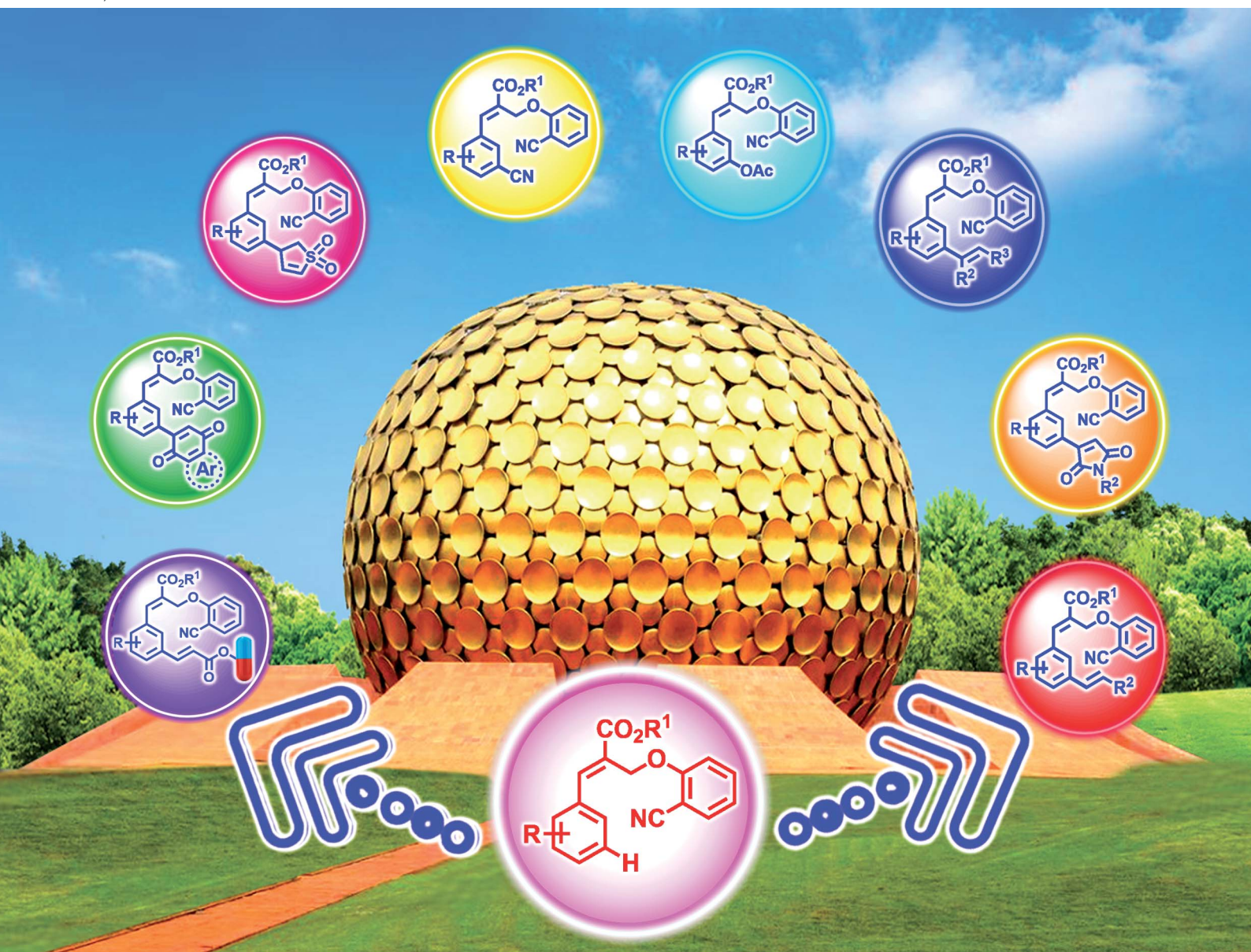


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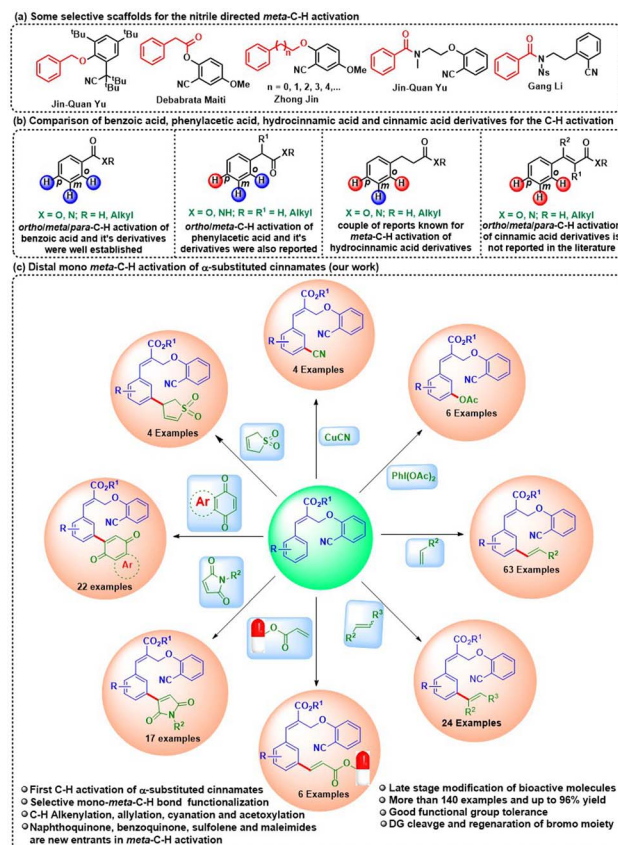
Distal *meta*-C–H functionalization of α -substituted cinnamates†

Manickam Bakthadoss¹* and Tadiparthi Thirupathi Reddy

Development of a novel strategy for the palladium-catalyzed selective *meta*-C–H activation of α -substituted cinnamates and their heterocyclic analogues with various alkenes using nitrile as a directing group (DG) has been described. Importantly, we introduced naphthoquinone, benzoquinones, maleimides and sulfolene as coupling partners in the *meta*-C–H activation reaction for the first time. Notably, allylation, acetoxylation and cyanation were also achieved through distal *meta*-C–H functionalization. This novel protocol also includes the coupling of various olefin-tethered bioactive molecules with high selectivity.

Over the last two decades, the transition metal-catalyzed functionalization of arene C–H bonds has been extensively studied using various directing groups. In particular, the *ortho*-C–H activation of arenes using various DGs is well established compared to *meta* and *para*-C–H bond activations.¹ Among various DGs, the nitrile group is employed as the DG for the *ortho*, *meta* and *para*-C–H functionalization of various arene compounds.² In the field of *meta*-C–H bond activation, various research groups such as Yu, Maiti, Jin, Tan, Li, Ackermann and others have developed a variety of scaffolds for the *meta*-C–H functionalization of aromatic compounds³ (Scheme 1a). In the C–H activation chemistry, benzoic acid derivatives have been utilized for selective *ortho*, *meta* and *para*-C–H functionalization while phenylacetic acid derivatives have been selectively utilized for *ortho* and *meta*-C–H functionalization. Similarly, hydrocinnamic acid derivatives are also utilized for *meta*-C–H functionalization. Though the C–H activation chemistry of benzoic acid, phenylacetic acid and hydrocinnamic acid derivatives was explored, the C–H activation of cinnamates was not reported in the literature (Scheme 1b). The C–H activation of the arene part of the cinnamates poses a remarkable challenge in C–H activation chemistry due to the unfavourable *transoid* geometry of the aryl moiety and ester