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Directing group assisted rhodium catalyzed *meta*-C–H alkynylation of arenes†

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Site-selective C–H alkynylation of arenes to produce aryl alkynes is a highly desirable transformation due to the prevalence of aryl alkynes in various natural products, drug molecules and in materials. To ensure site-selective C–H functionalization, directing group (DG) assisted C–H activation has been evolved as a useful synthetic tool. In contrast to DG-assisted *ortho*-C–H activation, distal *meta*-C–H activation is highly challenging and has attracted significant attention in recent years. However, developments are majorly focused on Pd-based catalytic systems. In order to diversify the scope of distal *meta*-C–H functionalization, herein we disclosed the first Rh(I) catalyzed *meta*-C–H alkynylation protocol through the inverse Sonogashira coupling reaction. The protocol is compatible with various substrate classes which include phenylacetic acids, hydrocinnamic acids, 2-phenyl benzoic acids, 2-phenyl phenols, benzyl sulfonates and ether-based scaffolds. The post-synthetic modification of *meta*-alkynylated arenes is also demonstrated through DG-removal as well as functional group interconversion.

Transition metal catalyzed C–H activation has evolved as a powerful synthetic tool as it offers a simplified route to incorporate several functional groups by converting the inert C–H bond into various carbon–carbon or carbon–heteroatom bonds.[1] The key to success in molecular diversification through C–H bond activation require recognition of a selective C–H bond amongst multiple C–H bonds.[2] Directed C–H activation in this regard provides a unique solution to ensure site-selective C–H activation in a predictable manner.[3] Directing ability of an attached functional group to accommodate transition metal catalysts to the closest proximity of the desired C–H bond ensured site-selective C–H functionalization. However, the progress of directed C–H activation is majorly centered around *ortho*-C–H activation, which typically proceeds *via* five- to seven-membered metallacyclic intermediates.[4] Nevertheless, distal *meta*-C–H functionalization[5] aided by directing group assistance has recently attracted significant attention.[6] The formation of a large macrocyclic pre-transition state (usually greater than 11-membered) is the prerequisite criterion to be successful in site-selective distal C–H activation.[7]

As far as *meta*-C–H activation is concerned, a "U-shaped" template was elegantly designed by the group of Yu to achieve selective *meta*-C–H activation relying on the linear, end-on, weak coordinating ability of nitrile-based directing groups.[8] Based on this seminal report, various nitrile-based templates were developed by Tan,[9a] Li[9b] and us[9c] to accomplish majorly *meta*-C–H olefination reaction. Later, our group developed a strong σ-coordinating pyrimidine-based directing group which allowed several functional groups to be incorporated selectively at the *meta*-position with different classes of substrates.[10] Despite the success in achieving various *meta*-selective functionalizations utilizing both weak and strong coordinating directing templates, developments were majorly focused on systems formed by the combination of the Pd-catalyst and MPAA-ligands (MPAA: mono-protected-amino acid).[11] Considering the rapid resurgence in template assisted *meta*-C–H functionalization under transition metal catalyzed conditions other than the Pd–MPAA catalytic system, we are intrigued to develop Rh-catalyzed methods for various *meta*-C–H functionalizations. In this context, Rh-catalyzed *meta*-C–H alkenylation using activated alkenes was achieved by the group of Yu[12] and us[13] in 2017 (Scheme 1a). In 2019, the Yu group also demonstrated *meta*-C–H alkenylation of hydrocinnamic acids using internal alkynes (Scheme 1b).[14] However, the wide applicability of Rh-catalysis for regioselective distal C–H functionalization[15] is yet to be explored. We, thus, became interested in examining the feasibility of *meta*-selective alkynylation reaction with the Rh-catalyst (Scheme 1c).

