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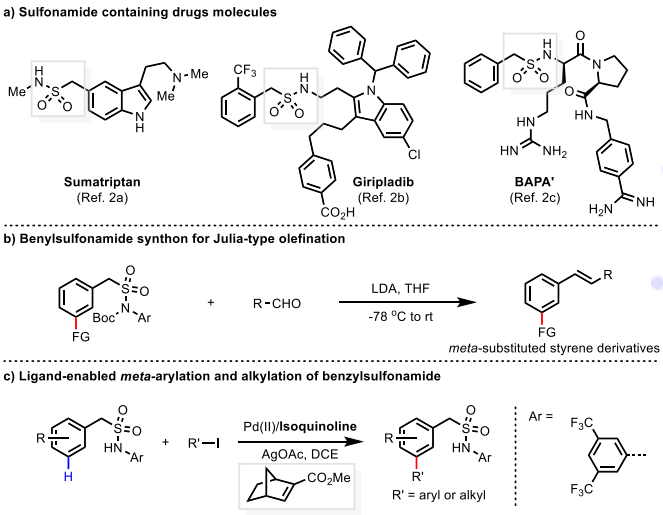
Meta-C–H Arylation and Alkylation of Benzylsulfonamide Enabled by a Pd(II)/Isoquinoline Catalyst

*Guolin Cheng,[+] Peng Wang,[+] and Jin-Quan Yu**

Abstract: *Palladium(II)-catalyzed meta-C–H arylation and alkylation of benzylsulfonamide using 2-carbomethoxynorbornene (NBE-CO₂Me) as a transient mediator are realized using a newly developed electron-deficient directing group and isoquinoline as a ligand. This protocol features broad substrate scope and excellent functional group tolerance. The meta-substituted benyzlsulfonamide can be readily transformed to sodium sulfonate, sulfonate ester, sulfonamide, as well as styrenes via Julia-type olefination. The unique impact of the isoquinoline ligand underscores the importance of subtle matching between ligands and the directing groups.*

Sulfonamide functional group is one of the most important pharmacophores for many agents possessing antibacterial, anti-carbonic anhydrase, diuretic, hypoglycemic, antithyroid, and antitumor activity.[1] Currently, over hundred marketed drugs contain sulfonamide derived core structures, notably in sumatriptan, and giripladib *et al* (Scheme 1a).[2] In addition, the alkyl sulfonamide functional group is a useful synthon that can be readily converted to alkene in the presence of aldehyde or ketone via a Julia-type olefination (Scheme 1b). Therefore selective C–H functionalization of sulfonamide substrates or sulfonamide containing drug molecules is highly valuable. Though directed *ortho*-C–H functionalization of aryl sulfonamide and benzylsulfonamide has been demonstrated,[3] diverse *meta*-functionalizations of those substrates remain scarce. Successful *meta*-functionalization of sulfonamide containing molecules will find broad utility in drug discovery and styrene synthesis.

Over the past decade, while substantial progress has been made in the transition-metal-catalyzed *meta*-C–H activations,[4-7] many of the established approaches are still limited in efficiency and scope.[4-7] For instance, although the devolopment of various U-shaped templates allows selective C–H functionalization of a wide range of substrates at the remote position,[4] these transformations are limited to olefinaiton,[4a] acetoxylation,[4b] arylation,[4c] and iodination reactions.[4d] Very recently, our group[7a] and others[7b] have developed a Pd(II)/norbornene relay approach to realize the *meta*-C–H arylation and alkylation reaction by combining the directed *ortho*-C–H activation and the Catellani's norbornene process.[8] Taking advantage of this new approach, serval unprecedented transformations such as *meta*-amination,[7f] alkynylation,[7f] and chlorination[7g] have been realized by developing a modified norbornene (NBE-CO₂Me, 2-carbomethoxynorbornene)[7c] and new ligand scaffolds.[7e,h] This new strategy could open a new avenue for *meta*-C–H functionalization of sulfonamide containing substrates. Herein, we report an isoquinoline enabled Pd(II)-catalyzed *meta*-C–H arylation and alkylation of benzylsulfonamide using 2-carbomethoxynorbornene as a transient mediator with broad substrate scope and functional group tolerance (Scheme 1c). This protocol represents an efficient method to acess the *meta*-arylated or alkyated benzylsulfonamide. Moreover, further Julia-type olefination of the *meta*-functionalized benzylsulfomamides affords a novel class of styrenes.