group which can also act as a DG. To circumvent this problem, we hypothesized that a cinnamate substrate bearing a branch at the α -position that contains a directing group, which in turn will bring the arene group and DG group into close proximity, will enable the C–H bond activation of the arene group *via* metal chelation. It is important to note that having an activated double bond in the scaffold (α -substituted cinnamate) and activating

a selective arene C–H bond poses additional challenges due to interfering reactions that are associated with the reactive olefinic site of the α , β -unsaturated ester.⁴



Scheme 1 *Meta*-C–H functionalization of various scaffolds and our work.

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Moreover, the reactive double bond and DG-containing substrate for the C–H activation reaction have never been explored. Therefore, the functionalization of the arene C–H bond in cinnamates is highly challenging and a very useful endeavour in the field of organic synthesis.

Cinnamic acid derivatives are privileged scaffolds that are an integral part of many natural products and biologically active molecules. Cinnamic acid derivatives have gained a lot of interest from researchers due to their important biological activities such as antiproliferative, antiangiogenic, antitumorogenic, and antioxidant properties.⁵ Cinnamic acid derivatives such as sinapic acid, caffeic acid, ferulic acid, and isoferulic acid have been shown to have a variety of pharmacological properties, including anticancer, antioxidant, immunomodulation and anti-inflammation activities.⁶ Because of the pharmacological relevance of cinnamic acid derivatives, there has been constant interest in the synthesis and functionalization of cinnamates. Since cinnamates are not functionalised *via* the C–H activation reaction so far, we initiated our study towards a distal C–H activation of cinnamates through the DG strategy. Herein, we disclose our discovery of diversity-oriented C–H functionalization (alkenylation, allylation, acetoxylation and cyanation) of α -substituted cinnamate derivatives by using nitrile as a DG to produce a library of mono-*meta*-functionalized α -substituted cinnamates with excellent *meta*-selectivity for the first time (Scheme 1c).

