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Para-Selective Arylation of Arenes: A Direct Route to Biaryls by **Norbornene Relay Palladation**

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Dedicated to Prof. Sourav Pal on the occasion of his 65th birthday

ABSTRACT: Biaryls are extremely important structural motifs in natural products, biologically active components and pharmaceuticals. Selective synthesis of biaryls by distinguishing the subtle reactivity difference of distal arene C-H bonds are significantly challenging. Herein we embarked on exploring the para-selective C-H arylation which is contemplated by a unique combination of a meta-directing group and norbornene as transient mediator. Upon direct meta-C-H palladation, one bond relay palladation has been envisioned in presence of norbornene and subsequently para-C-H arylation is achieved for phosphonates and phenols bearing sulfonates. 2.6disubstitutions. The protocol is amenable with electron deficient aryl iodides. Multisubstituted arenes and phenols were obtained by postsynthetic modification of the products. The protocol allowed to synthesize hexa-substituted benzene by sequential selective distal C-H functionalization.

An unprecedented upsurge has been observed over last few decades to perform the site selective transformations of inert C-H bonds. The selective C-H functionalizations eventually enriched synthetic toolbox to build up molecular complexity that are present in natural products, drug molecules and pharmaceuticals.¹ In this regard, directing group (DG) assisted C-H functionalization has been considered as one of the successful approaches. However, major success stories evolved around the proximal ortho-C-H activation as it provides required impetus to overrule steric or electronic controlled functionalizations by the formation of stable five to six membered metallacycle.² Selective functionalizations at distal meta- and para-position still remained less developed. While a few elegant approaches are known to expand the scope of arene meta-C-H functionalizations,3 in contrary, para-selective C-H functionalization⁴ are significantly limited to a few scaffolds. Nevertheless, Itami and co-workers have developed a protocol for para-selective borylation by utilising steric governance of ligand under iridium catalysis in 2015 (Scheme 1b).5 Chattopadhyay and co-workers demonstrated a L-shaped template to perform the Ir-catalyzed borylation of alkyl benzoate (Scheme 1c).⁶ Hiyama and co-workers have disclosed a C4selective alkylation of pyridine by utilizing the nickel and Lewis acid catalysis (Scheme 1d).7 Nakao group has revealed paraalkylation with nickel and para-borylation by iridium catalyst in association with Lewis acid.8 A Ru-catalyzed para-selective alkylation was achieved by Frost (Scheme 1e)^{9a} and Zhao group (Scheme 1f)^{9b,c} in 2017 and 2018, respectively. While all these reports are centered around borylation and alkylation, in 2015, we reported a D-shaped template to promote para-selective

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olefination under palladium catalysed conditions (Scheme 1a).^{10a} Subsequently we have expanded the scope of functionalization in a para-selective fashion by employing Pd10b-d as well Rh11 catalyst. Very recently, in 2020, Yu group has revealed an elegant protocol for para-selective arylation of hydrocinnamic acid (Scheme 1g) with the help of Pd/norbornene co-operative catalysis.12 The method also demonstrated a bimetallic approach where one end of a heterocycle is docked with a palladium-bound template and the distal C-H bond at the other end undergoes C-H activation by the appended cyano group subsequently further one bond relay process in presence of norbornene permits the selective functionalization at the "previously inaccessible remote C-H bond" of heterocycles. Controlling such a complex catalytic process, which enables site-selective distal C-H arylation of a wide range of heterocycles and hydrocinnamic acids, by proper combination of reagents will certainly be beneficial for modern organic synthesis. Scheme 1. Prior reports on para-selective functionalization



