C–H Activation

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Palladium(II)-Catalyzed *meta*-C–H Olefination: Constructing Multisubstituted Arenes through Homo-Diolefination and Sequential Hetero-Diolefination**

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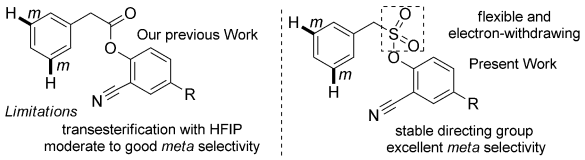
Abstract: *Divinylbenzene derivatives represent an important class of molecular building blocks in organic chemistry and materials science. Reported herein is the palladium-catalyzed synthesis of divinylbenzenes by meta-C–H olefination of sulfone-based arenes. Successful sequential olefinations in a position-selective manner provided a novel route for the synthesis of hetero-dialkenylated products, which are difficult to access using conventional methods. Additionally, 1,3,5-trialkenylated compounds can be generated upon successful removal of the directing group.*

Transition-metal-catalyzed functionalization of arene C–H bonds has been extensively investigated over the last two decades by using a variety of directing groups (DGs).[1] In the C–H activation realm, directing groups are almost universally *ortho*-selective.[2] Compared to *ortho*-functionalization, the related *meta*-selective reactions pose a significant challenge. In this regard, examples of *meta*-selective functionalization have only recently been reported and are based on steric and electronic bias.[3] An alternate template-based approach, initiated by the group of Yu[4] and subsequently extended by Tan and co-workers[5] as well as our group,[6] demonstrated *meta*-selective functionalization in the presence of a suitable directing group. These *meta*-selective C–H functionalizations are usually independent of the substitution pattern and electronic nature of the substrate. Importantly, activation of *meta* C–H bonds hinges upon the combined use of a weakly coordinating nitrile-based template with a protected amino-acid ligand.

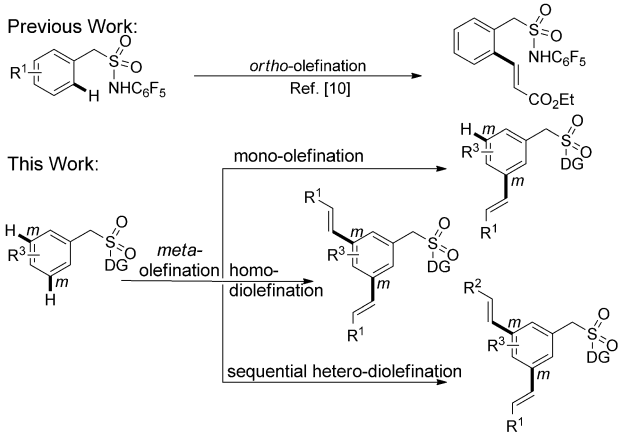
During our previous work on palladium-catalyzed *meta*-C–H olefination with arylacetic acid derived scaffolds,[6] a number of limitations were encountered: 1) unsuccessful diolefination, 2) transesterification of the directing group with the solvent hexafluoroisopropanol (HFIP), and 3) moderate to good *meta*-selectivity. Some of these drawbacks probably originate from the conformational and electronic bias of arylacetic acid based substrates. We reasoned that a more electron-withdrawing SO_2 group may reduce electron density at the *ortho*- and *para*-position of the sulfone-based substrates, and that the flexible nature of the sulfonyl (SO_2), compared to carbonyl (CO) moiety, in the scaffold would enhance the directing power of the nitrile (Scheme 1).[7] We



Scheme 1. Development of a new scaffold.

were particularly interested in the synthesis of di-alkenylated benzylsulfonyl scaffolds because of the importance of diolefinated compounds in organic synthesis and materials chemistry.[8] However the second olefination reaction is expected to be challenging since the electronic and steric properties of mono-olefinated species is completely different from those of the starting materials.[9] Such challenges were overcome and we herein disclose an approach for *meta*-selective homo-diolefination and sequential hetero-diolefination of C–H bonds of sulfone-based arenes (Scheme 2). Although *ortho*-C–H olefination of benzyl sulfonamides[10] and *ortho*-selective hetero-diolefinations have been documented,[9] *meta*-selective hetero-diolefination is yet to be reported.

Initially, benzylsulfonyl ester derivatives were tested with various of nitrile-based directing groups (Scheme 3; for structures see Figure 1).[6,11] Upon optimization, 2-hydroxybenzonitrile successfully delivered the diolefination product



Scheme 2. Outline of this work.

