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Broad-Scope Rh-Catalyzed Inverse-Sonogashira Reaction Directed by Weakly Coordinating Groups

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Supporting Information Placeholder

ABSTRACT: We report the alkynylation of C(sp²)-H bonds with bromoalkynes (inverse-Sonogashira reaction) directed by synthetically useful ester, ketone and ether groups under rhodium catalysis. Other less common directing groups such as amine, thioether, sulfoxide, sulfone, phenol ester, and carbamate are also suitable directing groups. Mechanistic studies indicate that the reaction proceeds by a turn-over limiting C-H activation step via an electrophilic-type substitution

KEYWORDS: *alkynylation, rhodium catalysis, C-H functionalization, inverse Sonogashira, metallacycle, Hammett correlation, DFT.*

INTRODUCTION

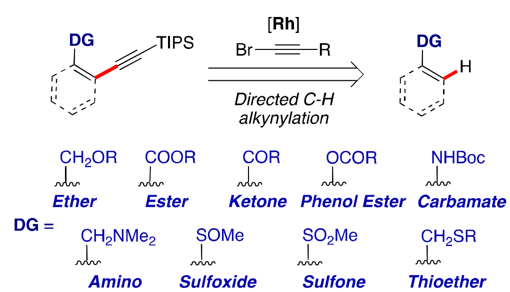
Alkynes are among the most versatile functional groups[1] and are widely present in natural products,[2] drugs,[3] and organic materials.[4] The chemistry of alkynes has gained particular momentum in recent years by the discovery of a wide variety of catalytic transformations triggered by gold(I), platinum(II) and other alkynophilic Lewis acids.[5] Therefore, the development of methods for the introduction of alkyne groups onto organic molecules is of high importance. To this end, the Sonogashira coupling reaction is the most general method for the formation of C(sp)-C(sp²) bonds from aryl or alkenyl (pseudo)halides and terminal alkynes.[6]

The main limitation of the Sonogashira coupling reaction resides in the synthetic availability of the required (pseudo)halides. An alternative approach that is better suited for the late-stage functionalization of complex molecules involves the alkynylation of C(sp²)-H bonds with terminal alkynes or activated acetylenes such as ethynylbenziodoxolone (EBX) reagents or haloalkynes using transition-metal catalysts.[7] Often named inverse-Sonogashira coupling, this methodology relies on the reactivity of electronically activated (hetero)arenes[8] or on a chelating group to assist a C-H activation process.[9] The former strategy is restricted to aromatic C(sp²)-H bonds, which need in addition to be acidic or electron-rich enough to undergo deprotonation or Friedel-Crafts type reaction. The latter has been achieved for both arenes and alkenes,[9b] with a variety of directing groups, typically amides or nitrogen coordinating groups such as heterocycles or imine derivatives (oxime, nitrone, azomethine).[9c] The applicability of this strategy in multi-step synthesis is however limited, as in most cases, the directing groups need to be installed and/or removed. Therefore, to render this approach useful, the development of new protocols using instead widely used functional groups serving as synthetic handles is highly desirable.[10]

Towards this goal, we recently reported a general *peri*-alkynylation of naphthols using ruthenium catalysis.[11] Benzoic acids can also be alkynylated at the *ortho*-position,[11,12] although the use of other versatile *O*-functionalities[13,14] as directing groups is still limited, mainly due to the challenging formation of a weakly coordinated metallacyclic intermediate.[15] In particular, despite intense efforts in the field of catalytic C(sp²)-H functionalization, only two examples of the use of benzyl ether as directing group has been reported in the context of C-H borylation.[16]

Here, we report the use of synthetically useful ether, ester, and ketone as directing groups for the direct alkynylation of C(sp²)-H bonds with bromoalkynes under rhodium catalysis (Scheme 1).[17] We also demonstrate for the first time that amine,[18] thioether,[19] sulfoxide,[20] sulfone,[21] carbamate[22] and phenol esters[23] are suitable directing groups in this transformation. Furthermore, our experimental and theoretical mechanistic study shows that this Rh-catalyzed alkynylation occurs by a turn-over determining C-H activation in which a five-membered ring metallacycle is formed by an electrophilic aromatic substitution-type process.