Alkynylation of arenes has been a reaction of great interest due to the ubiquity of aryl alkynes in various natural products, agrochemicals, pharmaceuticals, and in materials.[16] In addition to that, alkynes are considered as one of the most versatile synthons as they can serve as a transformative handle for further functionalization (through cycloaddition reaction, cross

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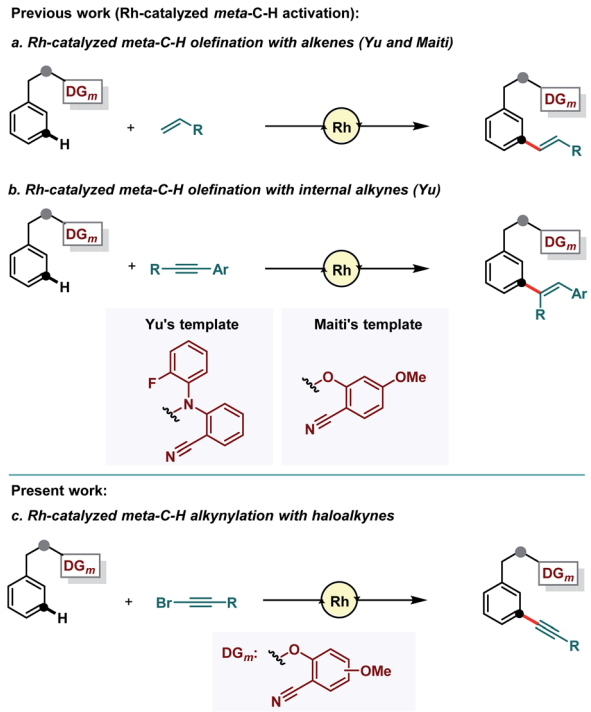


Scheme 1 Rh-catalyzed *meta*-C–H functionalization.

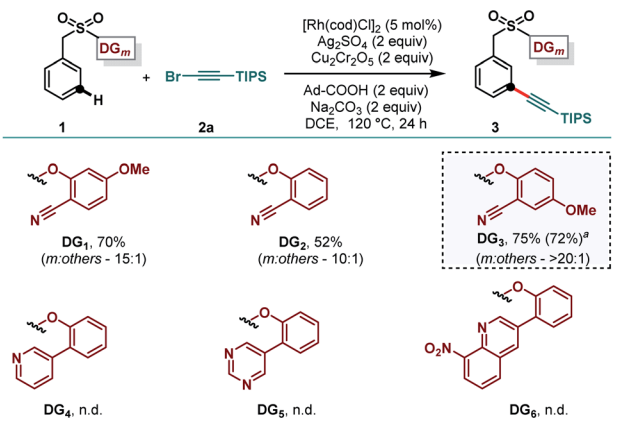
coupling reaction, metathesis reaction and many more).[17] Importantly, alkynes provide a linear and rigid spacer in molecular arrangement. Therefore, regioselective alkynylation of arenes would play a beneficial role in developing new materials, pharmaceuticals and other valuable compounds, where two presently known components can be attached through the C–C triple bond and a new drug or materials could be synthesized with improved activity. Despite the enormous success of the traditional Sonogashira coupling reaction in generating aryl alkynes,[18] direct C(sp^2)–H alkynylation is an extremely useful method as it precludes the use of pre-functionalized arenes.[19,20] Encouraged by the prospect of direct C(sp^2)–H alkynylation, we have developed a Pd-catalyzed *meta*-C–H alkynylation protocol using a pyrimidine-based directing group.[11g] In order to diversify the scope of template assisted *meta*-C–H functionalization involving transition metal catalysts other than palladium, herein we report *meta*-C–H alkynylation of structurally different classes of arenes *via* the inverse Sonogashira coupling reaction utilizing the Rh(I)-catalyst.