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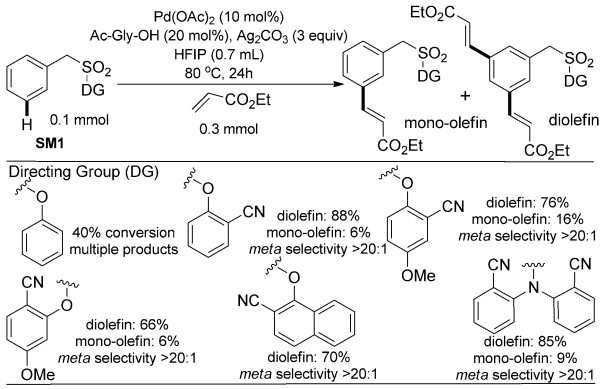


Scheme 3. Development of directing group. Yields and selectivities determined by ^{1}H NMR analysis of crude reaction mixture.

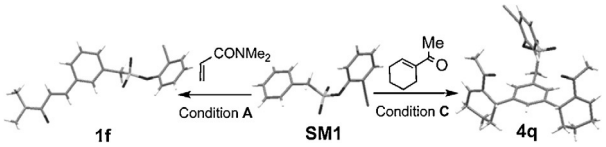
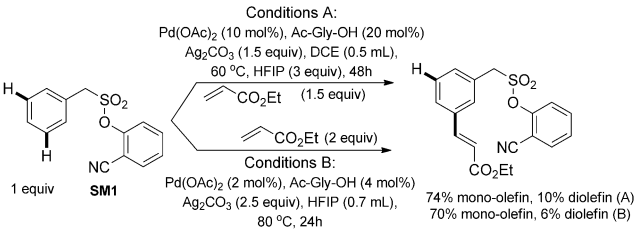


Figure 1. X-ray structures[15] of **SM1**, **1f**, and **4q**.

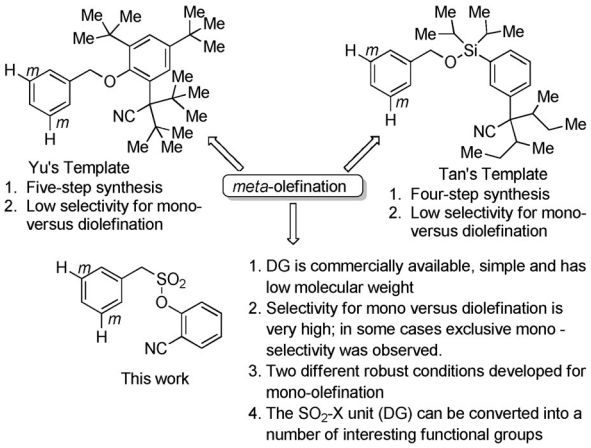
in 88% yield and with high selectivity (*meta*/other >20:1). Further optimization of the reaction parameters delivered two different catalytic conditions (A: with 10 mol% Pd in dichloroethane solvent and B: with 2 mol% Pd in HFIP solvent) for mono-olefination (Scheme 4).[11] The major



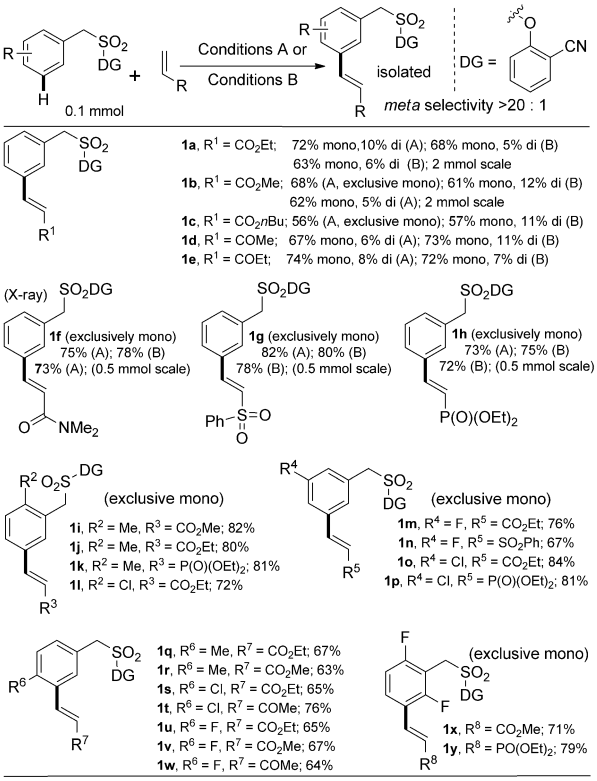
Scheme 4. Two protocols for mono-olefination. DCE = 1,2-dichloroethane. Yields and selectivities determined by ^{1}H NMR analysis of the crude reaction mixture.

advantages of the benzylsulfonate (our present scaffold) are as follows (Scheme 5): 1) the directing group is commercially available, simple, and has a low molecular weight. Notably, the templates of both Yu and Tan are synthesized through five- and four-step procedures, respectively; 2) in general, selectivity is very high (even for unbiased substrates). In a number of cases, exclusive mono-olefinated products were obtained. 3) two different robust conditions were developed for mono-olefination; 4) the SO_2-X unit (DG) can be converted into a number of interesting groups (see Schemes 11 and 12).

