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

Sheuli Sasmal,‡ Gaurav Prakash,‡ Uttam Dutta,‡ Ranjini Laskar, Goutam Kumar Lahiri (*) and Debabrata Maiti (‡)*

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-alkynylation 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 functionalization5 aided by directing group assistance has recently attracted significant attention.6 The formation of a large macroyclic 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,9 Li10 and us11 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.12 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 Yu13 and us14 in 2017 (Scheme 1a). In 2019, the Yu group also demonstrated meta-C–H alkenylation of hydrocinnamic acids using internal alkenes (Scheme 1b).15 However, the wide applicability of Rh-catalysis for regioselective distal C–H functionalization16 is yet to be explored. We, thus, became interested in examining the feasibility of meta-selective alkenylation reaction with the Rh-catalyst (Scheme 1c).

Alkenylation 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...
c coupling reaction, metathesis reaction and many more). Importantly, alkynes provide a linear and rigid spacer in molecular arrangement. Therefore, regioselective alkylation 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, direct C(sp2)–H alkylation is an extremely useful method as it precludes the use of pre-functionalized arenes.18 Encouraged by the prospect of direct C(sp2)–H alkylation, we have developed a Pd-catalyzed meta-C–H alkylation protocol using a pyrimidine-based directing group.19 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 alkylation 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 (DG1), and (bromomethyl)trisopropylsilane (2a) was chosen as the model substrate and alkylation reagent, respectively, to test the feasibility of the meta-selective inverse Sonogashira coupling reaction.19e Initial attempts of meta-C–H alkylation 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-alkylated compound was formed in 40% yield with moderate selectivity.21 Further optimization of reaction parameters revealed that a combination of Ag2SO4 and Cu2Cr2O5 as the oxidant was effective in delivering the desired product in 55% yield. The yield and selectivity were significantly improved while 1-adamantane carboxylic acid was used as an additive. Careful optimization of other reaction parameters led us to produce the desired meta-alkylated compounds in 70% yield and 10 : 1 meta-selectivity. Notably, RhCp*Cl2 and Rh2(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 (DG4 to DG6) were ineffective for the present transformation, the electronically modified cyano-based DG1 was found to be superior in comparison to DG1 and DG2 to deliver the desired product in 72% isolated yield with improved meta-selectivity (Table 1).

Table 1 Directing group (DG) optimization

| DG | Yield | Selectivity |
|----|-------|-------------|
| DG1 | 70% | 90:10 |
| DG2 | 52% | 80:20 |
| DG3, DG4 | 70% | 90:10 |
| DG5, DG6 | n.d. | n.d. |

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-alkylated 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 alkylnylated 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 alkylation would render a unique opportunity to study the impact of structurally modified pharmaceutical cores. However, DG1 was found to be more efficacious for meta-C–H alkylation of carboxylic acid derivatives. While ortho- and meta-methyl substituted phenylacetic acid derivatives (4a and 4c, respectively) provided the desired meta-alkylated compounds in good yields, pharmaceutically relevant...
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 alkylation 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 alkylation even when DG3 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 alkylation 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-alkenylation 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 2 Rh-catalyzed meta-C–H alkylation of benzyl sulfonate esters.

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

Scheme 4 Rh-catalyzed meta-C–H alkylation of ethers with variable linker lengths.
hydrocinnamic acid (8f), and 2-phenethyl ether (8i) furnishing good yields and selectivity. Importantly, meta-selective alkylation of the appended arene in 2-phenyl phenol (8g) was also achieved in excellent yield and selectivity by embedding the 2-cyano benzoic acid (DG7) 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.

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, alkylene 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. The meta-C–H activation resulted in a cyclophane type intermediate I, which is coordinated with bromoalkynes to produce II. Subsequent syn-insertion of alkylene to the rhodium–carbon bond would generate intermediate III. Further, an Ag-assisted β-bromide elimination reaction would lead to the generation of IV. Finally, ligand exchange released the expected alkynylated product and restarted the catalytic cycle by regenerating the active Rh-catalyst.
Conclusions

In summary, an unprecedented report on Rh-catalyzed meta-C–H alkylation of arenes was carried out either through the removal of the directing group or via functional group interconversion of the alkynyl 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.

Acknowledgements

This activity is funded by SERB-India (CRG/2018/003951 for D. M.), and the J. C. Bose Fellowship (SERB, G. K. L.). Financial support received as a fellowship from IIT Bombay (to S. S.), CSIR-India (to G. P.) is gratefully acknowledged.