Benzyl sulfonate ester (**1**) embedded with 2-hydroxy-4-methoxybenzonitrile (**DG_1**), and (bromoethynyl)triisopropylsilane (**2a**) was chosen as the model substrate and alkynylating reagent, respectively, to test the feasibility of the *meta*-selective inverse Sonogashira coupling reaction.[11g] Initial attempts of *meta*-C–H alkynylation using $[Rh(cod)Cl]_2$ as the catalyst, $Cu(TFA)_2$ as the oxidant and XPhos as the ligand in DCE solvent remained unsuccessful.[13] Subsequently, different copper-based and silver-based oxidants were examined and gratifyingly in the presence of silver sulfate the desired *meta*-alkynylated compound was formed in 40% yield with moderate selectivity.[21] Further optimization of reaction parameters revealed that a combination of Ag_2SO_4 and $Cu_2Cr_2O_5$ as the oxidant was effective in delivering the desired product in 55% yield. The yield and selectivity were significantly improved while 1-adamantanecarboxylic acid was used as an additive. Careful optimization of other reaction parameters led us to produce the desired *meta*-alkynylated compounds in 70% yield and 10 : 1 *meta*-selectivity.[21] Notably, $RhCp^*Cl_2$ and $Rh_2(OAc)_4$ were ineffective in producing the expected compound in synthetically acceptable yield and selectivity. Thereafter, we examined the efficacy of previously developed *meta*-DGs. While strongly coordinating pyridine, pyrimidine and quinoline-based DGs (**DG_4** to **DG_6**) were ineffective for the present transformation, the electronically modified cyano-based **DG_3** was found to be superior in comparison to **DG_1** and **DG_2** to deliver the desired product in 72% isolated yield with improved *meta*-selectivity (Table 1).

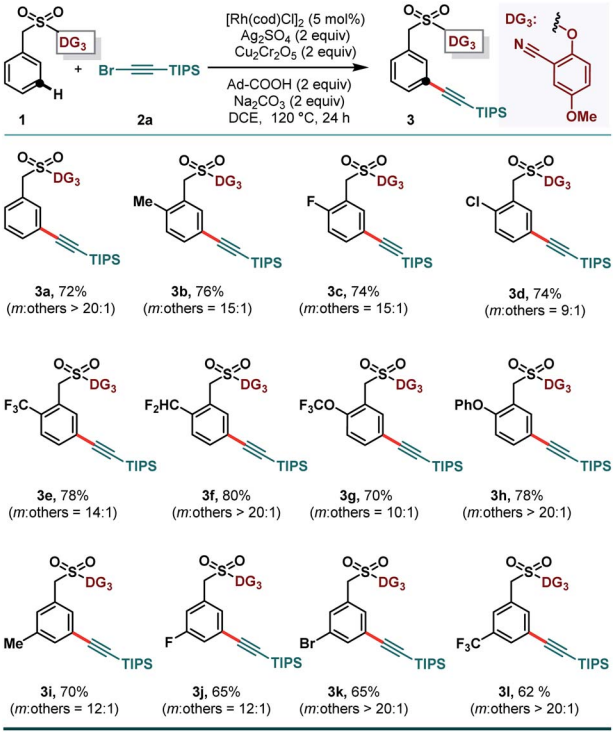
After having the optimized reaction conditions and the suitable directing group, we explored the scope of the reaction with respect to various benzyl sulfonate esters (**1**) (Scheme 2). Arenes bearing electron donating as well as electron withdrawing substituents at *ortho*- and *meta*-positions were well tolerated to deliver the desired *meta*-alkynylated products in synthetically useful yields and selectivity. Notably, *ortho*-chloro and *meta*-bromo substrates (**1d** and **1k**, respectively) were also compatible under the reaction conditions to produce *meta*-C–H alkynylated products without any interference, caused by the probable cross coupling reaction.

The versatility of the developed protocol was further demonstrated with phenylacetic acid, hydrocinnamic acid and benzoic acid derivatives (**4**) (Scheme 3). Considering the prevalence of phenylacetic acid derivatives in pharmaceuticals, *meta*-selective alkynylation would render a unique opportunity to study the impact of structurally modified pharmaceutical cores. However, **DG_1** was found to be more efficacious for *meta*-C–H alkynylation of carboxylic acid derivatives. While *ortho*- and *meta*-methyl substituted phenylacetic acid derivatives (**4a** and **4c**, respectively) provided the desired *meta*-alkynylated compounds in good yields, pharmaceutically relevant

Table 1 Directing group (DG) optimization



[a] Isolated yield.