Scheme 1. *Meta*-C–H arylation and alkylation of benzylsulfonamide.

Given our continued interest on the direct C–H functionalization of sulfonamide containing drugs and substrates,[3a] we chose benzylsulfonamide as the model substrate to examine the feasiblity of norbornene-mediated *meta*-functionalization. After systematic evaluation of different sulfonamide directing groups, the 3,5-bis(trifluoromethyl)aniline was found as the most efficient one, giving the desired *meta*-arylated products in 50% combined yield (mono/di = 2.1/1.0, see Supporting Information for more information) in the presence of $Pd(OAc)_2$ (10 mol%), pyridine (20 mol%), AgOAc (3.0 equiv.), NBE-CO_2Me (1.5 equiv.) in DCE at 100 °C. It is noteworthy that the pyridine ligand is crucial for this transformation as only trace products was observed in the absence of ligand. Next, we systematically evaluated the pyridine- and quinoline-type ligands employing **1a** as substrate and *p*-iodotoluene as coupling partner. While simple pyridine **L1** gave the desired *meta*-arylated product in 42% yield, 2-picoline dramatically increased the yield to 69%. 3- or 4-Picoline provided lower yield compared to the 2-picoline (**L3** or **L4** vs **L2**). Following this finding, other substituents at the 2-position of pyridine were investigated (**L5-8**). Unfortunately, both electron donating and electron withdrawing groups reduced the yields. 2,6-Lutidine (**L9**) and 2,3-lutidine (**L10**) were also evaluated, giving the desired product in 32% and 60% yields, respectively. Although the 5,6,7,8-tetrahydroquinoline (**L11**) resulted in 38% yield, quinoline (**L12**) significantly increased the yield to 85%. Other quinoline

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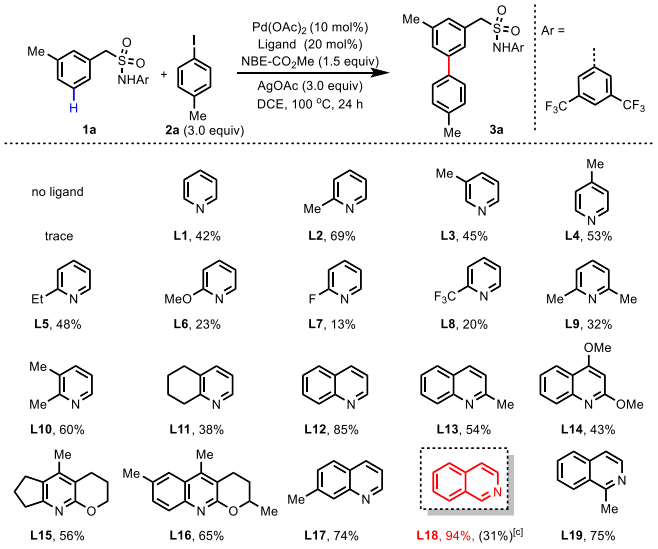
derivatives led to lower yields (43-74%, **L13-17**). Notably, isoquinoline (**L18**) was found as the most efficient ligand to promote this *meta*-C–H arylation reaction, affording 94% yield (see Supporting Information for more ligand screening). 1-methylisoquinoline decreased the yield to 75% (**L19**). Moreover, control experiments revealed that 2-carbomethoxynorbornene (NBE-CO_2Me) is crucial for this ligand-enabled *meta*-C–H functionalization of benzysulfonamide as 2-norbornene only gave 31% yield under the optimal conditions.