Notes and references

1 (a) L. McMurray, F. O. Hara and M. J. Gaunt, Chem. Soc. Rev., 2011, 40, 1885–1898; (b) J. Yamaguchi, A. D. Yamaguchi and K. Itami, Angew. Chem., Int. Ed., 2012, 51, 8960–9009; (c) X. Ribas, C–H and C–X Bond Function: Transition Metal Mediation, RSC Publishing, London, 2013; (d) J. Wencel-Delord and F. Glorius, Nat. Chem., 2013, 5, 369–375; (e) D. J. Abrams, P. A. Prowencher and E. J. Sorensen, Chem. Soc. Rev., 2018, 47, 8925–8967; (f) A. Tortajada, F. Juli-Hernandez, M. Borjesson, T. Moragas and R. Martin, Angew. Chem., Int. Ed., 2018, 57, 15948–15982; Angew. Chem., 2018, 130, 16178–16214.
2 Z. Huang and G. Dong, Acc. Chem. Res., 2017, 50, 465–471.
3 For selected references on C–H functionalizations, see: (a) J.-Q. Yu and Z. Shi, C–H Activation: Topics in Current Chemistry, Springer, New York, 2010, vol. 26; (b) A. Kapdi and D. Maiti, Strategies for Palladium-Catalyzed Non-directed and Directed C–H Bond Functionalization, Elsevier, Amsterdam, 2017.
4 Selected examples on DG assisted ortho-C–H functionalization: (a) S. Murai, F. Kakiuchi, S. Sekine, Y. Tanaka, A. Kamatani, M. Sonoda and N. Chatani, Nature, 1993, 366, 529–531; (b) T. W. Lyons and M. S. Sanford, Chem. Rev., 2010, 110, 1147–1169; (c) N. Kuhl, M. N. Hopkinson, J. Wencel-Delord and F. Glorius, Angew. Chem., Int. Ed., 2012, 51, 10236–10254; Angew. Chem., 2012, 124, 10382–10401; (d) G. Rouquet and N. Chatani, Angew. Chem., Int. Ed., 2013, 52, 11726–11743; Angew. Chem., 2013, 125, 11942–11959; (e) M. Zhang, Y. Zhang, X. Jie, H. Zhao, G. Li and W. Su, Org. Chem. Front., 2014, 1, 843–895; (f) L. Ackermann, Acc. Chem. Res., 2014, 47, 281–295; (g) Z. Chen, B. Wang, J. Zhang, W. Yu, Z. Liu and Y. Zhang, Org. Chem. Front., 2015, 2, 1107–1295; (h) Z. Huang, H. N. Lim, F. Mo, M. C. Young and G. Dong, Chem. Soc. Rev., 2015, 44, 7764–7786; (i) T. Gensch, M. N. Hopkinson, F. Glorius and J. Wencel-Delord, Chem. Soc. Rev., 2016, 45, 2900–2936; (j) B. Shrestha, P. Basnet, R. K. Dhungana, S. KC, S. Thapa, J. M. Sears and R. Giri, J. Am. Chem. Soc., 2017, 139, 10653–10656; (k) J. R. Hummel, J. A. Boerth and J. A. Eillman, Chem. Rev., 2017, 117, 9163–9227; (l) B. Li, K. Seth, B. Niu, L. Pan, H. Yang and H. Ge, Angew. Chem., Int. Ed., 2018, 57, 3401–3405; Angew. Chem., 2018, 130, 3459–3463; (m) C. Sambiagi, D. Schonbauer, R. Blieck, T. Dao-Huy, G. Pototschnig, P. Schaaf, T. Wiesinger, M. F. Zia, J. Wencel-Delord, T. Besset, B. U. W. Maes and M. Schnurch, Chem. Soc. Rev., 2018, 47, 6603–6743; (n) B. Niu, K. Yang, B. Lawrence and H. Ge, ChemSusChem, 2019, 12, 2955–2969; (o) D. Niroula, R. Sapkota, R. K. Dhungana, B. Shrestha and R. Giri, Isr. J. Chem., 2020, 60, 424–428.
5 (a) M. Tobisu and N. Chatani, Science, 2014, 343, 850–851; (b) J. Wang and G. Dong, Chem. Rev., 2019, 119, 7478–7528; (c) J. A. Leitch and C. G. Frost, Chem. Soc. Rev., 2017, 46, 7145–7153; (d) M. T. Mihai, G. R. Genov and R. J. Phipps, Chem. Soc. Rev., 2018, 47, 149–171; (e) U. Dutta, S. Maiti, T. Bhattacharya and D. Maiti, Science, 2021, 372, eabd5992; (f) S. K. Sinha, S. Guin, S. Maiti, J. P. Biswas, S. Porey and D. Maiti, Chem. Rev., 2022, 122, 5682–5841.