Scheme 1. C(sp²)-H Alkynylation With Bromo-Alkynes Directed by a Broad Range of Coordinating Groups under Rhodium Catalysis

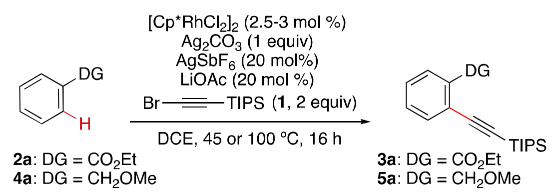


RESULTS AND DISCUSSION

Reaction Scope. Our studies began by evaluating the reactions of TIPS-protected bromoacetylene (**1**) with ethyl benzoate (**2a**) and benzyl methyl ether (**4a**). We discovered that a combination of $[Cp^*RhCl_2]_2$ (2.5 mol %), $AgSbF_6$ (20 mol %), Ag_2CO_3 (1 equiv), LiOAc (20 mol %) in 1,2-dichloroethane (DCE) at 45 °C provided **3a** in 69% yield (Table 1, entry 1). Control experiments showed the essential role of all reaction components (Table 1, entries 2-11). Thus, lower yields of **3a** were obtained at temperatures lower or higher than 45 °C (Table 1, entries 2 and 3). Similar results were obtained by decreasing the amount of Ag_2CO_3 to 0.5 equiv or replacing this silver salt by K_2CO_3 (Table 1, entries 4 and 5). Solvents different than DCE led to poor results (Table 1, entries 6-11). The use of other bromoalkynes, such as (bromoethynyl)benzene or 1-bromooctyne, led to no conversion.[24]

Although treatment of benzyl methyl ether (**4a**) with bromoacelytene **1** under essentially the same conditions did not lead to the product of alkynylation (Table 1, entry 12), simply increasing the temperature to 100 °C led to **5a** in 64 % yield (Table 1, entry 13). Using ethynyltriisopropylsilane instead of **1** did not afford **5a** (Table 1, entry 23). Replacing $[Cp^*RhCl_2]_2$ with other metal catalysts typically used in C-H functionalization did not lead to alkynylated product (Table 1, entries 24-26,). The alternative hydroxy-directed alkynylation of primary, secondary, or tertiary benzyl alcohol led to oxidation, decomposition, or unproductive reaction.

Table 1. Rh-Catalyzed *Ortho*-C-H Alkynylation of Ethyl Benzoate and Benzyl Methyl Ether: Optimization Conditions[24]



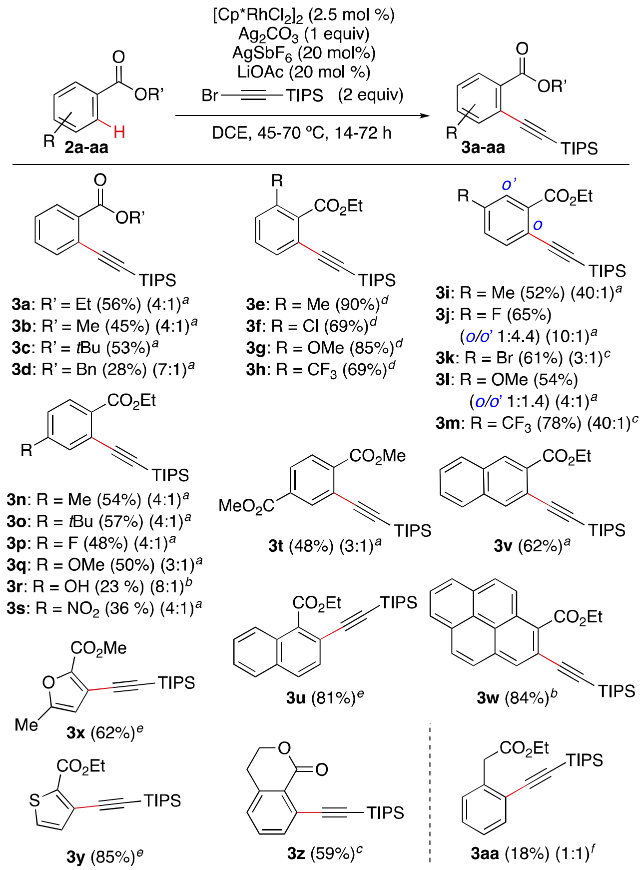
Entry	DG	Variation from the "standard conditions"[a]	Yield[b]
1	ester	none	58-69
2	ester	at 25 °C[c]	35
3	ester	at 65 °C[c]	16
4	ester	with Ag_2CO_3 (0.5 equiv)[d]	41
5	ester	with K_2CO_3 (1 equiv)[d]	5
6	ester	in dichloromethane[e]	8-14
7	ester	in toluene[e]	0
8	ester	in *tert*-AmOH[e]	0
9	ester	in Et_2O[e]	4
10	ester	in EtOAc[e]	18
11	ester	in MeOH[e]	0
12	ether	none	0
13	ether	at 100 °C[c]	50-64
14	ether	without $[Cp^*RhCl_2]_2$	0
15	ether	without Ag_2CO_3	0
16	ether	without LiOAc	0
17	ether	without $AgSbF_6$	0
18	ether	with AgOAc (1.2 equiv)[f]	<1.5
19	ether	AgOAc (1 equiv) + Ag_2CO_3 (0.2 equiv)[g]	12
20	ether	in toluene[e]	0
21	ether	in *tert*-amOH[e]	0
22	ether	in 1,4-dioxane[e]	0
23	ether	with TIPS-acetylene[h]	0
24	ether	with $[Cp^*IrCl_2]_2$[i]	0
25	ether	with $Pd(OAc)_2$[i]	0
26	ether	with $[RuCl_2(p\text{-cymene})]_2$[i]	<3