Different acrylates and α,β-unsaturated ketones produced the desired mono-olefination products in moderate to good yields (**1a**–**e**; Scheme 6) with excellent *meta*-selectivity (*meta*/others >20:1). Olefins with amide, phosphonate, and sulfone moieties resulted in *meta*-selective mono-olefination products

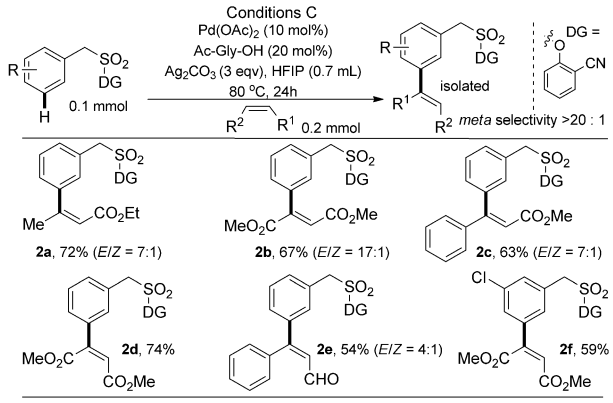


Scheme 5. Advantages of the present scaffold.



Scheme 6. The *meta*-selective mono-olefination. Yields and selectivities determined by ^{1}H NMR analysis of crude reaction mixture. See Figure 1 for X-ray structure.

exclusively (**1f**–**h**). Complete mono-selectivity was also obtained with both the *ortho*-methyl- and *ortho*-chloro-substituted benzylsulfonyl ester (**1i**–**l**) under the reaction conditions A. The *meta*-chloro- and fluoro-substituted benzylsulfonyl esters were olefinated selectively at the 5-position with different olefins (**1m**–**p**). In addition, this protocol is compatible with electron-donating and electron-withdrawing *para* substituents such as methyl (**1q** and **1r**), chloro (**1s** and **1t**), and fluoro (**1u**–**1w**). All *para*-substituted benzylsulfonyl esters produced 10–15% of the diolefination product along with monoalkenylated products. The 2,6-difluoro sulfonyles-

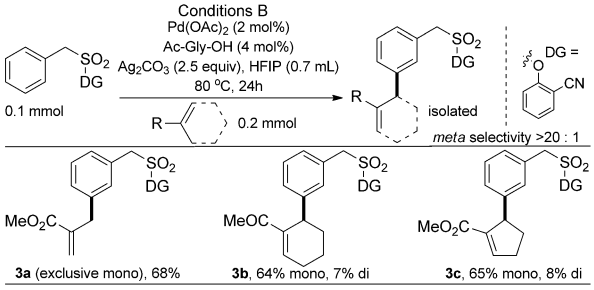


Scheme 7. Substrate scope with internal olefins. Yields and selectivities determined by ^{1}H NMR analysis of crude reaction mixture.

ter was olefinated to exclusively afford the *meta*-selective mono-olefinated products (**1x** and **1y**).

