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Ir(III)-Catalyzed Carbocarbation of Alkynes through Undirected Double C-H Bond Activation of Anisoles

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Abstract

A novel, electron-deficient cyclopentadienyl iridium(III) catalyst enables sequential cleavage of arene C(sp²)-H and methoxy C(sp³)-H bonds of anisoles, generating reactive metalacycles that insert difluoroalkynes to afford chromenes under mild reaction conditions. This transformation is an aryalkylation of an alkyne – a carbocarbation – *via* a non-chelate-assisted cleavage of two C-H bonds.

Graphical abstract

Reactions that involve metal-induced cleavage of hitherto considered inert C-H bonds¹ circumvent prefunctionalization of the starting materials, rendering the overall approach step-economical and sustainable. When applied to annulative processes, progress in this area has largely involved a single C-H bond cleavage event coupled with an X-H activation (X = a heteroatom, often the group directing the initial C-H activation) leading to heterocycles.² However, a double C-H activation leading to ring formation is nearly unknown.^{3,4}

Most schemes for transition metal-catalyzed C-H functionalization involve an initial C-H bond cleavage step, with formation of a singly bonded C-M species that may be further elaborated (Scheme 1). Prior work in this field extensively relied on substrates containing coordinating functional groups, which can bind to the metal catalyst and direct C-H activation and subsequent functionalization by formation of a chelate complex (Scheme 1a).

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Supporting Information. The Supporting Information is available free of charge on the ACS Publications website and includes: Supplementary Text, Figures S1–S7, Tables S1 and S2, NMR Spectra, X-ray Crystallographic Data, References (29–40). Metrical parameters for the structures of *met-1a*, **5** and **Ir3** are available free of charge from the Cambridge Crystallographic Data Centre (<https://www.ccdc.cam.ac.uk/>) under reference numbers CCDC 1570284, 1570285 and 1570286, respectively.

In recent years, the field of directed C-H bond functionalization has blossomed² with a plethora of novel transformations involving either C(sp²)-H⁵ or C(sp³)-H^{6,7,8} bond cleavage. In sharp contrast, non-chelate-assisted C-H activation reactions remain a particular challenge and rarity.^{9,10}

A key common feature of transition metal-catalyzed annulations is a metalacyclic intermediate that can firmly coordinate and insert an unsaturated coupling partner.¹¹ Subsequent C-X reductive elimination then forms the heterocyclic product (Scheme 1a). Depending on the nature of the heteroatom, these reactions are referred to as either carboaminations (X = N)¹² or carboxygenations (X = O).¹³ Heteroannulations have been complemented by variants that result in sequential functionalization of two C(sp²)-H bonds, with^{3,4,14,15} or without¹⁶ the assistance of directing groups, *i.e.*, carbocarbation (Scheme 1b). While this class of reactions is effective in forming aromatic carbocycles, variants involving C(sp³)-H bond activation that result in partially saturated carbocycles remain limited. The only existing reports on double C(sp²)-H/C(sp³)-H activation are: (*i*) a nickelcatalyzed oxidative annulation of formamides with alkynes,⁴ and (*ii*) a ruthenium-promoted spiroannulation of activated methylene compounds.³

Anisoles are among the most readily available and cheapest chemical feedstocks. Despite their great synthetic potential, transition metal-catalyzed functionalization of anisole molecules is still a formidable and rarely explored challenge due to the lack of coordinating heteroatoms that could effectively direct C-H bond activation.^{17,18} Regioselective borylation of arene C(sp²)-H bonds of anisoles has been achieved recently under iridium catalysis.¹⁰ On the other hand, catalytic functionalization of methoxy C(sp³)-H bonds remains rare. Earlier reports with palladium catalysts suffer from low yields, limited scope, and harsh reaction conditions.^{19,20}

Jakubikova and Ison recently reported a stoichiometric metalation of monosubstituted benzenes with iridium(III) complexes.¹⁷ Of more than 20 different arenes surveyed, all underwent C-H activation at the *para* position, regardless of electronics, with a single exception – anisole. Metalation on anisole resulted in metalacycle formation with concomitant dual C(sp²)-H and C(sp³)-H bonds activation. We speculated that this metalacycle could be intercepted by an alkyne coupling partner leading to a productive carbocarbation (Scheme 1c). Herein, we report the design and development of a catalytic system that enables the unprecedented double C-H functionalization of anisoles. This iridium-catalyzed reaction is initiated by a non-chelate-assisted C-H bond cleavage, a process that is shown to rely on the nature of the ancillary ligand used. Appealingly, the sequential C-H activations generate chromenes^{21,22,23} containing a monofluoroalkene sidechain, a peptide bond bioisostere commonly applied in medicinal chemistry.²⁴