[a] Standard reaction conditions: **2a** or **4a** (0.2 mmol), **1** (2 equiv), $[Cp^*RhCl_2]_2$ (2.5 mol% for DG = ester, 3 mol% for DG= ether), Ag_2CO_3 (1 equiv), $AgSbF_6$ (0.2 equiv), LiOAc (0.2 equiv), DCE, 16 h, 45 °C. [b] Yield of the monoalkynylated product determined by ^1H NMR using bromomesitylene as internal standard. [c] Instead of 45 °C. [d] Instead of Ag_2CO_3 (1 equiv). [e] Instead of DCE. [f] Instead of Ag_2CO_3 and LiOAc. [g] Without LiOAc. [h] Instead of **1**. [i] Instead of $[Cp^*RhCl_2]_2$.

Different alkyl benzoates **2a-d** could be *ortho*-alkynylated, with ethyl benzoate **2a** giving the highest yield (Scheme 2). Electron-donating alkyl or methoxy groups and electron-withdrawing substituents such as NO_2, CF_3, and different halides at the *ortho*, *meta* and *para* positions were well tolerated, affording alkynylated products **3e-w** in 23-90% yield. In the case of *meta*-substituted substrates **2i,k,m**, the alkynylation occurred at the least sterically hindered site. However, fluoro and methoxy derivatives **2j** and **2l** favor formation of the 1,2,3-trisubstituted compounds **3j** and **3l**, respectively.

The alkynylation of ethyl 1-naphthoate (**2u**) and ethyl pyrene-1-carboxylate (**2w**) does not take place at the *peri*-position, leading instead to *ortho*-fuctionalized products **3u** and **3w**, respectively. Reaction of ethyl 2-naphthoate (**2v**) afforded exclusively the product of alkynylation at C-3 (**3v**). Furan and thiophene esters were also alkynylated to give **3x** (62%) and **3y** (85%), respectively. The carbonyl group of isochroman-1-one is also an effective directing group, affording **3z** in 59% yield. On the other hand, the alkynylation of ethyl phenylacetate required heating at 90 °C and was less efficient, leading to **3aa** in 18% yield along with an equivalent amount of the dialkynylated product.

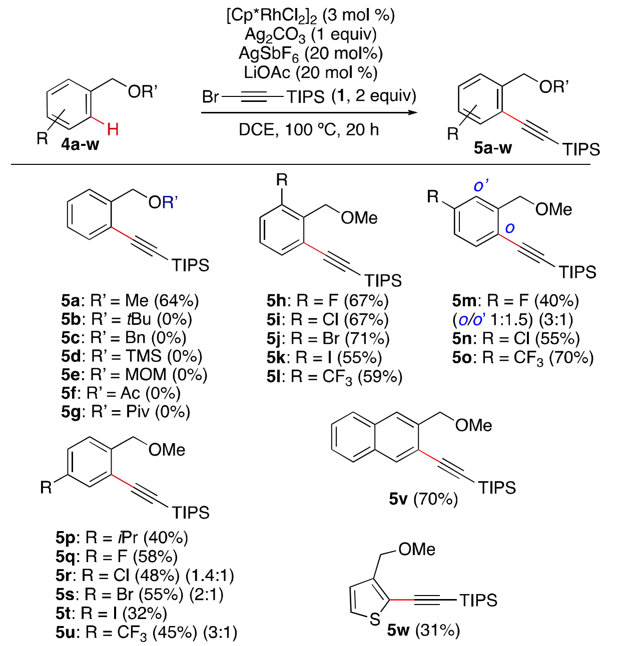
Scheme 2. Rh-Catalyzed *Ortho*-C-H Alkynylation of Alkyl Benzoates



Conditions: [a] 45 °C, 16-24 h. [b] 45 °C, 48 h. [c] 45 °C, 72 h. [d] 60 °C, 48 h. [e] 70 °C, 24-72 h. [f] 90 °C, 72 h. (0.2 mmol scale) Yields of isolated monoalkynylated products are shown. In cases in which diakynylated products were also formed, mono- *vs.* dialkynylation selectivity is shown in parentheses.