Nakao, 2016 e. Frost. 2017 f. Zhao, 2018 significantly building blocks Biaryls are important pharmaceuticals and agrochemicals owing to its stability and easy installation in organic-frameworks which provides required geometric rigidity and it is also well known as a unique spacer in organic materials.¹³ Additionally, it's extended π -conjugation can manipulate several physico-chemical properties such as conductance, light absorption and emission or magnetic properties which plays a crucial role in developing optoelectronic devices, liquid crystals and in several other organic materials.¹⁴ Therefore, it is extensively important to incorporate an arene ring selectively at para-position which will accelerate the development related to biaryl synthesis. We, in particular, were interested in *para*-C-H arylation relying on DG-assisted strategy. Unfortunately, till date, our D-shaped assembly for paraselective C-H functionalizations by palladium is successful only for olefination,^{10a,b} acetoxylation,^{10a,e} silvlation^{10c} ketonisation^{10d} and cyanation^{10f} reaction. However, the urge to find an alternate approach that would allow us to diversify the scope of parafunctionalizations, in particular, arylation has driven us to explore

the potential of one bond palladium relay Catellani chemistry.¹⁵ Inspired by the Pd-norbornene co-operative catalysis for meta-C-H functionalization with the help of *ortho*-DG,¹⁶ we envisaged that our previously developed meta-DG can facilitate the meta-C-H palladation, subsequent norbornene coordination and β migratory insertion will result a palladium relay process towards para-C-H activation. This para-C-H palladated species will now

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provide a platform to incorporate several functional moieties selectively at the para-position with suitable electrophilic coupling partner.





We anticipated and faced a series of potential issues for implementing the proposed para-C-H functionalization with norbornene (Scheme 2). Upon initial meta-C-H palladation (B) involving meta-DG, direct meta-functionalization can lead to the meta-functionalized products (C), which will prevent further palladation relay. On the other hand, if the meta-functionalization is overridden by the faster norbornene coordination and subsequent migratory insertion to allow the expected palladium relay, then there are two probable paths of C-H palladation; path A: ortho-palladation (D), which again prohibits desired distal C-H activation, Path B: the expected para-C-H palladation (E). In either case, reductive elimination leads to the formation of the benzocyclobutane moiety (F and G, respectively), which precludes the possibility of further C-H functionalization. Table 1. Optimization of template and DGs



Nevertheless, a faster electrophilic oxidative addition can suppress the unwanted cyclobutane formation. Finally, a sequence of reductive elimination, β -carbon elimination and protonation is followed to produce the desired parafunctionalized compound (I) and extrusion of norbornene. Similar reaction sequence is also followed in Path B to deliver the potential side product H. Yet another impending challenge is the competitive binding between active norbornene and the weak coordinating DG, which may prevent the initial meta-C-H activation.

Despite the aforementioned difficulties, we devoted our focus in finding a prudent combination of substrate, catalyst, ligand, norbornene derivative and electrophile. We started with phenylmethane sulfonate scaffold (T1) in presence of norbornene carboxylate (NBE-CO2Me) (2 equiv.), Pd(OAc)2 (10 mol%), N-Ac-Gly-OH (20 mol%), AgOAc (2 equiv.) and methyl-4-iodobenzoate (2 equiv.).^{15h, 16b} Unfortunately, we failed to desired para-arylated compound. We remained detect unsuccessful while 2-methyl phenylmethane sulfonate scaffold (T2) was treated in a similar fashion. These observations led us to realize that the steric congestion should be increased in the transition state of β -carbon elimination step. Hence, it is important to provide an ortho-substitution to ensure the necessary steric pulse. The proposition was also established by the study of Catellani and Dong.^{15b-d, 15k} It was found that the β carbon elimination was facilitated by the presence of orthodisubstitution.





40 mol% N-Ac-Gly-OH, ^breaction run for 36 h

Encouraged by these studies, we were delighted to obtain the para-selective arylation while 2,6-dichlorobenzylsulfonyl ester was treated with methyl-4-iodobenzoate in presence of Pd(OAc)₂ (10 mol%), N-Ac-Gly-OH (20 mol%), AgOAc (2 equiv.), and NBE-CO2Me (2 equiv.) in HFIP at 80 °C in 56% yield with para:others >20:1 selectivity. Incorporation of 2,6-disubstitution was beneficial in two ways; (i) it eliminates the possibility of norbornene relay to ortho-position and the subsequent side reactions, (ii) it provides the propulsive drive for β -carbon elimination, one of the crucial steps of the catalytic process.