To begin our investigation, we examined the activation of 4-(trifluoromethyl)anisole (**1a**). Ison's seminal work was performed with anisole as solvent;¹⁷ we settled on 5.0 equivalents relative to coupling partner in hydrocarbon solvents as a more synthetically tractable solution. In an initial screen of potential coupling partners, we identified *gem*-difluoroalkynes (**2**) as suitable substrates for oxidative annulation, presumably by virtue of their mild oxidizing potential combined with high thermal stability.²⁵ Disappointingly

however, heating **1a** and **2a** together with catalytic amounts of η^5 -pentamethylcyclopentadienyl iridium(III) complex $[\text{Cp}^*\text{IrCl}_2]_2$ (**Ir1**), DMSO (**L1**), and excess CsOAc leads to trace amounts of the desired chromene product (**3aa**).²⁶ We speculated that this was due to inactivation of the iridium(III) catalyst by fluoride.²⁷ Several fluoride ion scavengers were tested, with the target product observed in small amounts (12% yield) when employing trimethylsilyl acetate (**Si1**) as additive.²⁶ The use of a $\text{Cu}(\text{OAc})_2/\text{O}_2$ system for iridium re-oxidation results in an increased yield of 25% signaling catalyst turnover (Table 1, entry 1). Among other silanes tested, dimethyl diacetoxysilane (**Si2**) is optimal and, in combination with cesium adamantane-1-carboxylate (1-AdCO₂Cs), affords 57% yield of **3aa** (entry 2). In addition, a significant impact of Cp-ligand electronics²⁸ on reaction outcome is observed, with more electron-deficient **Ir2** and **Ir3** leading to higher yields (entries 3, 4). Correspondingly, a combination of catalyst **Ir3** bearing two *p*-CF₃ substituted phenyl rings²⁶ with cyclic sulfoxide **L2** affords chromene **3aa** in a respectable 75% yield (entry 5).

Of prime importance is the influence of ancillary ligand **L** on the success of the carboannulative process. Control experiments under identical conditions with the exclusion of DMSO did not produce any detectable annulation product. On this basis, we undertook a substantive mechanistic investigation that we here reveal is fully consistent with the inability of moderate-to-strongly binding ligands to dissociate from iridium(III), a process required during a key step in the catalytic cycle. This establishes the loosely-bound sulfoxides as privileged co-ligands that enable facile undirected C-H bond activation.

Anisole **1a** is metalated quantitatively when heated with stoichiometric amounts of $[\text{Cp}^*\text{IrCl}_2]_2$, DMSO and 1-AdCO₂Cs (Figure 1a). Omission of any one of these components does not lead to product. The structure of the resultant DMSO-bound metalacycle *met-1a* was established unequivocally by X-ray diffractometry.²⁶ Although remarkably stable at ambient temperature, *met-1a* recovers its catalytic activity when heated together with **1a** and **2a** under the standard reaction conditions. Indeed, the yields of product **3aa** are similar from reactions catalyzed by either *met-1a* (52%) or an equimolar mixture of $[\text{Cp}^*\text{IrCl}_2]_2$ and DMSO (57%, Table 1, entry 2). In an attempt to shed light on alkyne insertion into *met-1a*, we anticipated that 3-hexyne (**4**) could trap the relevant Ir(III) intermediate because it lacks the reactive *gem*-difluoromethylene group. Gratifyingly, *met-1a* inserts **4** cleanly under thermal conditions (Figure 1b), affording an Ir(III)- η^3 -allyl complex (**5**) that was also characterized by X-ray crystallography.²⁶ These experiments are fully consistent with *met-1a* being an off-cycle precursor to a reactive intermediate.