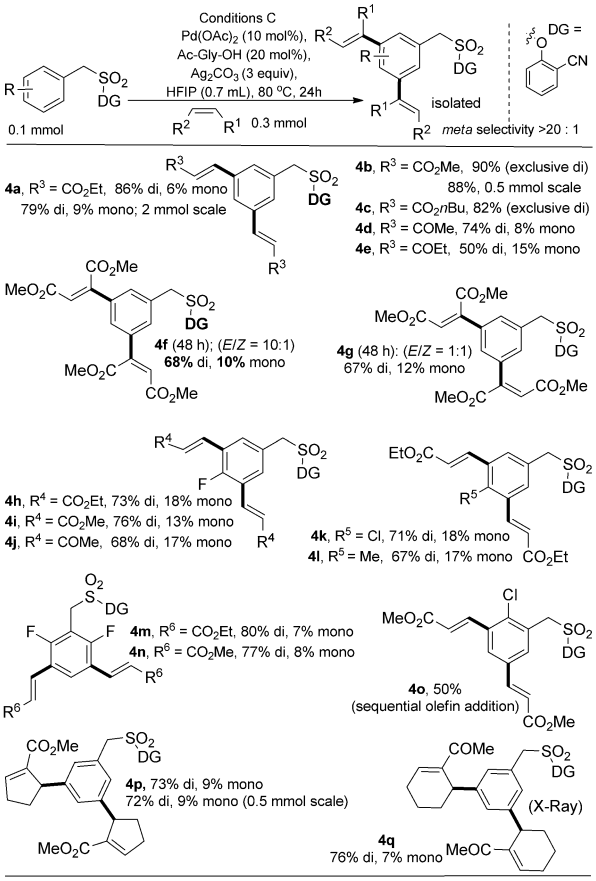
Interestingly under the reaction conditions C (Scheme 7), di-substituted *trans*-olefins (e.g. fumarate, crotonate, cinnamate, and cinnamaldehyde) were successfully employed.[12] Notably, exclusive mono-selectivities were observed in all the entries. Although, a mixture of *E* and *Z* isomers were detected, the *E* isomer was generated as the major product (**2a–c** and **2e**). With a *cis*-olefin such as dimethyl maleate, *E* isomers were formed exclusively (**2d** and **2f**). These phenomena indicate that the stereoselectivity is thermodynamic in origin.[13]

Similarly, reaction with methacrylate and cyclic trisubstituted olefins proceeded to provide *meta*-selective monoallyl benzene derivatives in good yields under the reaction conditions B (**3a–c**; Scheme 8). Formation of these allyl benzene derivatives could be explained by the regioselective β-H_b elimination rather than β-H_a elimination.[11,14] Unfortunately this reaction is not compatible with electron-neutral or electron-rich olefins such as substituted styrenes.



Scheme 8. Formation of *meta*-allyl benzene. Yields and selectivities determined by ^{1}H NMR analysis of crude reaction mixture.

We subsequently explored homo-diolefination at the *meta* positions under the reaction conditions C (Scheme 9). Different acrylates, α,β-unsaturated ketones, and disubstituted internal olefins produced dialkenylated products in good yields (**4a–g**). Notably, chloro, fluoro, and methyl benzylsulfonyl esters gave dialkenylated products (**4h–o**).



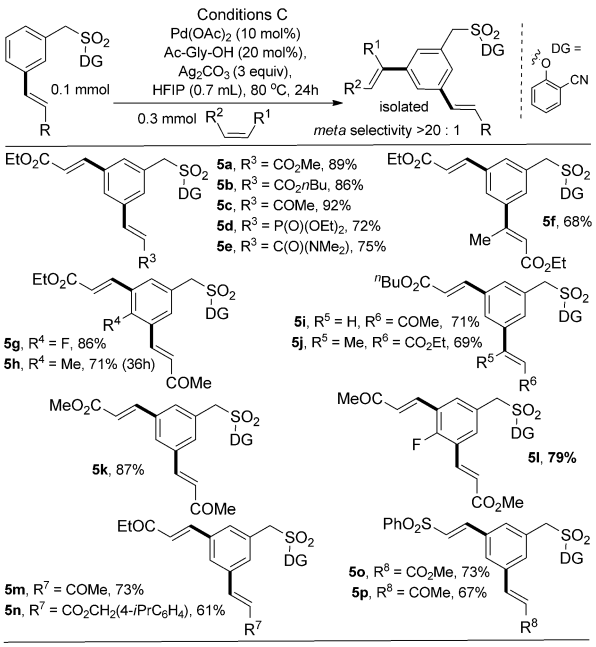
Scheme 9. Substrate scope for homo-diolefination. Yields and selectivities determined by ^{1}H NMR analysis of crude reaction mixture. See Figure 1 for X-ray structure.

The trisubstituted cyclic olefins also reacted well under the reaction conditions C to afford the *meta*-selective diallylbenzene derivatives in good yields (**4p** and **4q**).

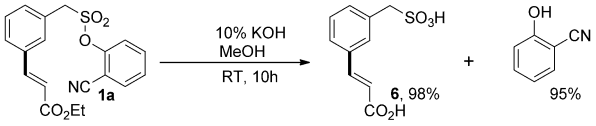
To obtain sequential olefination in a position-selective manner, mono-olefinated products were utilized. With the prefunctionalized olefinated product (Scheme 6), acrylates, methylvinyl ketone, ethylvinyl ketone, vinylsulfone, vinyl phosphonate, amide, and disubstituted olefins were incorporated at the remaining *meta*-position in an exclusive manner with good to excellent yields under the reaction conditions C (**5a–p**; Scheme 10). Hetero-diolefination reactions by sequential addition of two different olefins in a one-pot process gave the desired product (e.g., **5c**, 58% and **5k**, 52%) along with formation of other mono-olefinated and homo-diolefinated products.[11]

The 2-hydroxybenzonitrile group is easily removed by hydrolysis at room temperature by using KOH in methanol to produce the *meta*-substituted diacid **6** in excellent yield (Scheme 11).