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With the T_3 template we carried out the optimization study for other potential directing group including weak co-ordinating cyano based DGs (**DG**₁ to **DG**₃) as well as strong σ -coordinating pyrimidine-based DG (**DG**₄), which we have extensively studied recently. Simple 2-cyanophenol DG (**DG**₁) was found to be inferior compared to the other cyano-based DGs, whereas **DG**₂ was found to be superior than **DG**₃ and **DG**₄. Briefly accounting on different norbornene derivatives, it was observed that norbornene carboxylate (**N**₃) provided better reactivity in comparison to **N**₁ and **N**₂. Finally the detailed optimization studies revealed that 10 mol% Pd(OAc)₂, 20 mol% *N*-Ac-Gly-OH, 3 *equiv*. AgOAc and 1.5 *equiv*. NBE-CO₂Me were required to achieve the maximum yield and selectivity in presence of 3 *equiv*. of iodoarene at 110 °C in HFIP.





para:others ratio determined by ¹H NMR of crude reaction mixture, ^awith 20 mol% Pd(OAc)₂, 40 mol% *N*-Ac-Gly-OH, ^breaction run for 36 h

After having the optimized reaction conditions in hand, we turned our focus in diversifying the reaction scope. *para*-Arylated sulfonate scaffolds can act as important synthones in organic synthesis. Upon hydrolysis, sulfonic acid can be derived and the corresponding salts are used in coupling reactions. To diversify the scope of sulfonate scaffolds we tested several aryl iodides bearing ester (**3a** and **3b**) or nitro (**3c**) groups to provide the desired *para*-arylated compounds in good to excellent yields and selectivity. As mentioned earlier, 2,6-disubstitution was

unavoidable^{15b-d,15k,12} to harness the desired palladium relay reactivity to achieve *para*-selective arylation. Therefore, we diversified the scope of arenes with respect to various 2,6disubstituted templates. *ortho*-Chloro-fluoro-di-substituted sulfonate scaffolds (1d - 1k) were compatible under the reaction conditions and produced the desired product up to 81% (3d) yield in >20:1 selectivity. Strikingly, electron deficient di-fluoro substituted scaffolds have also been successfully employed for the desired biaryl synthesis under the present protocol without compromising yields and selectivity (3i and 3m). The desired biaryl compounds were confirmed by X-ray crystallography (3hand 3k).

Table 4. para-C-H Arylation of phenol scaffolds



(p:others >20:1) (p:others >20:1) (p:others >20:1) para:others ratio determined by ¹H NMR of crude reaction mixture

The generality of the protocol was further examined with respect to the benzylphosphonate scaffolds. Organophosphonates are prevalent structural motifs in bio-organic, pharmaceuticals, agrochemicals and in oragnocatalysis.¹⁷ Organophosphonates are also well known synthones in synthetic chemistry that includes alkene synthesis via Horner-Wadsworth-Emmons reaction.18 Therefore, of а range 2.6-disubstituted benzylphosphonate were employed for late stage para-arylation under the present reaction conditions. Substituents, irrespective of their steric and electronic nature are well tolerated under the present conditions. Electron rich and sterically encumbered 2,6dimethyl substituted phosphonate scaffolds delivered the paraarylated products smoothly up to 75% yield in excellent selectivity (6a). 2,6-Dihalo substituted arenes (6j - 6r) or 2fluoro-6-trifluoromethyl substituted arenes (6s - 6u), which are electronically poor substrates and C-H activation step is retarded, have easily delivered the para-arylated products without compromising in yields and selectivity. Aryl iodides containing electron withdrawing groups at ortho-, meta-, para- or even ortho-para-positions were easily coupled to deliver the desired products.

To diversify the scope of this protocol, we later on embarked on exploring the scope for *para*-arylation of phenols. A simple route to *para*-arylation of phenols will certainly be beneficial for drug diversification, natural product synthesis and biologically active components preparation. In this regard, we were able to demonstrate that both the electron rich and electron deficient phenol can be *para*-arylated under present reaction conditions.