Further insight was gained from an examination of isotopically labeled substrates. When subjecting deuterated anisole **1a-d₈** to the optimized catalytic conditions using buffered 1-adamantanecarboxylic acid as the proton source, considerable deuterium leaching is observed at the *ortho* and *para* positions of the arene ring (83% and 87% of deuterium retention, respectively) (Figure 1c). This indicates that arene C(sp²)-H activation is reversible under the present reaction conditions. Furthermore, based on a competition experiment between partially deuterated metalacycle *met-1b-d* and non-deuterated bromoanisole **1o**, it was demonstrated that deuterium atoms do not crossover between the

two molecules (Figure 1d). Additionally, a notable kinetic isotope effect (KIE) of 2.5 is obtained from a series of competition experiments between protio-anisole (**1b**) and deuterio-anisole (**1b-d₃**) (Figure 1e). Taken together, the above experimental observations imply that C(sp³)-H activation at the methoxy group of anisole is irreversible and turnover-limiting.

An influence of the steric bulk of the carboxylate base on the regioselectivity of anisole metalation is observed, with more hindered bases (1-AdCO₂Cs > PivOCs > AcOCs) leading to higher preference for cyclometalation over *para*-metalation (Figure 1f). In sharp contrast, when performed catalytically, the reaction affords exclusively the doubly C-H functionalized product even with a smaller base like CsOAc (Table 1, entry 1). These results are fully consistent with a non-chelate-assisted CH activation pathway, where the regioselectivity of the initial C(sp²)-H bond cleavage is driven solely by the irreversibility of subsequent C(sp³)-H activation.²⁹

Taken together, our mechanistic data is supportive of the following catalytic cycle (Figure 1g). The active catalyst is presumably the coordinatively unsaturated, cationic mono-acetato Cp*Ir(III) fragment **I** that is generated from [Cp*IrCl₂]₂, DMSO and CsOAc. Arene C(sp²)-H activation of anisole (**1b**) is proposed to take place by concerted metalation-deprotonation (CMD).³⁰ During this step: (i) the ancillary sulfoxide ligand is crucial for providing the optimal electronic environment at iridium(III) that enables efficient C-H bond cleavage, and (ii) this initial C-H activation does not rely on chelation control and can occur at either *ortho* or *para* positions. The resultant Ir(III)-aryl species **II** presumably exchanges DMSO for acetate in preparation for the second CMD event (**III**), which is consistent with the necessity of a weakly bound ancillary ligand for facile reactivity. Based on the KIE experiment, methoxy C(sp³)-H bond scission is the slowest step on the catalytic cycle, and it leads to formation of the five-membered iridacycle **IV**. Intermediate **IV** is at a bifurcation point from where it can: (i) coordinate difluoroalkyne **2** and drive the catalytic cycle forward, or (ii) reversibly re-coordinate back DMSO, leading to the isolable off-cycle intermediate *met-1b*. Alkyne coordination and migratory insertion affords the seven-membered iridacycle **VI**. Based on isolation and characterization of the Ir(III)-η³-allyl complex **5**, we propose that insertion initially takes place into the most reactive aryl C(sp²)-Ir bond. Intermediate **VI** is coordinatively unsaturated and poised for β-F elimination that leads to metal-bound fluoroallene **VII**. A second migratory insertion, this time of the allene into the less reactive C(sp³)-Ir bond, is followed by β-H elimination to liberate the chromene product (**3ba**). Re-oxidation of iridium(I) to iridium(III) with Cu(OAc)₂/O₂ and cleavage of the Ir-F bond with **Si2** regenerates the active catalyst and closes the catalytic cycle.

After deciphering key mechanistic aspects, we were now set to examine the scope of our undirected double C-H activation methodology (Scheme 2). We were pleased to find that a wide array of commercially available anisoles can be efficiently coupled with difluoroalkyne **2a** under the optimized conditions. As shown in Scheme 2a, this protocol is highly tolerant of a wide range of functional groups. Electron-releasing (as in anisoles **1e**, **1f**, and **1h**) and electron-withdrawing (as in anisoles **1d**, **1g**, and **1i**) substituents are tolerated at the *para*- and *meta*-positions, affording the product chromenes in good yields (73 to 82% yield). Disubstituted (**1c**, **1m**, **1n**, **1o**, **1p**, and **1q**) as well as bicyclic (**1l**) anisoles are equally competent substrates (71 to 80% yields). Even anisoles **1j**, **1k**, and **1r** that are more hindered