Whereas the alkynylation of **4a** leads to **5a** in 64% yield, substrates **4b-d** with bulkier alkyl or silyl groups failed to give the expected products (Scheme 3). Similarly, MOM-protected benzyl alcohol **4e** and esters **4f-g** were unreactive substrates. On the other hand, methyl benzyl ethers bearing diverse substituents at the *ortho*, *meta* or *para* positions such as *i*-Pr, CF_3, fluoro, chloro, bromo, or iodo lead to o-alkynylated products **5h-u** in 32-71% yields. As observed for the benzoates, the alkynylation of *meta*-substituted substrates **4n-o** occurred at the least sterically hindered site, whereas fluoro derivative **4m** led to a mixture of ortho-alkynylated derivatives **5m**, favoring the formation of the 1,2,3-trisubstituted product. Again, the alkynylation of naphthyl derivative **4v** takes place at C-3 to form **5v** in 70% yield. The reaction of thiophene **4w** provided **5w**, the product of C-2 alkynylation, which was isolated in 31% yield.

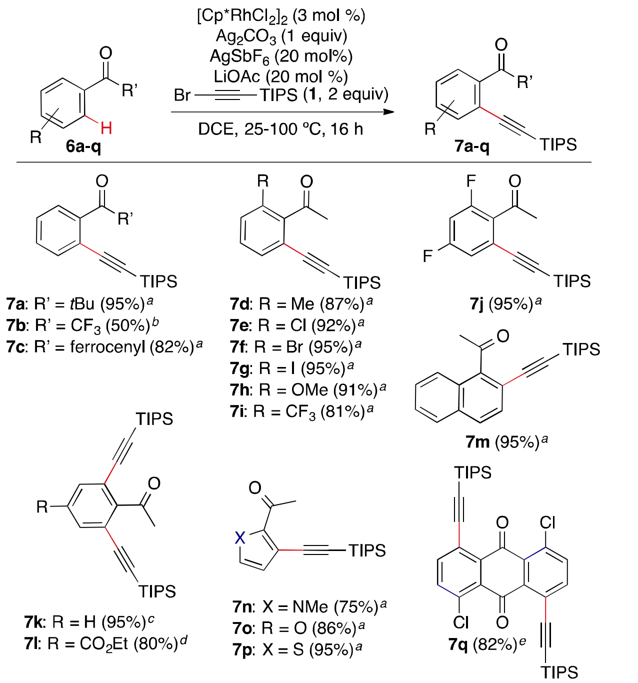
Scheme 3. Rh-Catalyzed *Ortho*-C-H Alkynylation of Benzyl Ethers



Yields of isolated monoalkynylated products are shown. In cases in which diakynylated products were also formed, mono- vs. dialkynylation selectivity is shown in parentheses.

Under conditions similar to those used for the reaction of the ester derivatives, a wide variety of aryl ketones **6a-p** could be alkynylated in a general manner to give **7a-p** in good to excellent yield (Scheme 4). Bis(alkynylated)acetophenone **7k** was obtained in quantitative yield from acetophenone at room temperature, while bulkier alkyl substituents allowed a mono-selective alkynylation, affording products **7a-c** in 50-95% yield. Diverse substituents at the *ortho* position of acetophenone were well tolerated to give products **7d-i** in 81-95% yield. 2-acetyl derivatives *N*-Methyl-pyrrole (**6n**), furan (**6o**), and thiophene (**6p**) were alkynylated at C-3 in 75-95% yield. The double alkynylation of 1,5-dichloroanthraquinone (**6q**) proceeded at 100 °C to give dialkynylated product **7q** in 82% yield.

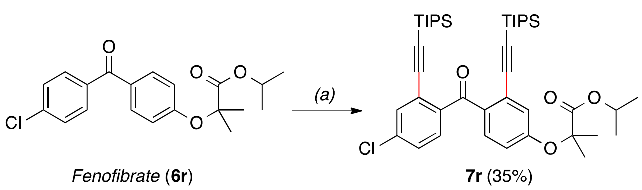
Scheme 4. Rh-Catalyzed *Ortho*-C-H Alkynylation of Aryl Ketones



Conditions: [a] 45 °C, (1 equiv **1**). [b] 90 °C, (1 equiv **1**). [c] 25 °C, (2 equiv **1**). [d] 45 °C, (2 equiv **1**). [e] 100 °C, (2 equiv **1**).