Table 1. Ligand evaluation for *meta*-C–H arylation of benzylsulfonamide.[a,b]



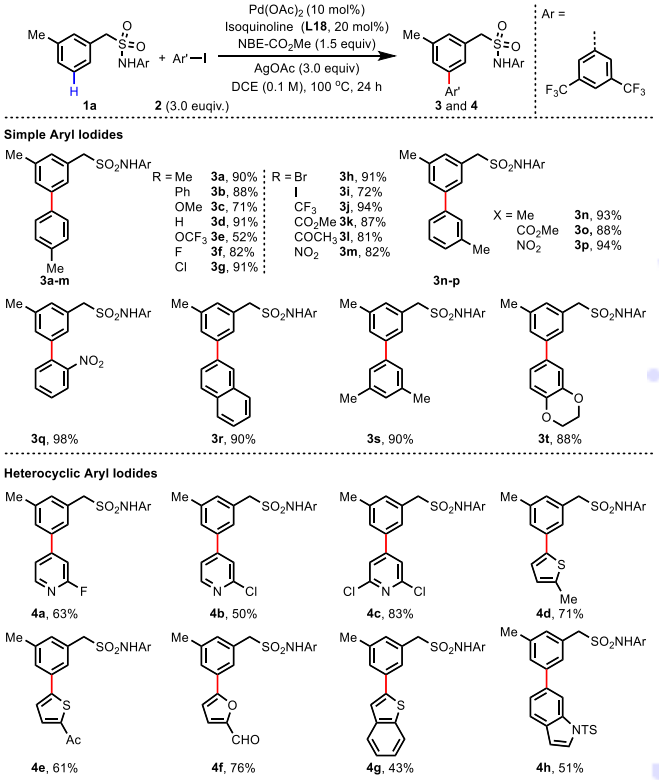
[a] Reaction conditions: **1a** (0.1 mmol), *p*-iodotoluene **2a** (3.0 equiv), $Pd(OAc)_2$ (10 mol %), Ligand (20 mol %), AgOAc (3.0 equiv), NBE-CO_2Me (1.5 equiv), DCE (1.0 mL), 100 °C, 24 h. [b] The yield was determined by ^{1}H NMR using CH_2Br_2 as the internal standard. [c] 2-Norbornene was used instead of 2-carbomethoxynorbornene.

Under the optimal conditions, the scope of aryl iodide coupling partners were examined first by employing 3-methyl benzylsulfonamide **1a** as the model substrate (Table 2). Various aryl iodides are compatible with this procedure affording the desired *meta*-arylated benzylsulfonamide in moderate to excellent yield. Functional groups, including Me, Ph, MeO, CF_3O, F, Cl, Br, I, CF_3, CO_2Me, Ac, and NO_2, are all tolerated (**3a-m**). 3-substituted aryl iodides (**3n-p**) and 2-substituted aryl iodides (**3q** and **5a**) are also suitable coupling partners. 2-Iodonaphthalene (**3r**) resulted in 90% yield, while 3,5-Disubstituted and 3,4-disubstituted aryl iodide (**3s** and **3t**) afforded the desired product in 90% and 88% yields, respectively.

Notably, the heterocyclic aryl iodides are highly reactive under those conditions (Table 2). A series of heterocyclic aryl iodides containing pyridine, thiophene, furan, benzothiophene, and indole scaffold are tolerated in this procedure affording the desired products in 43-83% yields (**4a-h**). The compatiablity of heterocylic aryl iodides is noteworthy, and highlights the effectiveness of the isoquinoline ligand.