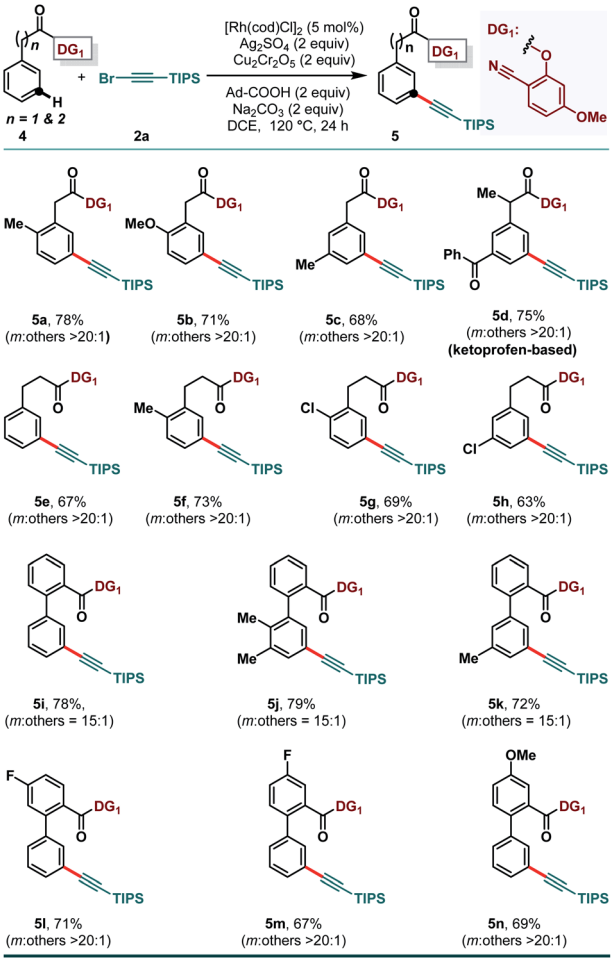


Scheme 2 Rh-catalyzed *meta*-C–H alkynylation of benzyl sulfonate esters.

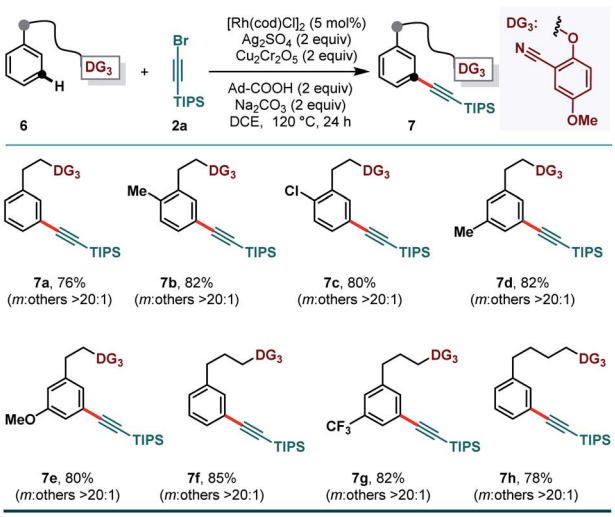
ketoprofen derived **4d** delivered the expected product (**5d**) in 75% yield. The phenylacetic acid derivative possessing the methoxy group also provided the useful yield of the *meta*-alkynylated product (**5b**) without compromising the *meta*-selectivity. The Rh-catalyzed method for *meta*-selective alkynylation was also successful with derivatized hydrocinnamic acids (**4e–4h**) and 2-phenylbenzoic acids (**4i–4n**). Notably, *ortho*-chloro and *meta*-chloro hydrocinnamic acid derivatives delivered the desired *meta*-alkynylated products (**5g** and **5h**, respectively) in good yield and selectivity.

While the distance and geometric relationship between the appended directing group and the desired site of C–H activation is the key parameter in accomplishing regioselective distal C–H activation, our developed method was efficacious in delivering the desired *meta*-selective alkynylation even when $\mathbf{DG_3}$ was tethered to the targeted arenes through flexible ether linkages. A number of substituted arenes bearing variable linker length were compatible under the reaction conditions to produce *meta*-alkynylated arenes (**7**) in excellent yield and uncompromised selectivity (Scheme 4).