A number of aryl iodides bearing functional groups such as ester, acyl, amide, nitro have been utilized for *para*-arylation (Table 4). **Scheme 3.** Removal of directing group



^astandard *para*-arylation conditions; ^bethylacrylate (2 equiv.), Pd(OAc)₂ (10 mol%), N-Ac-Gly-OH (20 mol%), Ag₂CO₃ (2 equiv.), HFIP, 80 °C, 24 h; ^cPhI(OAc)₂ & Ac₂O (2 equiv.), Pd(OAc)₂ (10 mol%), N-Ac-Gly-OH (20 mol%), HFIP, 80 °C, 24 h

The directing group was successfully removed from the paraarylated compounds to diversify the synthetic scope of present protocol (Scheme 3). para-Arylated phenylmethane sulfonic acid (10) and para-arylated phenylmethane phosphonic acid (12) were obtained in 78% and 74% yields, respectively, under basic hydrolysis of 3a and 6m (Scheme 3, eq. 1 and eq. 2, respectively). After procuring the para-arylation by palladium relay process, a direct meta-functionalization can be achieved with the help of appended meta-DG. In this context, paraarylated compound, 6m was employed under meta-olefination conditions and a di-meta-olefinated compound (13) was obtained in 66% yiled (Scheme 4, eq. 1). Thus a hexasubstituted benzene, 13 is easily accessible using this sequential functionalization strategy. Fully functionalized phenol, 15 which is difficult to prepare by other methods, was also synthesized using this protocol (Scheme 4, eq. 3). Neverthless, carboxylate directed ortho-functionalization of appended paraaryl group was also amenable without any interefernce from *meta*-DG. *ortho*-Acetoxylation of lower benzene in **6m** was thus offered **14** in 61% yiled (Scheme 4, *eq. 2*).

In summary, a para-selective arylation has been achieved employing our previously developed simple cyanophenol based meta-directing group. То attain the para-selective functionalization we relied on one bond relay palladation in presence of norbornene as the transient mediator. The scope of the protocol is demonstrated with respect to sulfonate, phosphonate and phenol substrates. Electron deficient, activated aryl iodides are coupled with 2,6-disubstituted arenes with precise para-selectivity. Notably, 2,6-disubstitution is unavoidable to harness the desired reactivity. Successful removal of appended directing group resulted in functionalized phenylmethane sulfonic acid and phenylmethane phosphonic acid. Sequential multifunctionalizations were also achieved to derive fully substituted benzene and phenol.

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REFERENCES

 For selected publications, see: (a) L. McMurray, F. O'Hara, M. J. Gaunt, *Chem. Soc. Rev.* 2011, *40*, 1885-1898; (b) J. Wencel-Delord, F. Glorius, *Nat. Chem.* 2013, *5*, 369-375; (c) D. J. Abrams, P. A. Provencher, E. J. Sorensen, *Chem. Soc. Rev.* 2018, *47*, 8925-8967; (d) A. Tortajada, F. J.-Hernández, M. Börjesson, T. Moragas, R. Martin, *Angew. Chem. Int. Ed.* 2018, *57*, 15948-15982; (e) J. W. Lee, K. N. Lee, M.-Y. Ngai, *Angew. Chem. Int. Ed.* 2019, *58*, 11171-11180; (f) K. N. Lee, M.-Y. Ngai, *Chem. Commun.* 2017, *53*, 13093-13112; (g) D. Qian, J. Sun, *Chem. Eur. J.* 2019, *25*, 3740-3751; (h) J. Li, S. Grosslight, S. J. Miller, M. S. Sigman, F. D. Toste, *ACS Catal.* 2019, *9*, 9794–9799; (i) A. J. Metrano, S. J. Miller, *Acc. Chem. Res.* 2019, *52*, 199-215; (j) S. Govaerts, A. Nyuchev, T. Noel, *J. Flow Chem.* 2020, *10*, 13-71.
 Selected examples on DG assisted *ortho*-functionalization: (a) S. Murai, F. Kakiuchi, S. Sekine, Y. Tanaka, A. Kamatani, M. Sonoda, N. Chatani, *Nature* 1993, 366, 529-531; (b) T. W. Lyons, M. S. Sanford, *Chem. Rev.* 2010, *110*, 1147-1169; (c) N. Kuhl, M. N. Hopkinson, J. Wencel-Delord, F. Glorius, *Angew. Chem. Int. Ed.* 2013, *52*, 11726-11743; (e) L. Ackermann, *Acc. Chem. Res.* 2014, *47*, 281-295; (f) Z. Huang, H. N. Lim, F. Mo, M. C. Young, G. Dong,