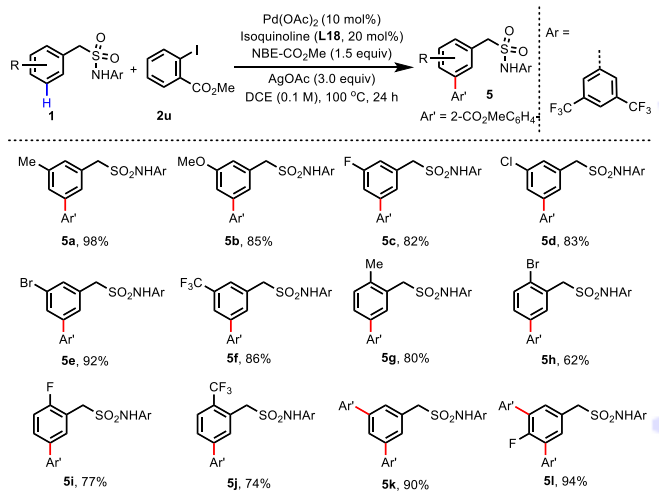
Next, the scope of benzylsulfonamide was evaluated using methyl 2-iodobenzoate as the coupling partner (Table 3). Substrates containing either electron-withdrawing or electron-donating substituents at the 3-position of the phenyl ring were arylated at the *meta*-position in excellent yields (**5a-f**). 2-substituted benzylsulfonamides are also tolerated, albeit with a slight lower yields (**5g-j**). Simple benzylsulfonamide **1k** was subjected to the standard conditions to afford the di-arylated product in 90% yield. 4-Fluorobenzylsulfonamide is also suitable substrate giving the di-arylated product 94% yield (**5l**).

Table 2. Scope of aryl iodides.[a,b]



[a] Reaction conditions: **1a** (0.1 mmol), Aryl iodide **2** (3.0 equiv), $Pd(OAc)_2$ (10 mol %), Isoquinoline (20 mol%), NBE-CO_2Me (1.5 equiv), AgOAc (3.0 equiv), DCE (1.0 mL), 100 °C, 24 h. [b] Isolated yield.

Table 3. *Meta*-arylation of benzylsulfonamides.[a,b]



[a] Reaction conditions: **1** (0.1 mmol), **2u** (3.0 equiv), $Pd(OAc)_2$ (10 mol %), Isoquinoline (20 mol%), NBE-CO_2Me (1.5 equiv), AgOAc (3.0 equiv), DCE (1.0 mL), 100 °C, 24 h. [b] Isolated yield.

The generality of this ligand-enabled *meta*-C–H functionalization approach for benzylsulfonamide was further demonstrated by the development of *meta*-C–H alkylation reaction (Table 4). A variety of alkyl iodides are suitable coupling partner under the optimized conditions. The functional groups including phenyl (**7d**), TBS-protected alcohol (**7e**), benzylic ether (**7f**), ester

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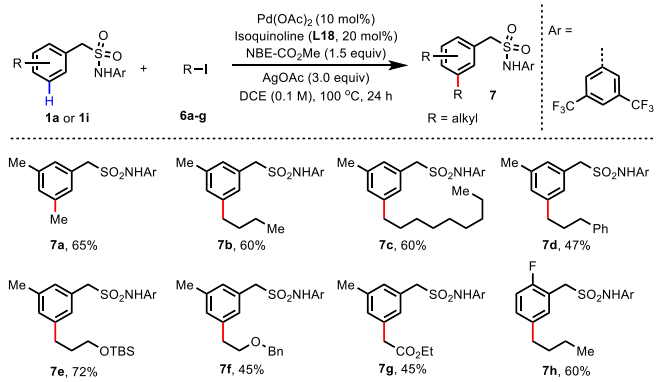
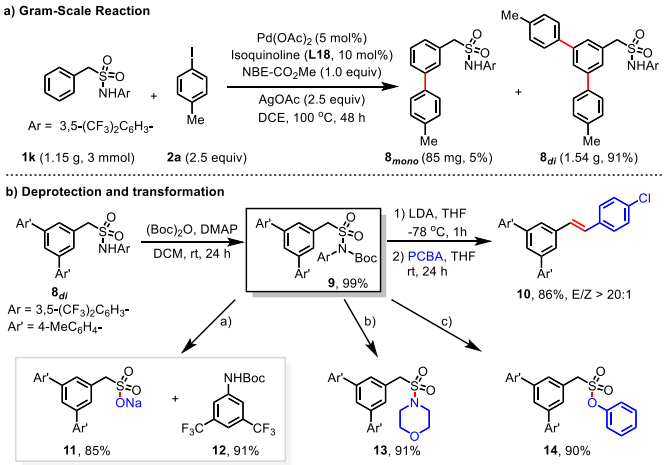
group (**7g**) are tolerated in this protocol, giving the desired *meta*-alkylated products in moderate to high yields. A benzylsulfonamide derivative **1i** was also evaluated providing the alkylated product **7h** in 60% yield.