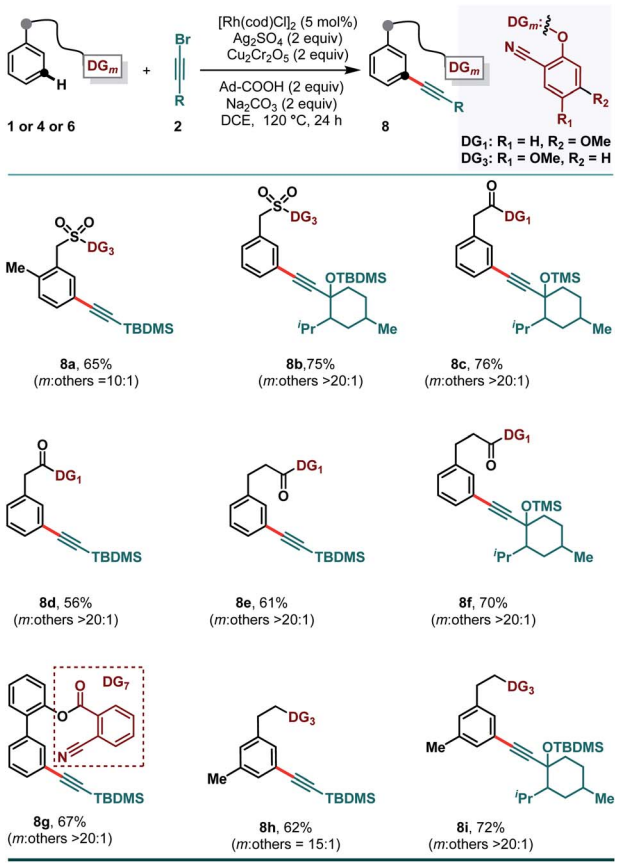
The compatibility of various classes of substrates was, thus far, examined with (bromoethynyl)triisopropylsilane (**2a**) as the alkynylating reagent. We further investigated the scope of the reaction with respect to other alkynyl bromides, derived from propargyl silyl ethers and with these derivatized alkynyl bromides the *meta*-alkynylation reaction proceeded smoothly (Scheme 5). Alkynyl bromide, derived from menthone, was easily coupled at the *meta*-position of the benzyl sulfonate scaffold (**8b**), ester derivative of phenylacetic acid (**8c**),



Scheme 3 Rh-catalyzed *meta*-C–H alkynylation of phenylacetic acids, hydrocinnamic acids and biphenyls.

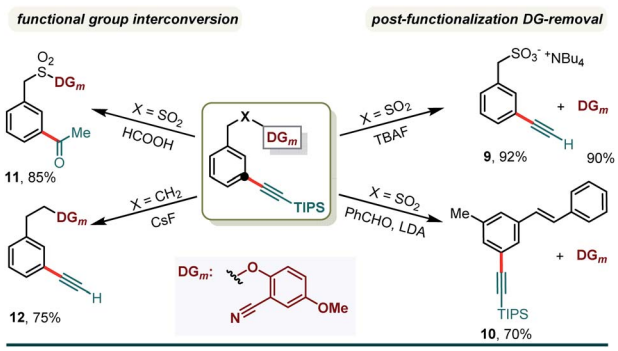


Scheme 4 Rh-catalyzed *meta*-C–H alkynylation of ethers with variable linker lengths.



Scheme 5 *meta*-C–H alkynylation with alkyne variants.

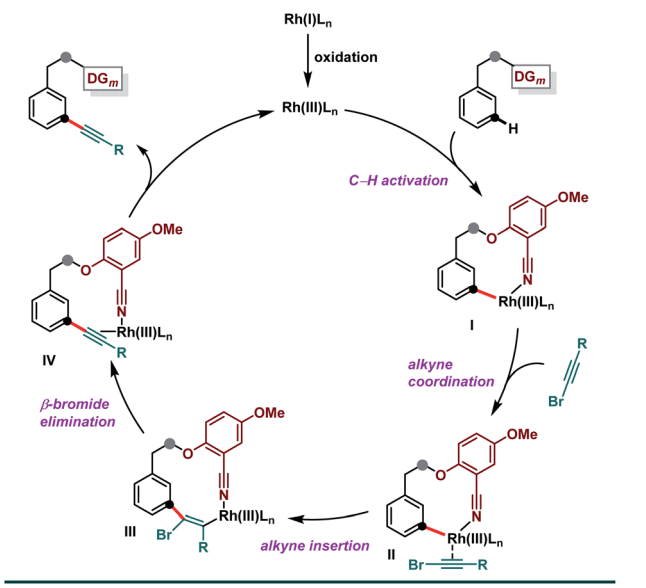
hydrocinnamic acid (**8f**), and 2-phenethyl ether (**8i**) furnishing good yields and selectivity. Importantly, *meta*-selective alkynylation of the appended arene in 2-phenyl phenol (**8g**) was also achieved in excellent yield and selectivity by embedding the 2-cyano benzoic acid ($\mathbf{DG_7}$) as the *meta*-directing group. It is worth noting that the reaction outcome in terms of yield and selectivity was not significantly impacted by the electronic nature of the substituents, establishing the fact that the directing ability of the cyano group could override the electronically controlled C–H activation.