Chem. Soc. Rev. 2015, 44, 7764-7786; (g) B. J. Knight, J. O. Rothbaum, E. M.
Ferreira, Chem. Sci. 2016, 7, 1982-1987; (h) T. Gensch, M. N. Hopkinson, F.
Glorius, J. Wencel - Delord, Chem. Soc. Rev. 2016, 45, 2900-2936; (i) Q. Li, B.
J. Knight, Chem. Eur. J. 2016, 22, 13054-13058; (j) B. Li, K. Seth, B. Niu, L.
Pan, H. Yang, H. Ge, Angew. Chem. Int. Ed. 2018, 57, 3401-3405; (k) C.
Sambiagio, D. Schonbauer, R. Blick, T. Dao-Huy, G. Pototschnig, P. Schaaf,
T. Wiesinger, M. F. Zia, J. Wencel-Delord, T. Besset, B. U. W. Maes, M.
Schnurch, Chem. Soc. Rev. 2018, 47, 6603-6743; (l) B. Niu, K. Yang, B.
Lawrence, H. Ge, ChemSusChem 2019, 12, 2955-2969; (m) H. Kim, R. S.
Thombal, H. D. Khanal, Y. R. Lee, Chem. Commun. 2019, 55, 13402-13405;

(n) R. S. Thombal, Y. R. Lee, Org. Lett. 2020, 22, 3397-3401.
3. Selected reports on meta-C-H functionalization: (a) T. Ishiyama, J. Takagi, K. Ishida, N. Miyaura, N. R. Anastasi, J. F. Hartwig, J. Am. Chem. Soc. 2002, 124, 390-391; (b) R. J. Phipps, M. J. Gaunt, Science 2009, 323, 1593-1597; (c) O. Saidi, J. Mardie, 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, 19298-19301; (d) J. Cornella, M. Righi, I. Larrosa, Angew. Chem. Int. Ed. 2011, 40, 9429-9432; (e) D. Leow, G. Li, T.-S. Mei, J.-Q. Yu, Nature 2012, 486, 518-522; (f) N. Hofmann, L. Ackermann, J. Am. Chem. Soc. 2013, 135, 5877-5884; (g) M. Tobisu, N. Chatani, Science 2014, 343, 850-851; (h) Y. Kuninobu, H. Ida, M. Nishi, M. A. Kanai, Nat. Chem. 2015, 127, 8635-8639; (j) S. Li, H. Ji, L. Cai, G. Li, Chem. Sci. 2015, 6, 5595-5600; (k) R. Bisht, B. Chattopadhyay, J. Am. Chem. Soc. 2016, 138, 84-87; (l) S. Li, L. Cai, H. Ji, L. Yang, G. Li, Nat. Chem. Soc. 2016, 7, 10443-10450; (m) H. P. L. Gemoets, G. Taudoto, K. Ver-straete, V. Hessel, T. Noël, Angew. Chem. Int. Ed. 2017, 56, 7161-7165; (n) U. Dutta, A. Modak, B. Bhaskararao, M. Bera, S. Bag, A.

WILEY-VCH

Mondal, D. W. Lupton, R. B. Sunoj, D. Maiti, *ACS Catal.* **2017**, *7*, 3162-3168; (o) H. P. L. Gemoets, G. Laudadio, K. Verstraete, V. Hessel, T. Noel, *Angew.* Chem. Int. Ed. 2017, 56, 7161-7165; (p) S. Li, H. Wang, Y, Weng, G. Li, Angew. Chem. Int. Ed. 2019, 58, 18502-18507; (q) S. Porey, X. Zhang, S. Bhowmick, V. Singh, S. Guin, R. S. Paton, D. Maiti, J. Am. Chem. Soc. 2020, 142, 3762-3774; (r) G. R. Genov, J. L. Douthwaite, A. S. K. Lahdenperä, D. C. Gibson, R. J. Phipps, *Science* **2020**, *367*, 1246-1251; (s) S. Bag, M. Petzold, A. Sur, S. Bhowmick, D. B. Werz, D. Maiti, *Chem. Eur. J.* **2019**, *25*, 9433 – 9437; (t) M. Brochetta, T. Borsari, S. Bag, S. Jana, S. Maiti, A. Porta, D. B. Werz, G. Zanoni, D. Maiti, *Chem. Eur. J.* **2019**, *25*, 10323-10327.