To execute our idea, we have synthesized the requisite model substrate (α -substituted cinnamate **1a**) *i.e.* methyl (*E*)-2-((2-cyanophenoxy)methyl)-3-phenylacrylate from the bromo derivative of the Baylis–Hillman adduct for the *meta*-C–H activation reaction (see the ESI†). The treatment of α -substituted cinnamate scaffold **1a** with ethyl acrylate **2a** as a coupling partner in the presence of palladium acetate (10 mol%), mono protected amino acid as a ligand (Form-Gly-OH, 40 mol%) and silver acetate (2 equiv.) as an oxidant in HFIP solvent at 80 °C for 24 h provided the *meta*-coupled product **3a** in low yield (20%) with high selectivity (*m* : others = 93 : 7). To improve the yield of the reaction, we screened various catalysts, ligands, oxidants and solvents (see the ESI†). The best result (72%, *m* : others = 95 : 5) was obtained when we performed the reaction with Pd(OAc)₂ (10 mol%), Ac-Gly-OH (40 mol%) and AgOAc (2 equiv.) in HFIP solvent at 80 °C for 12 h. Additionally, we also screened other directing groups having aldehyde, ketone and nitro functionalities for the *meta*-C–H activation reaction. Unfortunately, we did not obtain the desired product in any of the cases (see the ESI†). Therefore, we started our further studies with the nitrile group as the directing group which provided the desired *meta*-C–H activation product **3a** in 72% yield. Encouraged by this result, we explored the scope of various alkene coupling partners with **1a** under the optimized reaction conditions. Accordingly, first, we employed several acrylates **2a–j** with **1a** and obtained the corresponding mono-alkenylated products **3a–j** in very good yields (60–83%) with high *meta*-selectivity (Table 1). The electron-withdrawing acrylates containing alkyl, aryl and benzyl groups (**3e–j**) of differing complexities were well tolerated. Even symmetrical and unsymmetrical internal alkenes such as maleates (**2k–m**), *trans*-cinnamaldehyde (**2n**), methyl cinnamate (**2o**) and benzylideneacetone (**2p**) also delivered the desired *meta*-C–H olefinated products (**3k–**

Table 1 *Meta*-C–H olefination of **1a** with various alkenes^a

Alkene (2)	Product (3)	Yield (%)	<i>m</i> : others
2a	3a	72	95 : 5
2b	3b	70	96 : 4
2c	3c	66	95 : 5
2d	3d	69	100 : 0
2e	3e	74	98 : 2
2f	3f	78	94 : 6
2g	3g	71	84 : 16
2h	3h	73	86 : 14
2i	3i	83	94 : 6
2j	3j	60	96 : 4
2k	3k	81	100 : 0
2l	3l	82	100 : 0
2m	3m	86	100 : 0
2n	3n	66	90 : 10
2o	3o	63	86 : 14
2p	3p	68	88 : 12
2q	3q	60	93 : 7
2r	3r	64	90 : 10

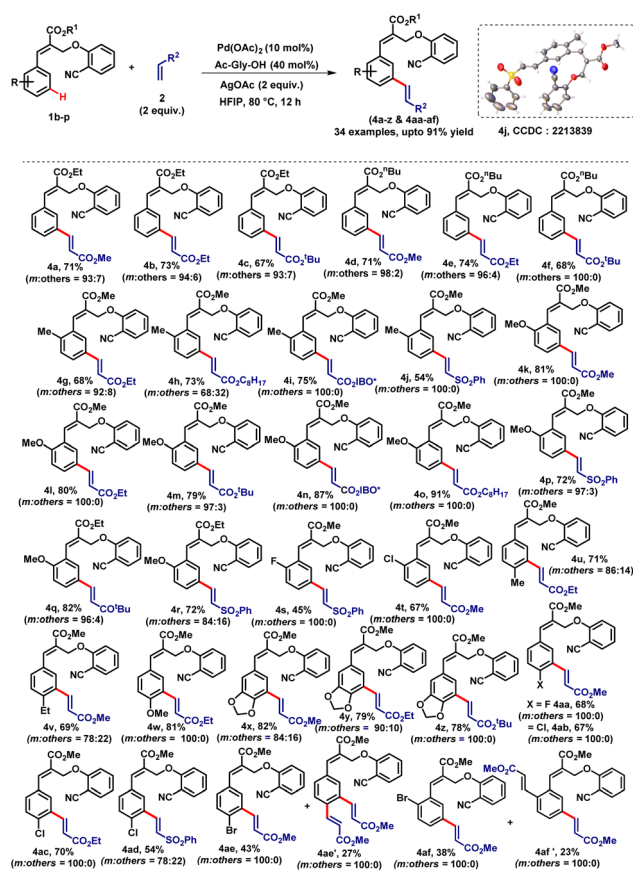
^a Isolated yields. The isomeric ratio was determined by ¹H-NMR.