6 For selected reviews and publications on distal C(sp)3–H functionalizations, see: (a) A. Dey, S. K. Sinha, T. K. Achar and D. Maiti, Angew. Chem., Int. Ed., 2019, 58, 10820–10843; (b) S. Sasmal, U. Dutta, G. K. Lahiri and D. Maiti, Chem. Lett., 2020, 49, 1406–1420.
7 G. Meng, N. Y. S. Lam, E. L. Lucas, T. G. Saint-Denis, P. Verma, N. Chekshin and J.-Q. Yu, J. Am. Chem. Soc., 2020, 142, 10571–10591.
8 D. Leow, G. Li, T.-S. Mei and J.-Q. Yu, Nature, 2012, 486, 518–522.
9 (a) S. Lee, H. Lee and K. L. Tan, J. Am. Chem. Soc., 2013, 135, 18778–18781; (b) S. Li, H. Ji, L. Cai and G. Li, Chem. Sci., 2015, 6, 5595–5600; (c) M. Bera, A. Maji, S. K. Sahoo and D. Maiti, Angew. Chem. Int. Ed., 2015, 54, 8515–8519; Angew. Chem., 2015, 127, 8635–8639.
Selected examples on DG-assisted C(sp²)–H alkynylation with alkynyl halide: (a) M. Tobisu, Y. Ano and N. Chatani, Org. Lett., 2009, 11, 3250–3252; (b) Y. Ano, M. Tobisu and N. Chatani, Org. Lett., 2012, 14, 354–357; (c) M. Shang, H.-L. Wang, S.-Z. Sun, H.-X. Dai and J.-Q. Yu, J. Am. Chem. Soc., 2014, 136, 11590–11593; (d) F. Xie, Z. Qi, S. Yu and X. Li, J. Am. Chem. Soc., 2014, 136, 4780–4787; (e) H. M.-F. Viart, A. Bachmann, W. Kayitare and R. Sarpogni, J. Am. Chem. Soc., 2017, 139, 1325–1329; (f) C. Feng and T.-P. Loh, Angew. Chem., Int. Ed., 2014, 53, 2722–2726; Angew. Chem., 2014, 126, 2760–2764; (g) Y.-H. Liu, Y.-J. Liu, S.-Y. Yan and B.-F. Shi, Chem. Commun., 2015, 51, 11650–11653; (h) N. Sauermann, M. J. Gonzalez and L. Ackermann, Org. Lett., 2015, 17, 5316–5319; (i) Z.-Z. Zhang, B. Liu, C.-Y. Wang and B.-F. Shi, Org. Lett., 2015, 17, 4094–4097; (j) Y.-J. Liu, Y.-H. Liu, X.-S. Yin, W.-J. Gu and B.-F. Shi, Chem.–Eur. J., 2015, 21, 205–209; (k) P. Wang, G.-C. Li, P. Jain, M. E. Farmer, J. He, P.-X. Shen and J.-Q. Yu, J. Am. Chem. Soc., 2016, 138, 14092–14099; (l) R. Boobalan, P. Gandeepan and C.-H. Chieng, Org. Lett., 2016, 18, 3314–3317; (m) V. G. Landge, G. Jaiswal and E. Balaraman, Org. Lett., 2016, 18, 812–815; (n) Z. Ruan, S. Lackner and L. Ackermann, ACS Catal., 2016, 6, 4690–4693; (o) Z. Ruan, N. Sauermann, E. Manoni and L. Ackermann, Angew. Chem., Int. Ed., 2017, 56, 3172–3176; (p) E. Tan, O. Quinonero, M. Elena de Orbe and A. M. Echavarren, ACS Catal., 2018, 8, 2166–2172, and the references therein.

Selected examples on C(sp²)–H alkynylation other than DG-assistance: (a) I. V. Seregin, V. Ryabova and V. Gevorgyan, J. Am. Chem. Soc., 2007, 129, 7742–7743; (b) J. P. Brand, J. Charpentier and J. Waser, Angew. Chem., Int. Ed., 2009, 48, 9346–9349; Angew. Chem., 2009, 121, 9510–9513; (c) N. Matsuyama, K. Hirano, T. Satoh and M. Miura, Org. Lett., 2009, 11, 4156–4159; (d) T. de Haro and C. Nevado, J. Am. Chem. Soc., 2010, 132, 1512–1513; (e) A. S. Dudnik and V. Gevorgyan, Angew. Chem., Int. Ed., 2010, 49, 2096–2098; (f) L. Ackermann, C. Kornhaas and Y. Zhu, Org. Lett., 2012, 14, 1824–1826, and the references therein.

For detailed information, see the ESI.†