4. Selected examples on para-C-H functionalization: (a) G. Brasche, J. Garcia-Fortanet, S. L. Buchwald, Org. Lett. **2008**, *10*, 2207-2210; (b) K. Sun, Y. Li, T. Xiong, J. Zhang, Q. Zhang, J. Am. Chem. Soc. **2011**, *133*, 1694-1697; (c) X. J. Am, G. Z. Liang, G. Zhang, J. Am. Chem. Soc. 2011, 133, 1094-1057, (c) X.
 Guo, C.-J. Li, Org. Lett. 2011, 13, 4977-4979; (d) X. Wang, D. Leow, J.-Q. Yu,
 J. Am. Chem. Soc. 2011, 133, 13864-13867; (e) W. C.-L. Ciana, R. J. Phipps,
 J. R. Brandt, F.-M. Meyer, M. J. Gaunt, Angew. Chem. Int. Ed. 2011, 50, 458-462; (f) T. Ball, G. C. Lloyd-Jones, C. A. Russell, Science 2012, 1644-1648; (g) J. P. Brand, J. Waser, *Org. Lett.* **2012**, *14*, 744-748; (h) W. Liu, L. Ackermann, *Org. Lett.* **2013**, *15*, 3484-3486; (i) L. X. C. Cambeiro, T. C. Ackermann, Org. Lett. 2013, 75, 3484-3485; (i) L. X. C. Cambero, T. C.
 Boorman, P. Lu, I. Larrosa, Angew. Chem. Int. Ed. 2013, 52, 1781-1784; (j) A.
 M. Suess, M. Z. Ertem, C. J. Cramer, S. S. Stahl, J. Am. Chem. Soc. 2013, 135, 9797-9804; (k) Z. Yu, B. Ma, M. Chen, H.-H. Wu, L. Liu, J. Zhang, J. Am.
 Chem. Soc. 2014, 136, 6904–6907; (l) Y. Xi, Y. Su, Z. Yu, B. Dong, E. J.
 McClain, Y. Lan, X. Shi, Angew. Chem. Int. Ed. 2014, 53, 9817-9821; (m) G. B.
 Boursalian, W. S. Ham, A. R. Mazzotti, T. Ritter, Nat. Chem. 2016, 8, 810-815; (n) B. Ma, Z. Chu, B. Huang, Z. Liu, L. Liu, J. Zhang, *Angew. Chem. Int. Ed.* **2017**, *56*, 2749-2753; (o) Y.-X. Luan, T. Zhang, W.-W. Yao, K. Lu, L.-Y. Kong, Y.-T. Lin, M. Ye, J. Am. Chem. Soc. 2017, 139, 1786-1789; (p) J.-M. Li, Y.-H. Wang, Y. Yu, R.-B. Wu, J. Weng, G. Lu, ACS Catal. 2017, 7, 2661-2667; (q) M. T. Mihai, B. D. Williams, R. J. Phipps, *J. Am. Chem. Soc.* **2019**, *141*, 15477-15482; (r) T. Adak, J. Schulmeister, M. C. Dietl, M. Rudolph, F. Rominger, A. S. K. Hashmi, Eur. J. Org. Chem. 2019, 3867–3876; (s) F. de Azambuja, M.-H. Yang, T. Feoktistova, M. Selvaraju, A. C. Brueckner, M. A. Grove, S. Koley, P. H.-Y. Cheong, R. A. Altman, Nat. Chem. 2020, 12, 489-496.

5. (a) Y. Saito, Y. Segawa, K. Itami, J. Am. Chem. Soc. 2015, 137, 5193-5198; (b) B. E. Haines, Y. Saito, Y. Segawa, K. Itami, D. G. Musaev, ACS Catal. 2016, 6, 7536-7546.

6. M. E. Hoque, R. Bisht, C. Haldar, B. Chattopadhyay, J. Am. Chem. Soc. 2017. 139. 7745-7748.

7. (a) Y. Nakao, Y. Yamada, N. Kashihara, T. Hiyama, J. Am. Chem. Soc. 2010, 132, 13666-13668; (b) C.-C. Tsai, W.-C. Shih, C.-H. Fang, C.-Y. Li, T.-G. Ong, G. P. A. Yap, J. Am. Chem. Soc. 2010, 132, 11887-11889.

