C–H Activation Hot Paper

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Regioselective and Redox-Neutral Cp*Ir^{III}-Catalyzed Allylic C–H Alkynylation

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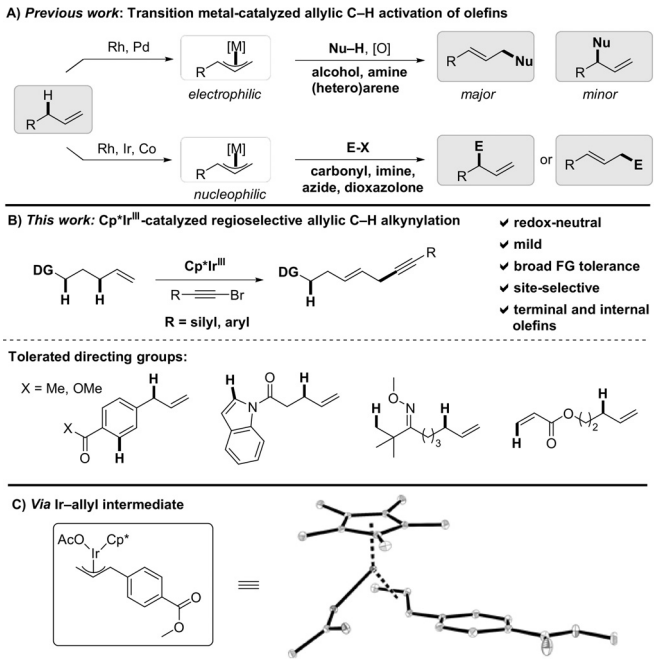
Abstract: *Herein, we report a Cp*Ir^{III}-catalyzed highly regioselective and redox-neutral protocol for the construction of 1,4-enynes from unactivated olefins and bromoalkynes via intermolecular allylic C–H alkynylation. The developed mild reaction conditions tolerate a broad range of common functional groups, even enabling selective alkynylation of allylic C–H bonds in the presence of other prominent directing groups. Mechanistic experiments including the isolation of a catalytically active Ir^{III}-allyl species support an intermolecular allylic C–H activation followed by an electrophilic alkynylation.*

Transition metal-catalyzed allylic C–H activation has emerged as a beneficial alternative to allylic substitution reactions,[1] enabling the utilization of unfunctionalized olefins as readily available substrates.[2] Since early reports from White and co-workers, Pd catalyzed allylic C–H functionalization[3a–c] has been intensively studied and expanded to the use of other transition metals such as Rh,[3d,e] Co,[3f–h] and Ir[3i–l] to afford metal-allyl intermediates (Scheme 1 A). Depending on the respective philicity, either different nucleophiles such as amines,[4a] alcohols,[4b] or (hetero)arenes[4c–d] or different electrophilic species including carbonyls,[3g] imines,[3h] dioxazolones[3i–l] or azides[4e] can be employed as coupling partners. Recent investigations showed that the nature of the metal-allyl complexes differs, if they are generated under either Rh or Ir catalysis. While Rh generates amphiphilic intermediates, Ir affords rather nucleophilic ones.[5] We sought to utilize this intrinsic nature of the Ir-allyl species to combine it with an electrophilic alkynylation reagent.[6] This would enable a direct allyl-alkyne coupling without the necessity to use prefunctionalized allylic substrates. As an electrophilic alkyne source, we envisioned bromoalkynes as preferable coupling partners due to their easy synthesis and enhanced reactivity in directed C(sp^3)–H and C(sp^2)–H activation.[7]

1,4-Enynes are multifaceted structural motifs in natural products and biologically active molecules, often showing promising anticancer activities.[8] The presence of multiple π-bonds opens up the opportunity for further functionalization, and therefore their synthesis has led to great interest in the synthetic community.[9] However, the majority of reports



Scheme 1. Transition metal-catalyzed allylic C–H activation.

focuses on the Tsuji–Trost type alkynylation of prefunctionalized olefins under Pd[10c] or Ir[10d] catalysis. Alternative strategies include Cu,[10f] Ni,[10a,b] Fe,[10e,g] or photoredox catalysis.[10h] However, most of these important reports are either again confined to the use of prefunctionalized allylic substrates, or only allow the alkynylation of cyclic or activated olefins.