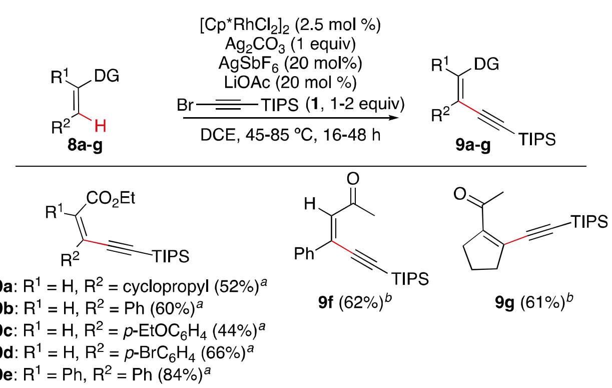
As an example of late-stage functionalization of a pharmaceutical compound, fenofibrate **6r** was alkynylated in 35% yield for the major product (Scheme 5).

Scheme 5. Late-stage Alkynylation of Fenofibrate



[a] Standard conditions for the Rh-catalyzed reaction using 2 equiv of bromoalkyne, at 50 °C, 14 h.

Scheme 6. Alkynylation of Vinyl C-H Bonds

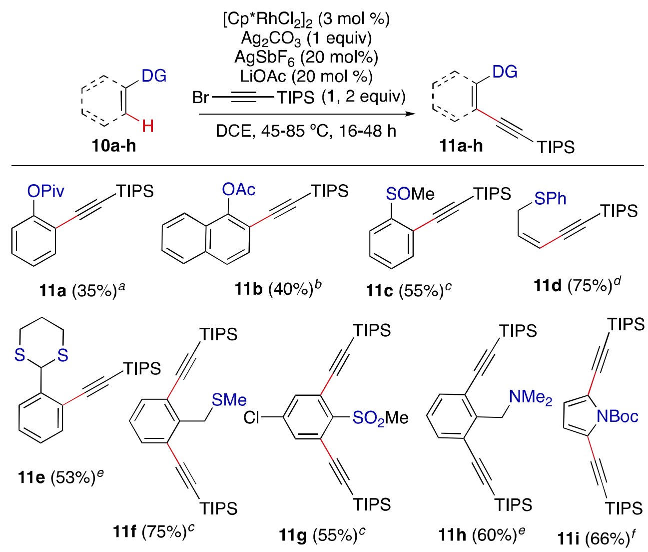


Conditions: [a] 85 °C 48 h, (2 equiv **1**). [b] 45 °C, 16 h (1 equiv **1**).

Stereocontrolled synthesis of conjugated enynes or acyclic tri- and tetra-substituted alkenes is a longstanding challenge in organic chemistry.[25] We were pleased to find that the alkynylation of vinyl C-H bonds of *α,β*-unsaturated esters **8a-e** and ketones **8f-g** proceeded under the standard conditions at 45-85 °C to afford a series of *Z*-configured 1,3-enynes **9a-g** in 44-84% yield, with total control of the stereoselectivity (Scheme 6).

Other Directing Groups. With slight modification of the reaction conditions, we discovered that other functional groups are viable chelating groups (Scheme 7). As rare examples of the use of simple phenol ester as directing group,[23] the *ortho*-alkynylation of phenol pivalate (**10a**) and 1-naphtol acetate (**10b**) led to **11a-b** in moderate yields. Although considered to bind too tightly to metals to be involved in catalytic processes, strongly coordinating groups could also be used under similar conditions. Thus, the reaction proceeds on substrates bearing sulfoxide, thioether, thioacetal, sulfone, or tertiary amine functional groups, giving products **11c-h** in 53-75% yield. Boc-protected pyrrole **10i** could also be dialkynylated to give product **11i** in 66% yield.