due to one blocked *ortho*-position participate equally well in the carboannulative process (72 to 77% yields). For all substrates, arene C(sp²)-H activation occurs exclusively *ortho* to the methoxy group. In *meta*-substituted anisoles (**1g**, **1h** and **1i**), C-H functionalization occurs solely at the least sterically hindered *ortho*-position and a single regioisomer of the product is observed. Even for substrates **1i** and **1o**, where the competitive *ortho*-position is electronically activated towards C-H bond cleavage by an electron-withdrawing fluoro substituent, metalation still takes place largely at the more sterically accessible carbon atom (>10:1 rr). One potential advantage of our iridium-mediated methodology is that it can be applied to more complex substrates for late-stage diversification. Indeed, the intriguing pentacyclic product **3sa** is formed in a respectable 58% yield by using two equivalents of an estrogen derivative as substrate. From a practical perspective, two equivalents are sufficient for many of the other anisole substrates as well, affording the corresponding chromenes (**3fa**, **3la**, **3ma**, **3ca**, **3pa** **3qa**, and **3ra**) with only minor decrease in yields. Furthermore, synthetic practicality was demonstrated by carrying out a 10-fold scale-up of this procedure for anisole **1b** (63% yield).

With respect to the difluoroalkyne coupling partner, both linear (**2a**) and branched (**2b**, **2d** and **2j**) substrates behave well, affording the anticipated products in good yields (63 to 81%) (Scheme 2b). Notably, the reaction efficiency decreases slightly when branching is introduced on the side of the *gem*-difluoromethylene group (**3bb** and **3bi**, 66% and 63% yield respectively). This is not surprising considering the costly steric interactions in the vicinity of β -H elimination. A highly regioselective annulation is observed for all cases, favoring coupling of the anisole C(sp²)-H bond with the distal sp-hybridized carbon atom of the difluoroalkyne. Moreover, the reaction is completely diastereoselective with solely the *Z*-isomer being formed, even for simple methyl-substituted compounds (**3bd** and **3be**). Most importantly, difluoroalkynes bearing functional groups such as protected alcohols (**2j** and **2k**), primary alkyl chlorides (**2h** and **2i**), a strained cyclopropyl ring (**2c**), an arene (**2k**), and even a TIPS-capped alkyne (**2l**) are all tolerated and no decrease in yield is witnessed (68 to 80%).

In summary, we have developed the first carbocarbation of triple bonds proceeding by undirected, sequential activation of C(sp²)-H and C(sp³)-H bonds of anisole. The reaction is catalyzed by a novel, electron-deficient cyclopentadienyl iridium(III) complex that requires an ancillary sulfoxide ligand. The described methodology is general in terms of scope and its synthetic application is facilitated by a thorough mechanistic understanding. The double C-H activation reaction reported herein provides non-orthodox access to chromene scaffolds and serves as a versatile platform for the development of catalytic methods for functionalization of feedstock chemicals.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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29. Our hypothesis is confirmed by previous reports, where: (i) an undirected pathway was established computationally for catalytic anisole borylations (ref. 10), and (ii) stoichiometric metalation of anisole was shown not to be subject to chelation control, both computationally and experimentally (ref. 17).
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Figure 1. Mechanistic experiments

(a) Interrogating the catalytic activity of metalacyclic intermediate *met-1a*. (b) Alkyne insertion into *met-1a*. (c) Probing the reversibility of arene C(sp²)-H activation, and (d) the irreversibility of methoxy C(sp³)-H activation. (e) Kinetic isotope effect study. (f) Ascertaining the undirected nature of C(sp²)-H activation. (g) Proposed catalytic cycle.

Scheme 1.

Transition metal-catalyzed, annulative carbocarbation of unsaturated bonds by C-H bond activation.

Scheme 2. Substrate scope^aOnly 2.0 equivalents of anisole were used.^bA 10-fold scale-up of anisole **1b** was used.

Reaction development.

Table 1

entry	[Ir]	Si	L	base	yield (%) ^a
1	Ir1	Si1	DMSO	CsOAc	25
2	Ir1	Si2	DMSO	1-AdCO ₂ Cs	57
3	Ir2	Si2	DMSO	1-AdCO ₂ Cs	63
4	Ir3	Si2	DMSO	1-AdCO ₂ Cs	69
5	Ir4	Si2	DMSO	1-AdCO ₂ Cs	55
6	Ir5	Si2	DMSO	1-AdCO ₂ Cs	58

^a Determined by ¹⁹F-NMR with 1,3,5-trifluorobenzene standard.