Hence, a regioselective approach for the direct formation of allyl-alkyne bonds to afford structurally valuable 1,4-enynes from unactivated olefins via mild C–H activation would be highly desirable (Scheme 1 B). Further, this approach would allow for an orthogonal synthetic procedure if allylic C–H alkynylation could outcompete traditional directing groups.

Based on the above mentioned strategy, we began our investigation for allylic alkynylation using allylbenzene (**1a**) and (bromoethynyl)triisopropylsilane (**2a**) with [Cp*IrCl$_2$]$_2$ as the catalyst, AgOAc as the base, and AgSbF$_6$ as the additive at 40 °C in DCE (Table 1, for a detailed optimization table see the Supporting Information). Initially, we found that **3a** was formed in 52% yield with high regioselectivity (>20:1, Table 1, entry 1). To our delight, switching the solvent to TFE increased the yield to 64% (entry 2). Upon screening different bases, we found that AgOAc could be replaced by KOAc at an elevated temperature without a significant decrease in yield and regioselectivity (entry 3).

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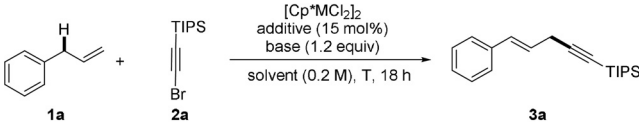
Table 1: Optimization of the reaction conditions.[a]



1a 2a 3a

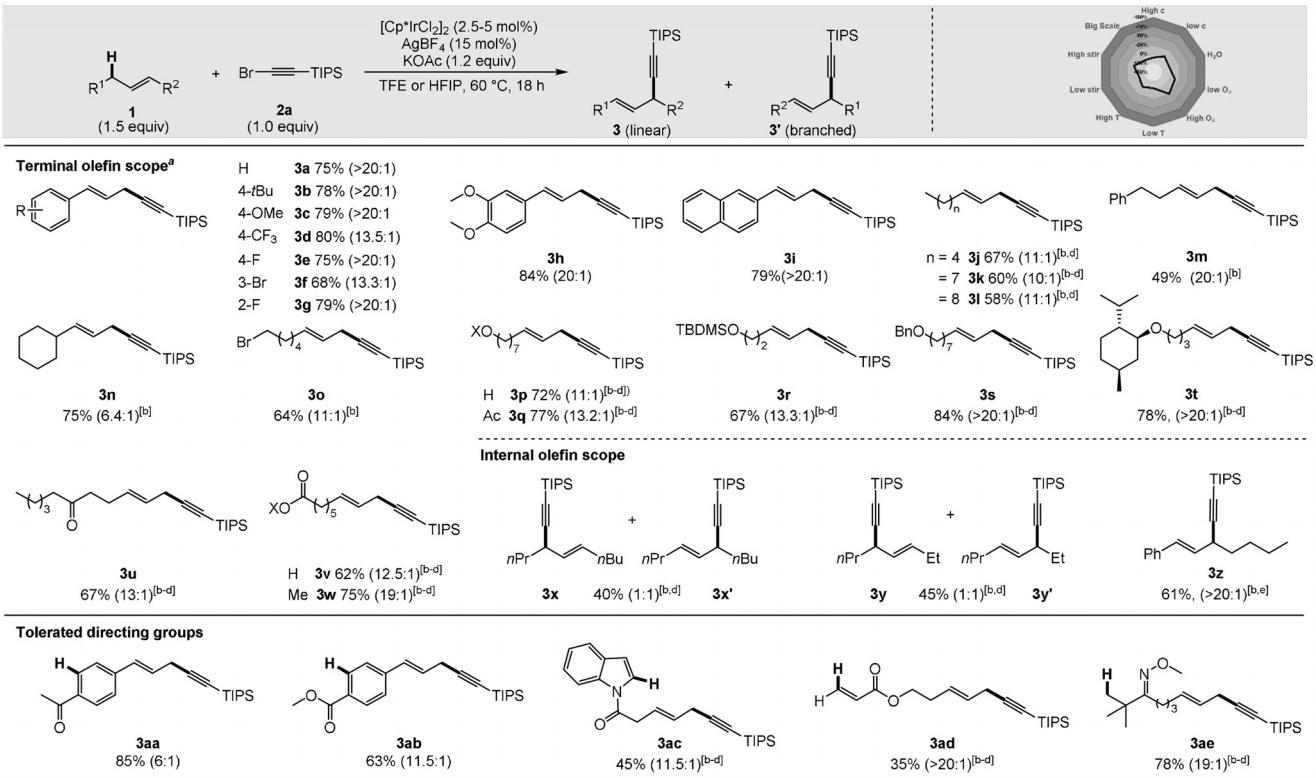
entry	[cat.] [mol%]	additive	base	solvent	T [°C]	yield[b,c]
1	[Ir] 5.0	$AgSbF_6$	AgOAc	1,2-DCE	40	52%
2	[Ir] 5.0	$AgSbF_6$	AgOAc	TFE	40	64%
3	[Ir] 5.0	$AgSbF_6$	KOAc	TFE	60	60%
4	[Ir] 5.0	$AgBF_4$	KOAc	TFE	60	84%
5	[Ir] 2.5	$AgBF_4$	KOAc	TFE	60	83%
6[d]	[Ir] 2.5	$AgBF_4$	KOAc	TFE	60	79%
7	[Rh] 3.5	$AgBF_4$	KOAc	TFE	60	trace
8	[Rh] 3.5	$AgSbF_6$	AgOAc	TFE	40	67%
9	–	$AgBF_4$	KOAc	TFE	60	–
10	[Ir] 2.5	–	KOAc	TFE	60	–

