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

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Supporting Information

ABSTRACT: We report the alkylation 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 turnover-limiting C–H activation step via an electrophilic-type substitution.

KEYWORDS: alkylation, rhodium catalysis, C–H functionalization, inverse Sonogashira, metallacycle, Hammett correlation, DFT

INTRODUCTION

Alkynes are among the most versatile functional groups and are widely present in natural products, drugs, and organic materials. 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. 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 alkynyl (pseudo)halides and terminal alkynes. 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 alkylation of C(sp²)–H bonds with terminal alkynes or activated acetylenes such as ethynylbenziodoxolone (EBX) reagents or haloalkynes using transition-metal catalysts. Often named inverse-Sonogashira coupling, this methodology relies on the reactivity of electronically activated (hetero)arenes or on a chelating group to assist a C–H activation process. 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 a Friedel–Crafts type reaction. The latter has been achieved for both arenes and alkynes with a variety of directing groups, typically amides or nitrogen coordinating groups such as heterocycles or imine derivatives (oxime, nitro, azomethine). The applicability of this strategy in multistep 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.

Toward this goal, we recently reported a general peri-alkylation of naphthols using ruthenium catalysis. Benzoic acids can also be alkynylated at the ortho position, although the use of other versatile O functionalities as directing groups is still limited, mainly due to the challenging formation of a weakly coordinated metallocyclic intermediate. In particular, despite intense efforts in the field of catalytic C(sp²)–H functionalization, only two examples of the use of benzyl ether as a directing group have been reported in the context of C–H borylation.

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

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*RhCl₂]₂ (2.5 mol %), AgSbF₆ (20

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mol %), Ag₂CO₃ (1 equiv), and 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 Ag₂CO₃ to 0.5 equiv or replacing this silver salt by K₂CO₃ (Table 1, entries 4 and 5). Solvents different from DCE led to poor results (Table 1, entries 6−11). The use of other bromoalkynes, such as (bromoethyl)benzene and 1-bromoocetone, led to no conversion.

Although treatment of benzyl methyl ether (4a) with bromoacetylene 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*RhCl₂]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.

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 NO₂, CF₃, and different 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 Ag₂CO₃ to 0.5 equiv or replacing this silver salt by K₂CO₃ (Table 1, entries 4 and 5). Solvents different from DCE led to poor results (Table 1, entries 6−11). The use of other bromoalkynes, such as (bromoethyl)benzene and 1-bromoocetone, led to no conversion.

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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,l favor formation of the 1,2,3-trisubstituted compounds 3j,l respectively.

The alkylation 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,w in 23−90% yield. In the case of meta-substituted substrates 2i,k,m, the alkylation occurred at the least sterically hindered site. However, fluoro and methoxy derivatives 2j,l favor formation of the 1,2,3-trisubstituted compounds 3j,l respectively.

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Stereocontrolled synthesis of conjugated enynes or acyclic tri- and tetrasubstituted alkenes is a longstanding challenge in organic chemistry. We were pleased to find that the alkynylation of vinyl C−H bonds of αβ-unsaturated esters and ketones proceeded under the standard conditions at 45−85 °C to afford a series of Z-configured 1,3-enynes 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 a simple phenol ester as a directing group, the ortho alkynylation of phenol pivalate and 1-naphthol acetate led to in moderate yields. Although they are 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, and tertiary amine functional groups, giving products 11c−h in 53−75% yield. Boc-protected pyrrole could also be dialkynylated to give product 11i in 66% yield.

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 in the presence of water and in the absence of bromoalkyne 1 (Scheme 8i). The intermolecular...
acetate ligand through the six-membered cyclic transition state \( \text{TS}_{1-2a} \) \( (\Delta G^\ddagger = 19.8 \text{ kcal/mol}) \). The alternative four-membered cyclic transition state \( (\Delta G^\ddagger = 34.6 \text{ kcal/mol}) \) or the intermolecular acetate-assisted C–H activation \( (\Delta G^\ddagger = 51.2 \text{ kcal/mol}) \) would require much higher energy barriers.\(^{24,32}\) The resulting \( \text{Int2a} \) undergoes dissociative ligand exchange with bromoacetylene \( 1b \) through \( \text{Int3a} \) (not shown) to form the (\( \eta^2 \)-alkyne)rhodium complex \( \text{Int4a} \). Subsequent alkyne insertion \( (\Delta G^\ddagger = 11.2 \text{ kcal/mol}) \) to give \( \text{Int5a} \) by AgOAc-assisted bromide elimination \( (\Delta G^\ddagger = 2.3 \text{ kcal/mol}) \) leads to \( \text{Int7a} \) and then \( \text{Int8a} \). The catalytic cycle restarts upon ligand exchange, delivering the final alkynylated product \( 3ab \) and regenerating \( \text{Int1a} \).

Analysis of the Mulliken atomic charges in \( \text{Int1a} \), \( \text{TS}_{1-2a} \), and \( \text{Int2a} \)\(^{24}\) shows that the process involves an ambiphilic metal ligand activation.\(^{24}\) 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

Figure 2. Calculated structures for the C–H activation via \( \text{TS}_{1-2a} \).\(^{24}\)

\( \text{TS}_{1-2a} \), the carbon involved in the C–H activation shows a certain sp\(^3\) character (the Rh–C–H angle is 73.8°).\(^{24,32}\) The C–Rh distance (2.23 Å) in \( \text{TS}_{1-2a} \) is slightly longer than that of the metallacycle \( \text{Int2a} \) (2.02 Å), whereas the C–H distance is lengthened from 1.09 Å in \( \text{Int1a} \) to 1.30 Å in \( \text{TS}_{1-2a} \), which suggests that the formation of the Rh–C bond precedes the cleavage of the C–H bond in a concerted, but asynchronous, process.

Alternative alkylation pathways were also considered, although they proved to be less favored.\(^{24,33}\) For instance, the oxidative addition of the C(sp\(^3\))–Br bond to the metal center in \( \text{Int4a} \) to form a Rh(V) intermediate\(^{33}\) demands a highly unlikely activation energy of 41.6 kcal/mol. On the basis of the computed energies, the C–H metatallaion 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.\(^{24}\) Consistent with the experimental results, among the different substrates, the C–H functionalization of the ketones is the most energetically favored \( (\Delta G^\ddagger = 18.4 \text{ kcal/mol}) \), whereas the corresponding to the benzyl ethers is the most energetically costly \( (\Delta G^\ddagger = 20.6 \text{ kcal/mol}) \).

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

In the case of m-fluorobenzoate, the C–H activation preferentially occurs at the ortho (ΔG° = 17.8 kcal/mol, Table 2, entry 6) rather than the para position (ΔG° = 19.5 kcal/mol, Table 2, entry 5) respect to the fluoro substituent. This o-fluorine effect has been experimentally observed with m-fluoro-substituted benzoate 3j (Scheme 2) or benzyl ether compound 5m (Scheme 3), as the metal–carbon bond strength would be increased at this position.34

■ CONCLUSIONS

In summary, we have found that the alkylation 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 o–C–H functionalization of weakly coordinating benzyl ethers. The Rh-catalyzed alkylation of aryl esters and aryl ketones takes place under milder conditions (45–70 °C for esters and 25–90 °C for ketones) in comparison to those recently reported using Ir catalysis (120 °C). The alkylation 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, thiocarbonyl, thiaal, sulfoxide, sulfone, phenol ester, and carbamate can also be used as directing groups for the alkylation. Our mechanistic study shows that the alkylation reaction proceeds by a turnover-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 at DOI: 10.1021/acscatal.7b04395.

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

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Notes

The authors declare no competing financial interest.

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