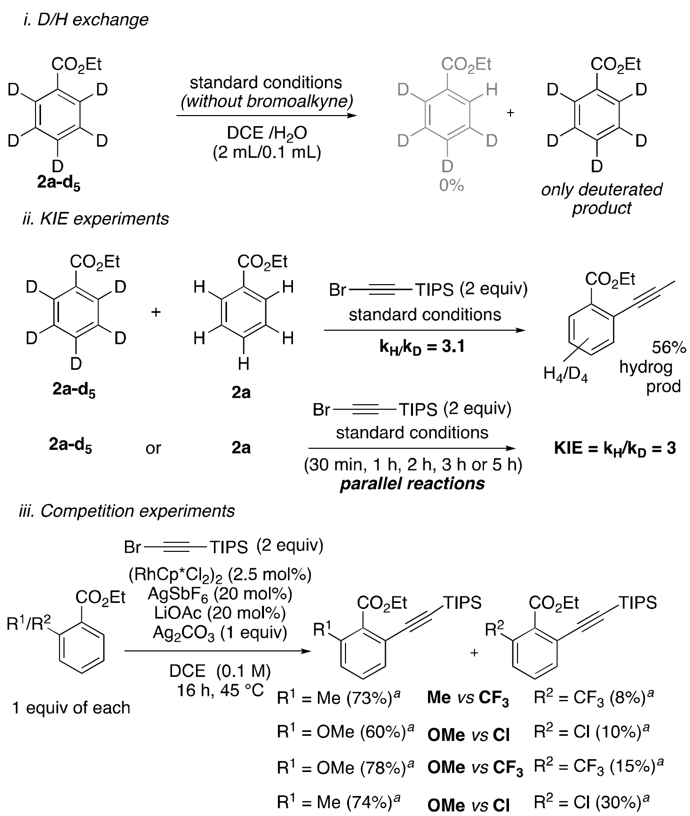
Scheme 7. Rhodium-Catalyzed C(sp2)-H Alkynylation with Other Directing Groups



Conditions: [a] 90 °C, 72 h. [b] 70 °C, 24 h. [c] 100 °C, 16 h. [d] 50 °C, (**1**, 1.1 equiv), 16 h [e] 90 °C, 16 h. [f] 45 °C, 16 h.

Mechanistic studies. Several experiments were carried out in order to shed light on the reaction mechanism. First, the C–H functionalization step was found to be irreversible according to the reaction of **2a-d$_5$** in the presence of water and in the absence of bromoalkyne **1** (Scheme 8, i). The intermolecular and parallel competition experiments between deuterated and hydrogenated labelled substrates (Scheme 8, ii) showed the same kinetic isotope effect (KIE = 3.1) in both cases, indicating that the C-H bond cleavage probably occurs in the rate-determining step of the catalytic cycle,[26] which is consistent with related rhodium-catalyzed C-H-functionalizations.[27] Finally, the intermolecular competition between electron rich and electron poor substrates (Scheme 8, iii) suggests that substrates bearing electron donating groups (Me or MeO) at the *meta* position of the C-H functionalization site are more reactive. This result indicates that the C-H-functionalization step might occur through an electrophilic aromatic substitution-type mechanism.[12b,28]

Scheme 8. D/H Exchange, Kinetic, and Competition Experiments[24]



[a] Yield of the monoalkynylated product determined by ^{1}H NMR using bromomesitylene as internal standard.

A Hammett correlation was found (R^2 = 0.99 using σ_p^+) for *meta*-substituted substrates (Figure 1).[29] A negative ρ value also suggests that electron density decreases at the aryl ring in the product-determining step, which is in accordance with a C-H functionalization step occurring through an electrophilic aromatic substitution-type mechanism.

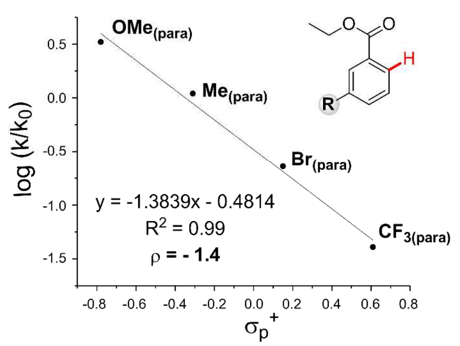
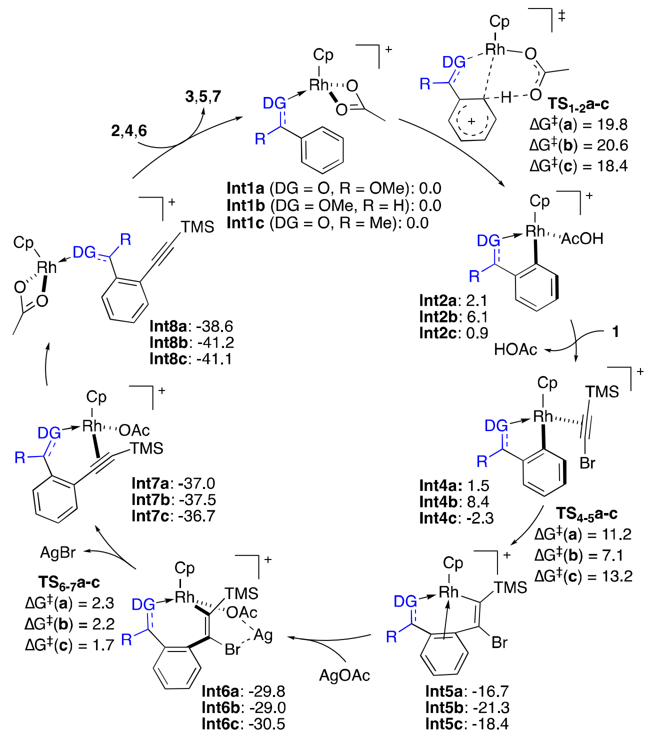


