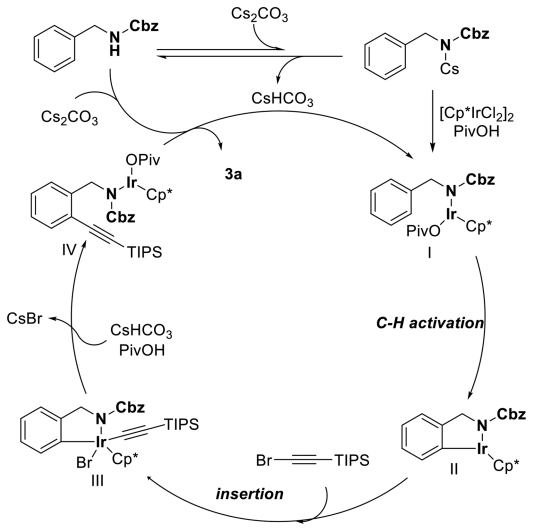
Scheme 7. Plausible Catalytic Cycle



In conclusion, we have demonstrated a convenient and practical protocol employing Cbz-amide as the directing group and an Ir(III) complex as the catalyst for the synthesis of *ortho*-alkynylated arylalkylamines. Herein, we have also explored the effectiveness of Cbz-amide as a directing group in assisting the C−H functionalization reactions of arylalkylamines. Further, various substrates were well tolerated in this protocol, affording the alkynylated products in moderate to good yields. The reactions also produced optimal yields on the gram scale. Thus, the utilization of Cbz-amide as the directing group would offer an effective approach for the synthesis of *ortho*-functionalized arylalkylamines in the laboratory as well as large-scale syntheses. Further applications and mechanistic studies including DFT calculations are now in progress.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b00797.

Experimental procedures and spectroscopic data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

Dedicated to Professor Xiyan Lu on the occasion of his 90th birthday.

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