p) in very good yields (63–86%) with excellent *meta*-selectivity. Notably, di-substituted *trans*-olefinic coupling partners (**2n–p**) provided the *meta*-C–H activation products **3n–p** (Table 1) with *E* and *Z* isomers where the *E* isomer was found to be the major isomer. This selectivity clearly indicates that the selective *E*-double bond formation is thermodynamic in origin. Interestingly, olefins such as methyl vinyl ketone (**2q**) and phenyl vinyl sulfone (**2r**) also worked well and led to the corresponding *meta*-coupled products **3q** and **3r** in 60% and 64% yields respectively. The compound **3a** was further confirmed by single-crystal X-ray diffraction analysis.

To study the substrate scope, we prepared various α -substituted cinnamates (**1b–p**) and treated them with different types of coupling partners (**2**) under the optimized reaction conditions which smoothly afforded the desired distal *meta*-coupled products (**4a–z** & **4aa–af**) in very good yields with high *meta*-selectivity (Table 2). We observed that the electron-donating substituents on arene worked well and smoothly led to the mono *meta*-olefinated products. The halogen containing substrates also provided the mono *meta*-olefinated products with good yields. Notably, *ortho*-substituted cinnamates provided *meta*-coupled products (**4g–t**) with excellent regioselectivity by reacting at the less hindered position. The *ortho* and *para* bromo cinnamate derivatives afforded the *meta*-olefinated products **4ae** and **4af** in 43% and 38% yields along with the interesting diolefinated products **4ae'** and **4af'** in 27% and 23% yields respectively *via* sequential C–H activation and Heck coupling reactions. The structure of compound **4j** was further confirmed by single-crystal X-ray diffraction analysis.

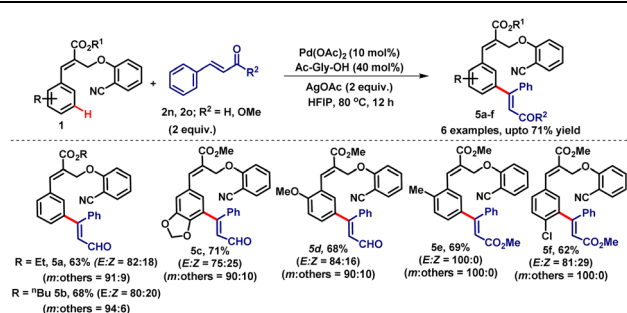
Furthermore, we employed less utilized α , β -unsaturated alkenes such as cinnamaldehyde (**2n**) and methyl cinnamate (**2o**)



Table 2 Scope of α -substituted cinnamates and alkenes^{a,b}

^a Isolated yields. The isomeric ratio was determined by ¹H-NMR. ^b IBO = isobornyl.

for the *meta*-selective C–H olefination reaction. The treatment of cinnamates (**1**) with cinnamaldehyde (**2n**)/methyl cinnamate (**2o**) under the optimized reaction conditions led to the anticipated *meta*-coupled products (**5a–f**) in good yields (Table 3). We observed the formation of *E* and *Z* isomers in the products where the thermodynamically controlled *E*-isomer was found to be the major isomer.

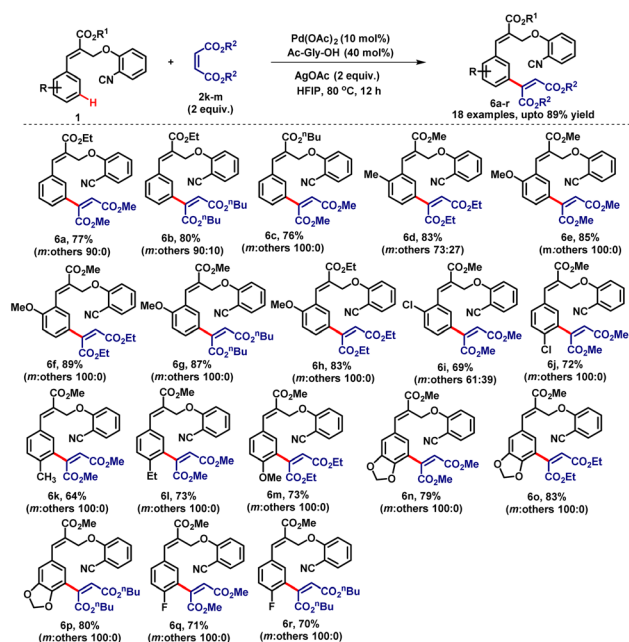
Table 3 Scope of α -substituted cinnamates and α , β -unsaturated alkenes^a

^a Isolated yields. The isomeric ratio was determined by ¹H-NMR.