[a] Conditions: **1a** (0.20 mmol), **2a** (0.10 mmol). [b] Yields were determined by GC-FID analysis using 1,3,5-trimethoxybenzene as internal standard. [c] Regioisomeric ratio >20:1, determined by GC-MS. [d] Using 1.5 equiv of **1a**.

After changing the additive to $AgBF_4$ we were pleased to obtain **3a** in 84% yield maintaining the high regioselectivity (entry 4). This alteration allowed a decrease of the catalyst loading maintaining similar yields (entry 5). Finally, we were able to lower the olefin equivalents (entry 6).

Using Rh as the catalyst under the same conditions no reaction was observed (entry 7). However, product **3a** could be obtained after changing the base to AgOAc, but with less reactivity (entry 8). Control experiments proved that both catalyst and additive were essential for the reaction outcome (entry 9–10). Other literature known electrophilic alkynylation reagents failed to deliver any desired product (see the Supporting Information).

With the optimized conditions in hand, we intended to investigate the scope of the developed protocol. Our method was shown to be able to convert a variety of different olefins bearing aliphatic or aromatic substituents with good yields only being slightly affected by the electronics of the respective substrate. For example, unsubstituted allylbenzene gave the corresponding 1,4-enyne product **3a** in 75% yield. Allylarenes bearing electron-neutral (**1b**, **1i**), electron-donating (**1c, 1h**), or electron-withdrawing groups (**1d–1g**) reacted smoothly, delivering products (**3b–3i**) in high yields and with excellent regioselectivity. Afterwards, we proceeded to explore the reactivity of different aliphatic allylic systems. Unactivated olefins with different chain lengths were subjected to the alkynylation reaction conditions and the corresponding linear products (**3j–3n**) were afforded in moderate to high yields. Bromine substitution of the olefin did not exert any detrimental effect on its reactivity, resulting in the formation of **3o** in 64% yield. To further enhance the applicability of our protocol we demonstrated its tolerance towards common functional groups, such as free alcohol (**3p**),