Table 4. *Meta*-alkylation of benzylsulfonamides.[a,b]



[a] Reaction conditions: **1a** or **1i** (0.1 mmol), **6** (3.0 equiv), $Pd(OAc)_2$ (10 mol%), Isoquinoline (20 mol%), NBE-CO_2Me (1.5 equiv), AgOAc (3.0 equiv), DCE (1.0 mL), 100 °C, 24 h. [b] Isolated yields.

The scalability of this *meta*-C–H reaction was demonstrated by the *meta*-arylation reaction. Employing **1k** as model substrate in the presence of 5 mol% $Pd(OAc)_2$, 10 mol% isoquinoline, and 1.0 equivalent of NBE-CO_2Me, the di-arylated product (**8*di***) was obtained in 91% yield, along with the mono-arylated product (**8*mono***) in 5% yield (Scheme 2a). Boc-Protection of the *meta*-arylated product with $(Boc)_2O$ afforded intermediate **9** in 99% yield. Subsequent hydrolysis gave the corresponding sodium sulfonate **11** in 85% yield. It is noteworthy that the Boc-protected 3,5-bistrifluoromethyl aniline (directing group) can also be recovered in 91% yield. Furthermore, the intermediate **9** can be readily transformed to other sulfonamides (**13**), sulfonate ester (**14**) in excellent yields (Scheme 2b). These transformations indicate the versatility of this reaction for diversifying the benzylsulfonamide containing drug molecules. An important synthetic application is also demonstrated by the coupling of **9** with aldehyde under Julia olefination conditions to give the *trans*-alkenes **10** in 86% yield, thus providing a new avenue for making a novel class of *meta*-substituted styrenes.



Scheme 2. Gram-scale reaction and deprotection. Conditions: a) MeONa (2.2 equiv), MeOH, rt, 24 h; b) Morpholine (2.0 equiv), n-BuLi (2.4 equiv), THF , rt, 5 h; c) PhONa (2.0 equiv), DMF, rt, 24 h.

In summary, *meta*-C–H arylation and alkylation of benzylsulfonamide are realized using 2-carbomethoxynorbornene as the transient mediator and isoquinoline as the ligand. This protocol features borad substrates sope and functional group tolerance. The compatiabilty of heterocylic aryl idodies and alkyl idodides is an important advantage over other *meta*-C–H functionalization protocols . *Meta*-substituted sulfonate esters, sulfonamides, as well as styrene derivatives can be obtained via this approach.

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Keywords: *meta*-C–H arylation · alkylation · isoquinoline · palladium · sulfonamide

[1] a) J. Drews, *Science* **2000**, *287*, 1960. b) A. Scozzafava, T. Owa, A. Mastrolorenzo, T. C. Supuran, *Curr. Med. Chem.* **2003**, *10*, 925. c) L. Levy, *Drugs Future* **1992**, *17*, 451. d) A. Kalgutkar, R. Jones, A. Sawant, In Metabolism Pharmacokinetics and Toxicity of Functional Groups, RSC Drug Discovery Series No. 1, (D. A. Smith, Ed.), RSC: Cambridge, U.K., 2010; Chapter 5. e) C. Hansch, P. G. Sammes, J. B. Taylor, in Comprehensive Medicinal Chemistry, Vol. 2; Pergamon Press, Oxford, UK, 1990, Chapter 7.1.