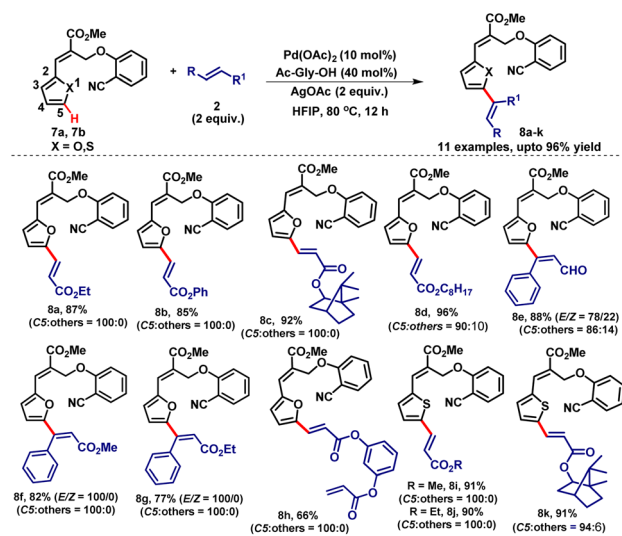
Similarly, various α -substituted cinnamate derivatives **1** with symmetrical olefin coupling partners such as maleates (**2k–m**) were investigated. The desired mono-olefinated products (**6a–r**) were formed in very good yields (64–89%) with excellent *meta*-selectivity (Table 4). The *ortho*-substituted substrates provided the *meta*-coupled products (**6d–i**) with high regioselectivity (coupled selectively at a less hindered position). The *cis*-olefinic coupling partner such as maleates (**2k–m**) provided the *E*-isomers exclusively, which indicates that the stereoselectivity in the double bond is thermodynamic in origin.

The versatility of this reaction was further demonstrated by subjecting the heterocyclic substrates having furan **7a** and thiophene **7b** moieties for *meta*-C–H olefination with a variety of mono and di-substituted alkenes. The heteroaromatic scaffolds **7a** and **7b** were found to be compatible to furnish the corresponding C5-olefinated products **8a–k** in very good yields with excellent regioselectivity (Table 5). Among the C5-olefinated products **8f** and **8g** were formed with excellent *E*-selectivity with excellent C5-selectivity.

To exemplify the efficacy of our new protocol, the α -substituted cinnamate **1a** was coupled with various bioactive molecule appended acrylates (**2s–x**) such as methyl salicylate (**2s**, treatment for minor aches and pain), chalcone (**2t**, treatment for viral disorders and stomach cancer and used in food additives and cosmetic formulation ingredients), paracetamol (**2u**, treatment for fever and aches), estrone (**2v**, hormone therapy), thymol (**2w**, antiseptic) and sesamol (**2x**, antioxidant) as coupling partners. Regardless of the steric bias of the bioactive coupling partners, excellent mono *meta*-selective olefinated products

Table 4 Scope of α -substituted cinnamates and symmetrical alkenes^a

^a Isolated yields. The isomeric ratio was determined by ¹H-NMR.

Table 5 Scope of heterocyclic (furan and thiofuran) substrates and alkenes^a

^a Isolated yields. The isomeric ratio was determined by ¹H-NMR.

(3s–x) were obtained in moderate to good yields (51–69%) with excellent selectivity (Table 6).

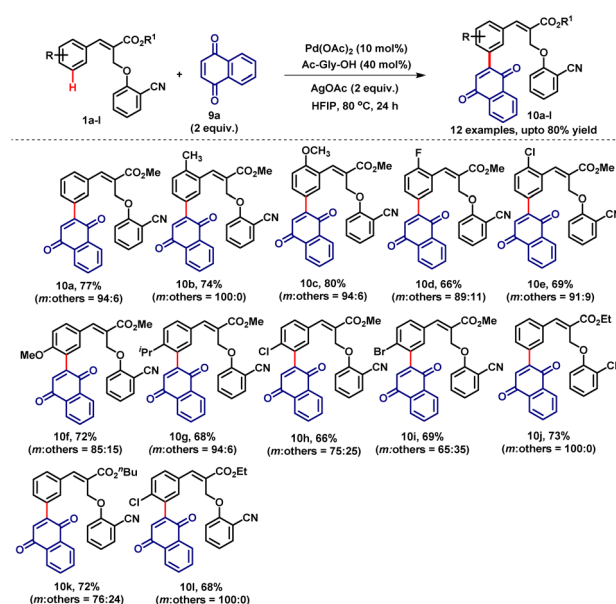
Then we turned our focus on quinones as coupling partners for the *meta*-C–H activation reaction. Quinones and their analogs are found in various pharmaceuticals and natural products and these units are versatile building blocks in the synthesis of various organic scaffolds.^{7a,b} There have been no studies in the literature to date on the insertion of naphthoquinone and benzoquinone as coupling partners in *meta*-C–H bond activation chemistry. Moreover, utilizing naphthoquinone and benzoquinone as coupling partners in the C–H activation reaction with α -substituted cinnamate **1a** is more challenging due to more reactive sites as well as because the carbonyl groups of naphthoquinone and benzoquinone can also act as DGs which may lead to competitive reactions at multiple reactive sites and may produce multiple products.^{7c,d} To examine the robustness of our novel strategy for *meta*-selective C–H bond olefination, we employed naphthoquinone **9a** and benzoquinone **9b** as coupling partners. Accordingly, the reaction of α -substituted cinnamate **1a** with naphthoquinone **9a** under the optimized reaction conditions smoothly provided the desired mono-*meta*-naphthoquinone coupled product **10a** in 77% yield with very good selectivity (*m*: others = 94:6). We also investigated the scope of