Figure 1. Hammett Plot for the Reaction of m-Substituted Benzoates[24]

To get a deeper insight into the reaction mechanism, we performed DFT calculations (Scheme 9).[30,31] According to our studies, the C-H functionalization of methyl benzoate (**2b**) proceeds from **Int1a** by the intramolecular assistance of the acetate ligand through the 6-membered cyclic transition state **TS$_{1-2}$a** ($\Delta G^‡$ = 19.8 kcal/mol). The alternative 4-membered cyclic transition state ($\Delta G^‡$ = 34.6 kcal/mol) or the intermolecular acetate-assisted C-H activation ($\Delta G^‡$ = 51.2 kcal/mol) would require much higher energy barriers.[24,32]

The resulting **Int2a** undergoes dissociative ligand exchange with bromoacetylene **1b** through **Int3a** (not shown)[24] to form the (η^2-alkyne)rhodium complex **Int4a**. Subsequent alkyne insertion ($\Delta G^‡$ = 11.2 kcal/mol) to give **Int5a**, followed by AgOAc-assisted bromide elimination ($\Delta G^‡$ = 2.3 kcal/mol) leads to **Int7a** and then, **Int8a**. The catalytic cycle restarts upon ligand exchange, delivering the final alkynylated product **3ab** and regenerating **Int1a**.

Scheme 9. Proposed Mechanism of the Rh-Catalyzed C(sp^2)-H Alkynylation based on DFT Calculations[a]



[a] Free energies in kcal/mol.

Analysis of the Mulliken atomic charges in **Int1a**, **Ts$_{1-2}$a** and**Int2a**[24] shows that the process involves an ambiphilic metal ligand activation.[32e] Both an electrophilic metal center and an intramolecular basic ligand are key for the heterolytic scission of the C-H bond and formation of the C-Rh bond (Figure 2). In **TS$_{1-2}$a**, the carbon involved in the C-H activation shows a certain sp^3 character (the Rh-C-H angle is 73.8 °).[24] The C-Rh distance (2.23 Å) in **TS$_{1-2}$a** is slightly longer to that of the metallacycle **Int2a** (2.02 Å), whereas the C-H distance is lengthened from 1.09 Å in **Int1a** to 1.30 Å in **TS$_{1-2}$a**, which suggests that the formation of the Rh-C bond preceeds the cleavage of the C-H bond in a concerted, but asynchronous process.

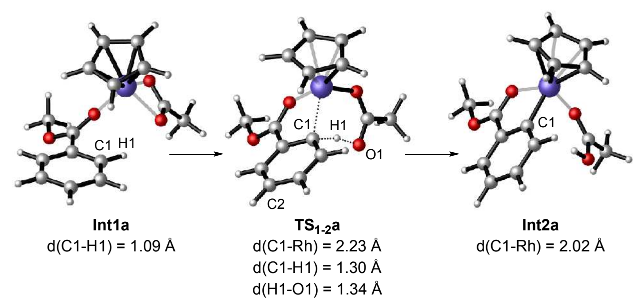
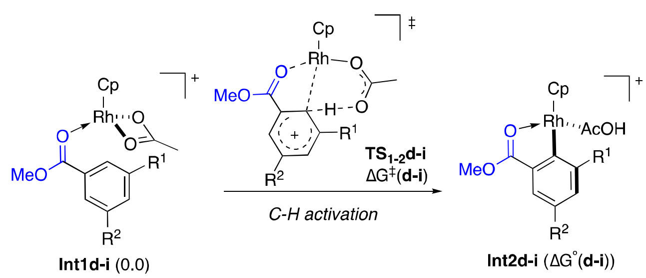


Figure 2. Calculated Structures for the C-H Activation via $TS_{1\text{-}2}$a.[24]

Alternative alkynylation pathways were also considered, although they proved to be less favored.[24] For instance, the oxidative addition of the C(sp)-Br bond to the metal center in **Int4a** to form a Rh(V) intermediate[33] demands a highly unlikely activation energy of 41.6 kcal/mol. Based on the computed energies, the C-H metalation is the rate-determining step, which is in agreement with the experimental results. Similar energy profiles were found in the case of methyl benzyl ether **4a** (Scheme 9, pathway **b**) and acetophenone **6k** (Scheme 9, pathway **c**) which means that the same reaction mechanism presumably operates for them.[24] Consistently with the experimental results, among the different substrates, the C-H functionalization of the ketones is the most energetically favored ($\Delta G^{\ddagger}$ = 18.4 kcal/mol), whereas the corresponding to the benzyl ethers is the most energetically costly ($\Delta G^{\ddagger}$ = 20.6 kcal/mol).