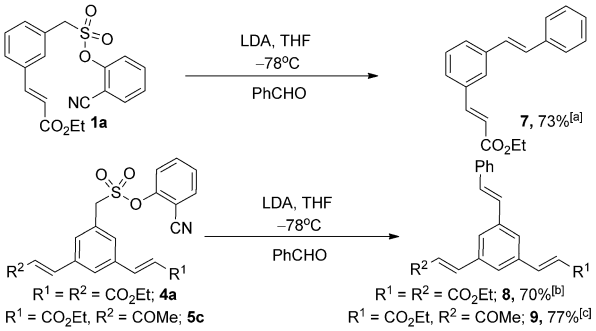
Additionally, the SO_2-DG scaffold can be easily cleaved by a modified Julia olefination. All mono-, di-, and hetero-diolefinated products, **1a**, **4a**, and **5c** were reacted with benzaldehyde in presence of LDA at −78 °C to afford the corresponding 1,3-divinyl and 1,3,5-trivinylbenzene derivatives, **7**, **8**, and **9** in good yields (Scheme 12).



Scheme 10. Sequential hetero-diolefination. Yields and selectivities determined by ^{1}H NMR analysis of crude reaction mixture.



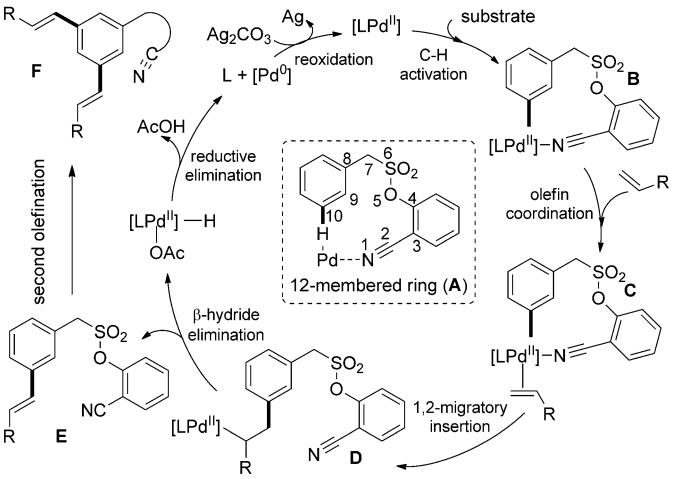
Scheme 11. Hydrolysis of directing group.



Scheme 12. Modified Julia olefination of **1a**, **4a**, and **5c**. [a] **7a** (*Z* isomer) 13%, **7b** (*E* isomer) 60%. [b] **8a** (*Z* isomer) 6%, **8b** (*E* isomer) 64%. [c] **9** (*E* isomer) 77%, (*Z* isomer) trace.[11] LDA = lithium diisopropylamide, THF = tetrahydrofuran.

Kinetic experiments conducted on **SM1** to obtain the di-olefinated product **4a** distinctly showed the intermediacy of the mono-olefinated product **1a**.[11] A separate set of studies for the formation of **4a** from the mono-olefinated compound revealed a first-order rate dependency with respect to **1a**.[11]

A proposal on the reaction course is presented in Scheme 13 on the basis of previous reports.[4–6] The linear weakly binding nitrile group in the substrate is proposed to



Scheme 13. Proposed catalytic cycle.

make a 12-membered cyclophane-like pre-transition state (**A**). Because of the high electrophilicity, the nitrile-bound Pd^{II} center is likely to be reactive towards the *meta*-C–H bond. Formation of the mono-olefinated product **E** from **B** will involve 1) C–H activation, 2) olefin binding, 3) 1,2-migratory insertion, and 4) β-hydride elimination.

In summary, we have developed complementary methods for *meta*-selective mono-, di-, and sequential hetero-diolefinations of sulfone-based arene motifs with a 2-hydroxybenzonitrile template. Substituents are tolerated at all positions on the arene framework. The strategy for sequential *meta*-C–H olefination provides a novel route for the synthesis of *meta*-selective bis(alken)ylated compounds having two different olefins, compounds which are difficult to access using conventional methods.

Keywords: C–H activation · olefination · palladium · sulfur · synthetic methods

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[15] CCDC 1043571 (**SM1**), 1043569 (**1f**), and 1043570 (**4q**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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