various α -substituted cinnamates (**1**) with naphthoquinone (**9a**) which resulted the desired *meta*-naphthoquinone coupled products (**10b–l**) in very good yields (65–74%) (Table 7). Notably, high regioselectivity (less hindered position) was observed for *ortho* substituted substrates that produce the *meta*-coupled products (**10b–e**). Then, we focused our attention towards the reaction of **1a** with benzoquinone **9b** as the coupling partner under the optimized reaction conditions. However, we did not observe the formation of the expected *meta*-coupled product. It is important to note that benzoquinone is more reactive and known for undergoing cyclisation with aromatic substrates. It is very challenging to retain the benzoquinone moiety unaltered after the reaction. To circumvent this problem, we performed the reaction at room temperature instead of 80 °C. Pleasingly, the reaction smoothly furnished the expected mono-*meta*-benzoquinone coupled product **10m** in good yield (66%).

Furthermore, various cinnamates (**1b–g**) were subjected to benzoquinone **9b** and afforded the corresponding *meta*-coupled products (**10n–s**) in moderate to very good yields (55–80%) with high *meta*-selectivity (Table 8).

Additionally, substituted benzoquinones (**9c & 9d**) were also treated with cinnamates **1** which resulted in a mixture of regioisomeric products **10t–v** in good yields. It is important to note that in both cases (naphthoquinone & benzoquinone) exclusively *meta*-coupled products have been observed even though various reactive sites and various functional groups are present with comparable reactivities.

Next to check the generality and applicability of the reaction, we concentrated on utilizing maleimides as coupling partners for the *meta*-C–H activation reaction. Maleimide derivatives are an integral part of various natural products and pharmaceuticals.

Table 7 *Meta*-C–H olefination of α -substituted cinnamates with naphthoquinone^a

^a Isolated yields. The isomeric ratio was determined by ¹H-NMR.

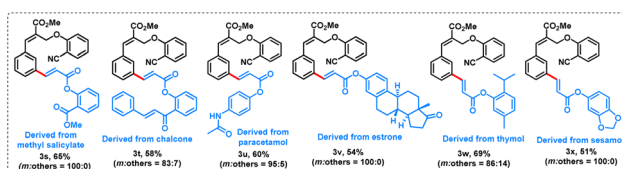
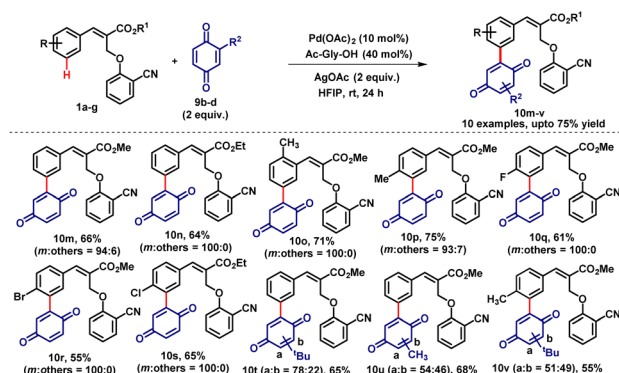
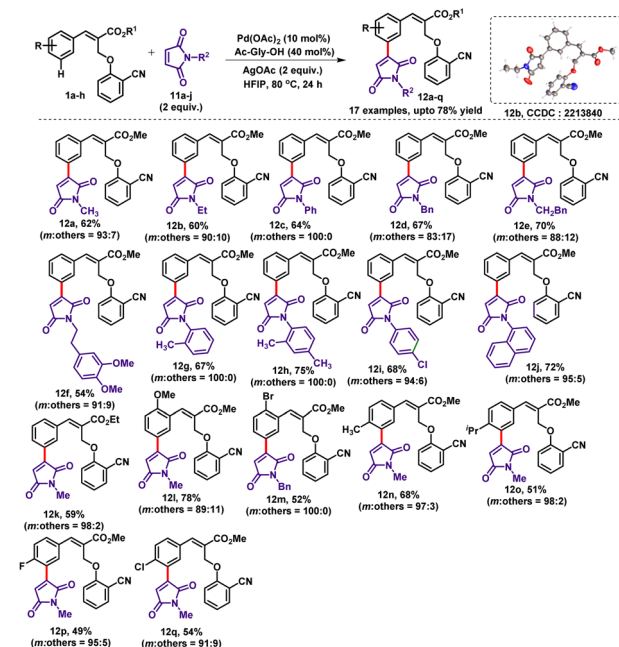
Table 6 Scope of bioactive acrylates for the *meta*-C–H olefination