In addition, the C-H activation step was computed for differently *m*-substituted methyl benzoates to study the influence of the electronic effects on the energy barrier. Calculations showed that the more electron-rich the substituent is, the lower the activation energy results (Table 2, entries 1-4). This is in total agreement with the experimental results observed for *m*-substituted ethyl benzoates (Figure 1) and supports an electrophilic substitution-type mechanism for the formation of the five-membered ring rhodacycle.

Table 2. Substituent effect in the Activation Energy of the C-H Activation of Benzoates[a]



Entry	R^1	R^2	$TS_{1\text{-}2}$d-i	$\Delta G^{\ddagger}$ (d-i)	Int2d-i	ΔG° (d-i)
1	H	OMe	**$TS_{1\text{-}2}$d**	17.2	**Int2d**	2.9
2	H	Me	**$TS_{1\text{-}2}$e**	18.9	**Int2e**	3.3
3	H	Br	**$TS_{1\text{-}2}$f**	20.8	**Int2f**	3.1
4	H	CF_3	**$TS_{1\text{-}2}$g**	21.5	**Int2g**	3.4
5	H	F	**$TS_{1\text{-}2}$h**	19.5	**Int2h**	2.5
6	F	H	**$TS_{1\text{-}2}$i**	17.8	**Int2i**	2.7

[a] Free energies in kcal/mol.

In the case of *m*-fluoro benzoate, the C-H activation preferentially occurs at the *ortho*- ($\Delta G^{\ddagger}$ = 17.8 kcal/mol, Table 2, entry 6) rather than the *para*-position ($\Delta G^{\ddagger}$ = 19.5 kcal/mol, Table 2, entry 5) respect to the fluoro substituent. This *ortho* fluorine-effect has been experimentally observed with fluoro-*meta*-substituted benzoate **3j** (Scheme 2) or benzyl ether compounds **5m** (Scheme 3), as the metal-carbon bond strength would be increased at this position.[34]

CONCLUSIONS

In summary, we have found that alkynylation of benzyl methyl ethers, aryl esters and aryl ketones can be carried out using rhodium catalysis in a general manner. This is the first report of a broad-range *ortho*-C-H functionalization of weakly-coordinating benzyl ethers. The Rh-catalyzed alkynylation of aryl esters and aryl ketones takes place under milder conditions (45-70 °C for esters and 25-90 °C for ketones) than those recently reported using Ir catalysis (120 °C). The alkynylation of vinyl C-H bonds of α,β-unsaturated esters and ketones is also possible using rhodium catalysis. Furthermore, other uncommon functional groups such as amine, thioether, thioacetal, sulfoxide, sulfone, phenol ester, and carbamate can also be used as directing group for the alkynylation. Our mechanistic study shows that the alkynylation reaction proceeds by a turn-over limiting C-H activation step via an electrophilic-type substitution, followed by insertion of the bromoalkyne and bromide elimination.

ASSOCIATED CONTENT

Supporting Information.

The Supporting Information is available free of charge on the ACS Publications website.

Additional details, experimental procedures, characterization data for compounds and computational results (PDF).

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Notes

No competing financial interests have been declared.

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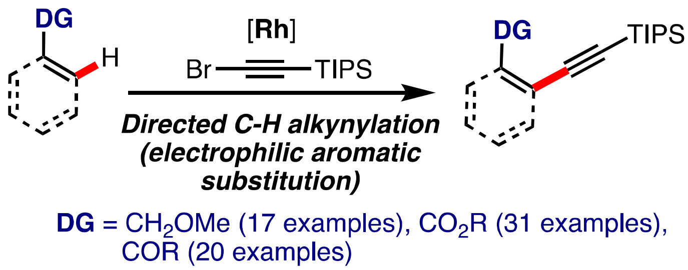
Table of Contents graphic:



Keywords : C−H Activation, Alkynylation, Rhodium catalysis, Weakly coordinating groups, Synthetic method, DFT calculations.