Scheme 6 Post-synthetic modification of *meta*-functionalized arenes and DG-removal.

Post functionalization DG removal is crucial in DG-assisted C–H functionalization methods (Scheme 6). The appended *meta*-directing group was successfully cleaved producing the benzyl sulfonic acid derivative (**9**) when the corresponding *meta*-alkynylated benzyl sulfonate (**3a**) was treated with TBAF. Additionally, the sulfonate linker was modified to form a styrene derivative *via* modified Julia reaction conditions and a *meta*-alkynylated styrene (**10**) was prepared in 70% yield. In both the cases, the directing group was recovered in quantitative amount, highlighting the practicality of the developed method. As alluded earlier, alkyne is one of the versatile synthons and an acyl group was readily incorporated at the *meta*-position (**11**) *via* functional group interconversion. We majorly used TIPS-acetylene bromide as a coupling partner to introduce TIPS-acetylene, a masked ethynyl motif, at the *meta*-position. Easy removal of the triisopropyl silyl (TIPS) group resulted in the *meta*-ethynyl arene (**12**), which can be further used in the Sonogashira cross coupling reaction or in the cross dehydrogenative coupling reaction. Notably, these cross-coupling reactions would allow various structural units to be assembled, which are important pharmacophores or prevalent in materials, through a carbon–carbon triple bond.

A plausible mechanism is outlined in Scheme 7, in which *in situ* oxidation of Rh(I) to Rh(III) takes place prior to the participation of the Rh-catalyst in the catalytic process. The linear coordination of the nitrile group directs the Rh(III)-catalyst to the *meta*-C–H bond of the targeted arenes.[12,13] The *meta*-C–H activation resulted in a cyclophane type intermediate **I**, which is coordinated with bromoalkynes to produce **II**. Subsequent *syn*-insertion of alkyne to the rhodium–carbon bond would generate intermediate **III**. Further, an Ag-assisted β-bromide elimination reaction would lead to the generation of **IV**.[11g,19p] Finally, ligand exchange released the expected alkynylated product and restarted the catalytic cycle by regenerating the active Rh-catalyst.



Scheme 7 Plausible mechanism of Rh-catalyzed *meta*-C–H alkynylation.

Conclusions

In summary, an unprecedented report on Rh-catalyzed *meta*-C–H alkynylation of arenes, aided by a weakly coordinating cyano-based directing template, was developed using bromoalkynes as the coupling partner. The generality of the developed protocol was demonstrated by transforming various classes of substrates including benzyl sulfonate esters, phenyl acetic acids, elongated alkyl ethers, 2-phenyl benzoic acids and 2-phenyl phenols to the corresponding *meta*-C–H alkynylated compounds. The post-synthetic modification of the synthesized *meta*-alkynylated arenes was carried out either through the removal of the directing group or *via* functional group interconversion of the alkyne functionality. Considering the recent upsurge in site-selective distal C–H functionalization through template assistance, the present Rh-catalyzed method is expected to have a significant impact on future development.

Data availability

All experimental data, and detailed experimental procedures are available in the ESI.†

Author contributions

U. D. and D. M. conceived the project. S. S., G. P., U. D. and R. L. completed the experimental work. D. M. and G. K. L. supervised the work. All authors contributed to writing the manuscript.

Conflicts of interest

The authors declare no conflict of interest.

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