Table 8 *Meta*-C–H olefination of α -substituted cinnamates with benzoquinones^a^a Isolated yields. The isomeric ratio was determined by ¹H-NMR.

Maleimide derivatives have been used as coupling partners in *ortho*-C–H activation and are not employed for *meta*-C–H activation chemistry.⁸ Therefore, we focused our attention towards the incorporation of *N*-substituted maleimides as coupling partners at the *meta*-position of the substrate **1**. Accordingly, the reaction of **1a** with *N*-methyl maleimide **11a** under the standard reaction conditions delivered the desired *meta* coupled product **12a** in 62% yield with excellent selectivity (*m*:others = 93:7). Furthermore, α -substituted cinnamate (**1a**) was treated with different types of *N*-alkyl and aryl maleimides **11b–j** which produced the expected mono-*meta*-olefinated products **12a–j** in moderate to very good yields (54–72%) with excellent selectivity (Table 9).

Table 9 Scope of maleimides for the *meta*-C–H olefination^a^a Isolated yields. The isomeric ratio was determined by ¹H-NMR.

Furthermore, various α -substituted cinnamates (**1**) were treated with *N*-substituted maleimides (**11a** & **11d**) under the optimised reaction conditions which provided the anticipated *meta*-coupled products **12k–q** in good yields with high selectivity.

The *ortho*-substituted cinnamates regioselectively produced the *meta*-coupled products (coupled selectively at less hindered positions) **12l** and **12m** in good yields. The compound **12b** was further confirmed by single-crystal X-ray diffraction analysis. Sulfolene and its derivatives are important building blocks in organic synthesis and also an integral part of many biologically active molecules.⁹ In the C–H activation chemistry, sulfolene has never been used as a coupling partner. Therefore, we envisaged that sulfolene could be utilised as a coupling partner in the C–H activation reactions. Accordingly, we treated sulfolene (**2aa**) with substrate **1** under the standard reaction conditions. To our delight, the desired *meta*-selective 4-aryl 2-sulfolene derivatives (**13a–d**) have been formed in excellent yields (73–81%) with high selectivity (Table 10). The formation of the 4-aryl 2-sulfolene derivatives could be explained by the regioselective elimination of more acidic β -H_a rather than β -H_b elimination.

To expand the robustness of the α -substituted cinnamates for other C–H functionalization reactions, we planned to carry out acetoxylation and cyanation reactions to generate the corresponding *meta*-coupled products utilising appropriate reagents.¹⁰ Accordingly, the α -substituted cinnamates (**1**) were treated with diacetoxyiodobenzene under the standard reaction conditions which produced the *meta*-coupled product in 49% yield with good selectivity (*m*:others = 86:14). However, when we replaced Ac-Gly-OH with Boc-Ala-OH the yield of the reaction increased from 49% to 58% with excellent selectivity (*m*:others = 97:3).

Furthermore, the scope of the reaction was checked with various cinnamates having different substitutions and producing the desired *meta*-coupled products (**14a–f**) in 56–62% yields with high *meta*-selectivity (Table 11). We observed that the *meta*-coupled products **14c** and **14d** were formed with high regioselectivity (coupled selectively at a less hindered position).

Similarly, we also applied the same strategy for the *meta*-cyanation reaction. Accordingly, the treatment of cinnamate **1a** with CuCN led to the *meta*-cyanated product **15a** in 45% yield with excellent selectivity (*m*:others = 93:7). The scope of the