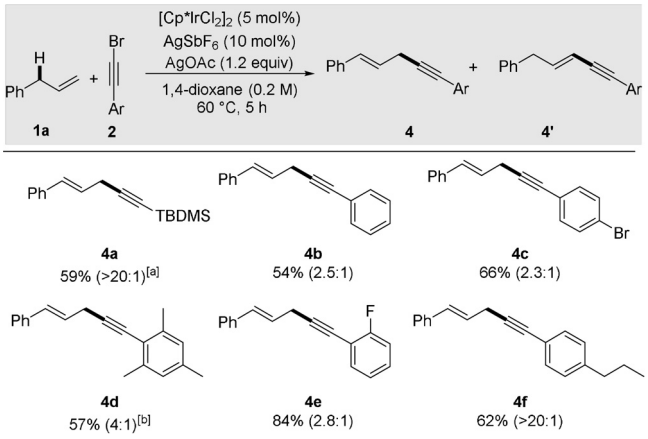
Scheme 2. Scope of the allylic C–H alkynylation of unactivated olefins. [a] Major isomers were characterized, regioisomeric ratios were determined by GC-MS or ^{1}H NMR. Reaction conditions: **1** (0.3 mmol), **2a** (0.2 mmol). [b] 5 mol% $[Cp^*IrCl_2]_2$ was used. [c] **1** (0.2 mmol), **2a** (0.3 mmol) were used. [d] KOAc (2 equiv) and HFIP (0.2 M) were used, reaction time 12 h. [e] AgOAc (1.2 equiv) was used as base.

ester (**3q**, **3w**), silyl (**3r**), and benzyl ethers (**3s**) delivering the respective products in moderate to high yields with high regioselectivity.

To our delight, menthol derivative (**3t**) could be efficiently synthesized and in addition, ketone (**3u**) as well as free carboxylic acid (**3v**) were well tolerated. Next, we proceeded to test internal olefins in our alkynylation protocol. In accordance with our expectations, mixtures of regioisomers (**3x**–**3y**) were accessed in moderate yields for alkyl-alkyl substituted olefins. However, aryl-alkyl substituted product, (**3z**) was afforded with high regioselectivity. Extending the generality of our procedure, we were able to scale our reaction up to 2.0 mmol obtaining product **3a** in 74% yield. We next investigated the sensitivity of our protocol to examine its reproducibility and applicability (Scheme 2, for details see the Supporting Information). The reaction was shown to be insensitive towards all examined parameters including temperature, concentration, oxygen level, moisture and stirring rate.[11]

In order to enable orthogonal and chemoselective C–H functionalization, the tolerance of established directing groups would be crucial to allow a stepwise implementation of functionality.[12] Therefore, we submitted several substrates bearing prominent directing groups such as a ketone, ester or even an oxime ether to the developed reaction conditions. To our delight, we were able to observe selective allylic alkynylation affording the respective products (**3aa**–**3ae**) in moderate to high yields.[13]

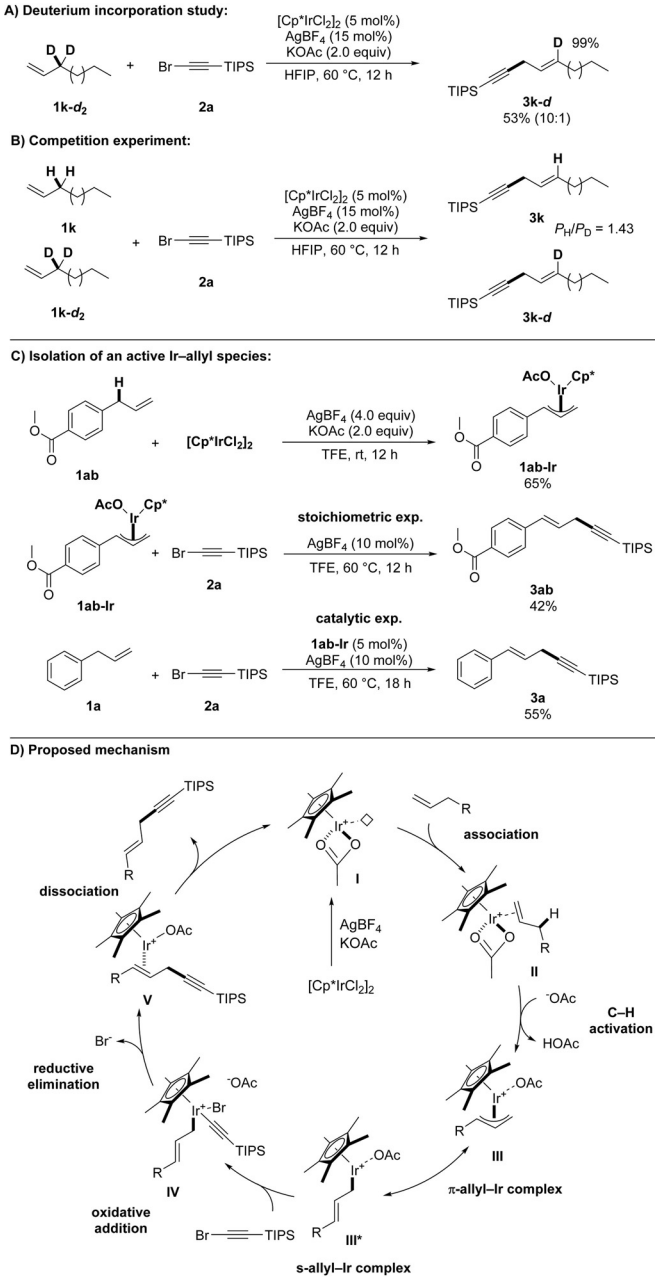
Furthermore, we investigated the alkyne scope (Scheme 3). Pleasingly, (*tert*-butyldimethylsilyl)acetylene **2b** underwent alkynylation and delivered **4a** in good yield and with excellent regioselectivity. Interestingly, aryl-substituted alkynyl bromides showed good reactivity when switching the solvent to 1,4-dioxane, the base to AgOAc and the additive to $AgSbF_6$. Bromoethynylarenes containing different substituents could be utilized under these conditions furnishing products (**4b**–**4f**) in moderate to high yields and 1,3-enynes were observed as byproducts due to isomerization.