[2] a) F. D. King, A. M. Brown, L. M. Gaster, A. J. Kaumann, A. D. Medhurst, S. G. Parker, A. A. Parsons, T. L. Patch, P. Raval, *J. Med. Chem.* **1993**, *36*, 1918. b) G. Kokotos, A. J. Feuerherm, E. Barbayianni, I. Shah, M. Saether, V. Magrioti, T. Nguyen, V. Constantinou-Kokotou, E. A. Dennis, B. Johansen, *J. Med. Chem.* **2014**, *57*, 7523. c) F. Sielaffa, E. Böttcher-Friebertshäuserb, D. Meyera, S. M. Saupea, I. M. Volka, W. Gartenb, T. Steinmetzer, *Bioorg. Med. Chem. Lett.* **2011**, *21*, 4860.

[3] For selected examples of directed *ortho*-C–H functionalization of sulfonamides, see: a) H.-X. Dai, A. F. Stepan, M. S. Plummer, Y.-H. Zhang, J.-Q. Yu, *J. Am. Chem. Soc.* **2011**, *133*, 7222. b) M. V. Pham, B. Ye, N. Cramer, *Angew. Chem. Int. Ed.* **2012**, *51*, 10610. c) W. Ma, R. Mei, G. Tenti, L. Ackermann, *Chem. Eur. J.* **2014**, *20*, 15248. d) W. Xie, J. Yang, B. Wang, B. Li, *J. Org. Chem.* **2014**, *79*, 8278. e) W. J. Kerr, M. Reid, T. Tuttle, *ACS Catal.* **2015**, *5*, 402. f) D. Kalsi, B. Sundararaju, *Org. Lett.* **2015**, *17*, 6118.

[4] For selected examples of template directed *meta*-C–H functionalization, see: a) D. Leow, G. Li, T.-S. Mei, J.-Q. Yu, *Nature* **2012**, *486*, 518. b) R. Tang, G. Li, J.-Q. Yu, *Nature* **2014**, *507*, 215. c) L.Wan, N. Dastbaravardeh, G. Li, J.-Q. Yu, *J. Am. Chem. Soc.* **2013**, *135*, 18056. d) L. Chu, M. Shang, K. Tanaka, Q. Chen, N. Pissarnitski, E. Streckfuss, J.-Q. Yu, *ACS Cent. Sci.* **2015**, *1*, 394. e) Y. Kuninobu, H. Ida, M. Nishi, M. Kanai, *Nat. Chem.* **2015**, *7*, 712. f) H. J. Davis, M. T. Mihai, R. J. Phipps, *J. Am. Chem. Soc.* **2016**, *138*, 12759. g) M. Bera, A. Maji, S.K. Sahoo, D. Maiti, *Angew. Chem. Int. Ed.* **2015**, *54*, 8515. h) A. Maji, B. Bhaskararao, S. Singha, R. B. Sunoj, D. Maiti, *Chem. Sci.* **2016**, *7*, 3147. i) Z. Zhang, K. Tanaka, J.-Q. Yu, *Nature* **2017**, *543*, 538.

[5] For examples of Ru(II) catalyzed *meta*-C–H functionalization via *ortho*-cyclometallation, see: a) O. Saidi, J. Marafie, A. E. W. Ledger, P. M. Liu, M. F. Mahon, G. Kociok-Köhn, M. K. Whittlesey, C. G. Frost, *J. Am. Chem. Soc.* **2011**, *133*, 19298. b) N. Hofmann, L. Ackermann, *J. Am. Chem. Soc.* **2013**, *135*, 5877. c) C. J. Teskey, A. Y. W. Lui, M. F. Greaney, *Angew. Chem. Int. Ed.* **2015**, *54*, 11677. d) Z. Fan, J. Ni, A. Zhang, *J. Am. Chem. Soc.* **2016**, *138*, 8470.

[6] For other examples of *meta*-C–H functionalizations through steric or the electronic influence: a) T. Ishiyama, J. Takagi, K. Ishida, N. Miyaura, N. R. Anastasi, J. F. Hartwig, *J. Am. Chem. Soc.* **2002**, *124*, 390. b) J.-Y. Cho, M. K. Tse, D. Holmes, R. E. Maleczka Jr., M. R. Smith III, *Science* **2002**, *295*, 305. c) R. Bisht, B. Chattopadhyay, *J. Am. Chem. Soc.* **2016**, *138*, 84. d) R.