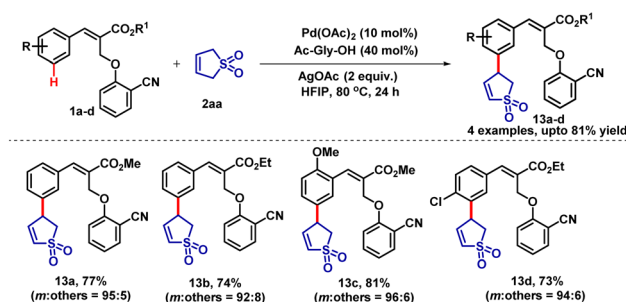
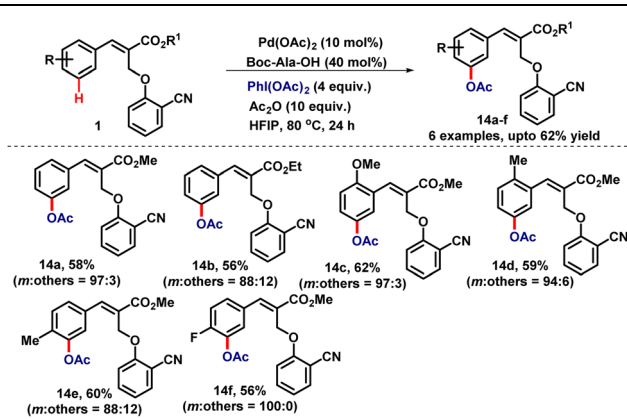
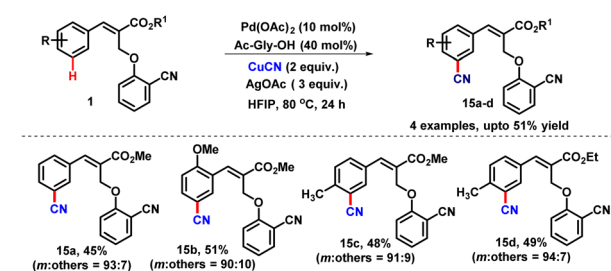
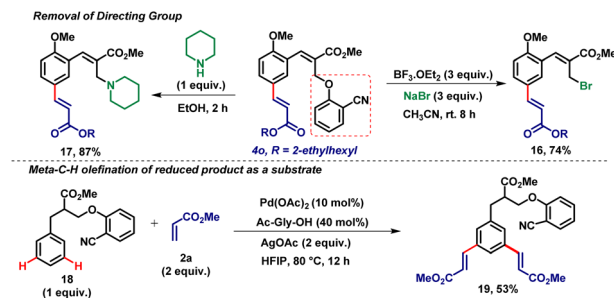
Table 10 *Meta*-C–H allylation of cinnamates^a^a Isolated yields. The isomeric ratio was determined by ¹H-NMR.

Table 11 *Meta*-C–H acetoxylation of cinnamates^a^a Isolated yields. The isomeric ratio was determined by ¹H-NMR.

reaction was further checked under the same reaction conditions which provided the *meta*-cyanated products (**15b–d**) in moderate yields with high selectivity as depicted in Table 12. We observed that the *meta*-coupled product **15b** formed with high regioselectivity (coupled selectively at a less hindered position).

Finally, the DG *i.e.* the 2-hydroxybenzonitrile group was easily removed and produced the *meta*-olefinated product **16** in 74% yield using NaBr and BF_3OEt_2 by the regeneration of the initially utilized bromo moiety of the Bailly–Hillman adduct (Scheme 2). On the other hand, the directing group was replaced with the piperidine moiety which produced the corresponding allylamine product **17** with 87% yield (Scheme 2). In order to confirm the importance of the olefinic double bond present in the cinnamate scaffold, we have synthesized the corresponding reduced product **18** and subjected it to the C–H olefination reaction with methyl acrylate **2a** under the optimized reaction conditions. In this case, a di-*meta*-olefinated product **19** was obtained in 53% yield (Scheme 2) which indicates that the double bond facilitates the formation of mono-*meta*-coupled products.

Finally, a representative catalytic cycle is proposed for the distal mono *meta*-C–H olefination where the palladium complex was confirmed through HRMS (see the ESI†).

Table 12 *Meta*-C–H cyanation of cinnamates^a^a Isolated yields. The isomeric ratio was determined by ¹H-NMR.Scheme 2 Removal of the DG and synthesis of the *meta*-di-olefination product.

Conclusions

In conclusion, we have developed a novel strategy for the distal *meta*-C–H olefination of α -substituted cinnamates with different kinds of coupling partners with high *meta*-selectivity for the first time. The new entrants such as naphthoquinone, benzoquinones, maleimides and sulfone have been shown to be coupling partners in the *meta*-C–H activation reaction. The *meta*-C–H functionalization has been further extended to allylation, acetoxylation and cyanation reactions. Importantly, several bioactive molecules tethered to olefins such as estrone, paracetamol, methyl salicylate, chalcone, thymol and sesamol were also utilised as coupling partners. The present diversity-oriented methodology is novel and general with a wide range of substrate scope (more than 140 examples) and tolerates diverse functional groups. This novel strategy also opens a new avenue for making a library of a wide variety of *meta*-functionalized cinnamate scaffolds for biological screening.

Conflicts of interest

There are no conflicts to declare.

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