Scheme 3. Scope of bromoalkynes. Reaction conditions: **1a** (0.2 mmol), **2** (0.3 mmol). r.r. was determined by GC-MS. [a] Conditions and r.r.(l:b) according to Scheme 2. [b] **1a** (0.3 mmol) **2** (0.2 mmol) were used.

Several experiments were performed to gain insight into the reaction mechanism. First, we submitted deuterated substrate **1k**-d_2 to the standard reaction conditions, and the corresponding product **3k**-*d* was obtained without proton incorporation in the alkynylated product (Scheme 4A). This result suggests that the allylic C–H activation is irreversible.

Second, the kinetic isotope effect was determined in a competition experiment ($P_H/P_D = 1.43$) indicating that the C–H activation is most likely not involved in the rate-determining step (Scheme 4B).[14] In addition, stoichiometric studies were conducted in order to synthesize a potentially active Ir-allyl species. Pleasingly, we were indeed successful to isolate the Ir-allyl complex **1ab-Ir** under C–H activation conditions (Scheme 4C). This intermediate could be structur-



Scheme 4. Mechanistic experiments and proposed catalytic cycle.

ally characterized by X-ray single crystal diffraction.[15] The subsequent alkynylation reaction with **2a** delivered **3ab** in 42% yield. In addition, we applied **1ab-Ir** in a catalytic experiment with substrate **1a**. To our delight, product **3a** was obtained in 55%. Based on these experimental results and precedent literature[7g] we propose the following catalytic cycle for the allylic C–H alkynylation reaction. Initially, $[Cp^*IrCl_2]_2$ is activated by $AgBF_4$ and KOAc, forming cationic Ir-species **I**. The olefinic substrate coordinates to the metal center to give intermediate **II**. Subsequently, π-allyl-Ir complex **III**, which is assumed to be in an equilibrium with σ-allyl species **III***, is formed upon base-assisted irreversible C–H activation.[16] Afterward, the Ir catalyst undergoes oxidative addition in the C–Br bond of the bromoalkyne to generate an Ir^V species **IV** which undergoes reductive elimination furnishing intermediate **V**. Subsequent dissociation releases the desired product and the catalytically active complex **I** is regenerated.

In conclusion, our method allows the conversion of a variety of unactivated olefins, bearing various aliphatic and aromatic substituents into valuable 1,4-enynes under mild conditions. We showed that a multitude of functional groups was tolerated, notably also different common directing groups. Detailed mechanistic studies include the isolation of the key intermediate and support the formation of a classical π-allyl-Ir^{III} complex. We believe that this work explores a new reactivity in Ir catalysis and opens up new possibilities in the synthesis of 1,4-enynes and allylic C–H functionalization in general.[17]

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Conflict of interest

The authors declare no conflict of interest.

Keywords: 1,4-enynes · alkynylation · allylic C–H activation · allyl-iridium complex · regioselectivity

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