10.1002/anie.201704411

J. Phipps, M. J. Gaunt, *Science* **2009**, *323*, 1593. e) Y.-H. Zhang, B.-F. Shi, J.-Q. Yu, *J. Am. Chem. Soc.* **2009**, *131*, 5072. For an example using a traceless directing group relay strategy: f) J. Luo, S. Preciado, I. Larrosa, *J. Am. Chem. Soc*. **2013**, *136*, 4109.

[7] For selected examples using Pd/norbornene relay process to achieve *meta*-C–H arylation, see: a) X.-C. Wang, W. Gong, L.-Z. Fang, R.-Y. Zhu, S. Li, K. M. Engle, J.-Q. Yu, *Nature* **2015**, *519*, 334. b) Z. Dong, J. Wang, G. Dong, *J. Am. Chem. Soc*. **2015**, *137*, 5887. c) P.-X. Shen, X.-C. Wang, P. Wang, R.-Y. Zhu, J.-Q. Yu, *J. Am. Chem. Soc.* **2015**, *137*, 11574. d) J. Han, L. Zhang, Y. Zhu, Y. Zheng, X. Chen, Z.-B. Huang, D.-Q. Shi, Y. Zhao, *Chem. Comm.* **2016**, *52*, 6903. e) P. Wang, M. E. Farmer, X. Huo, P. Jain; P.-X. Shen, M. Ishoey, J. E. Bradner, S. R. Wisniewski, M. E. Eastgate, J.-Q. Yu, *J. Am. Chem. Soc.* **2016**, *138*, 9269. f) P. Wang, G.-C. Li, P. Jain, M. E. Farmer, J. He, P.-X. Shen, J.-Q. Yu, *J. Am. Chem. Soc.* **2016**, *138*, 14092. g) H. Shi, P. Wang, S. Suzuki, M. E. Farmer, J.-Q. Yu, *J. Am. Chem. Soc*. **2016**, *138*, 14876. h) P. Wang, M. E. Farmer, J.-Q. Yu, *Angew. Chem. Int. Ed.* **2017**, *56*, 5125.

[8] For reviews on norbornene mediated *ortho*-C–H functionalizations, see: a) M. Catellani, *Top. Organomet. Chem.* **2005**, *14*, 21. b) A. Martins, B. Mariampillai, M. Lautens, *Top. Curr. Chem.* **2010**, *292*, 1. c) N. Della Ca', M. Fontana, E. Motti, M. Catellani, *Acc. Chem. Res.* **2016**, *49*, 1389. For indole C-2 C–H functionalizations using norbornene as a transient mediator: d) L. Jiao, T. Bach, *J. Am. Chem. Soc.* **2011**, *133*, 12990. e) L. Jiao, E. Herdtweck, T. Bach, *J. Am. Chem. Soc*. **2012**, *134*, 14563.

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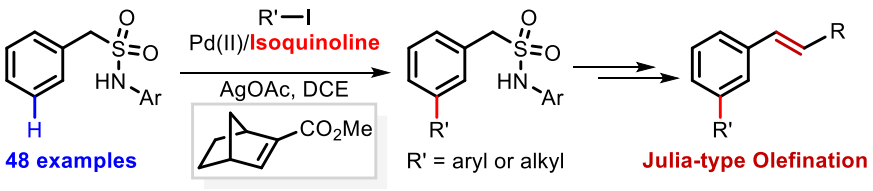
Meta-C–H Arylation and Alkylation of Benzylsulfonamide Enabled by Pd(II)/Isoquinoline Catalyst



Palladium(II)-catalyzed *meta*-C–H arylation and alkylation of benzylsulfonamide using 2-carbomethoxynorbornene (NBE-CO_2Me) as a transient mediator are realized using isoquinoline as a ligand. This protocol features broad substrate scope and excellent functional group tolerance. The *meta*-substituted benyzlsulfonamide can be readily transformed to sodium sulfonate, sulfonate ester, sulfonamide, as well as styrenes via Julia-type olefination.