8. (a) S. Okumura, S. Tang, T. Saito, K. Semba, S. Sakaki, Y. Nakao, *J. Am. Chem. Soc.* **2016**, *138*, 14699-14704; (b) L. Yang, K. Semba, Y. Nakao, Angew. Chem. Int. Ed. **2017**, *56*, 4853-4857; (c) S. Okumura, Y. Nakao, Org. Lett. **2017**, *19*, 584–587. 9. (a) J. A. Leitch, C. L. McMullin, A. J. Paterson, M. F. Mahon, Y. Bhonoah, C.

G. Frost, Angew. Chem. Int. Ed. 2017, 56, 15131-15135; (b) C. Yuan, L. Zhu, C. Chen, X. Chen, Y. Yang, Y. Lan, Y. Zhao, Nat. Commun. 2018, 9, 1189; (c) Yuan, L. Zhu, R. Zeng, Y. Lan, Y. Zhao, Angew. Chem. Int. Ed. 2018, 57, 1277-1281

10. (a) S. Bag, T. Patra, A. Modak, A. Deb, S. Maity, U. Dutta, A. Dey, R. Kancherla, A. Maji, A. Hazra, M. Bera, D. Maiti, J. Am. Chem. Soc. 2015, 137, 11888-11891; (b) T. Patra, S. Bag, R. Kancherla, A. Mondal, A. Dey, S. Pimparkar, S. Agasti, A. Modak, D. Maiti, Angew. Chem. Int. Ed. 2016, 55, 7751-7755; (c) A. Maji, S. Guin, S. Feng, A. Dahiya, V. K. Singh, P. Liu, D. Maiti, Angew. Chem. Int. Ed. 2017, 56, 14903-14907; (d) A. Maji, A. Dahiya, G. Lu, T. Bhattacharya, M. Brochetta, G. Zanoni, P. Liu, D. Maiti, Nat. Commun. **2018**, *9*, 3582; (e) M. Li, M. Shang, H. Xu, X. Wang, H.-X. Dai, J.-Q. Yu. Org. *Lett.* **2019**, *21*, 540-544; (f) S. Pimparkar, T. Bhattacharya, A. Maji, A. Saha, R. Jayarajan, U. Dutta, G. Lu, D. W. Lupton, D. Maiti, *Chem. Eur. J.* **2020**. DOI: 10.1002/chem.202001368.

11. U. Dutta, S. Maiti, S. Pimparkar, S. Maiti, L. R. Gahan, E. H. Krenske, D. W. Lupton, D. Maiti, Chem. Sci. 2019, 10, 7426-7432.

12. H. Shi, Y. Lu, J. Weng, K. L. Bay, X. Chen, K. Tanaka, P. Verma, K. N.

Houk, J.-Q. Yu, *Nat. Chem.* 2020, *12*, 399-404.
Houk, J.-Q. Yu, *Nat. Chem.* 2020, *12*, 399-404.
(a) R. D. Taylor, M. MacCoss, A. D. G. Lawson, *J. Med. Chem.* 2014, *57*, 5845-5859; (b) M. Simonetti, D.M. Cannas, X. Just-Baringo, I. J. Vitorica-Yrezabal, I. Larrosa, *Nat. Chem.* 2018, *10*, 724-731.
J. L. Segura, N. Martín, *J. Mater. Chem.* 2000, *10*, 2403-2435.

 (a) M. Catellani, T. Frignani, A. Ragoni, Angew. Chem. Int. Ed. 1997, 36, 119-122;
 (b) M. Catellani, Synlett 2003, 3, 298-313;
 (c) A. Martins, B. Mariampillai, M. Lautens, Top. Curr. Chem. 2009, 292, 1-33; (d) D. I. Chai, P. Marampillai, M. Lautens, *Top. Curr. Chem.* 2009, 292, 1-33; (d) D. I. Chai, P. Thansandote, M. Lautens, *Chem. Eur. J.* 2011, *17*, 8175-8188; (e) Z. Dong, *Ong. J. Am. Chem. Soc.* 2013, *135*, 18350-18353; (f) J. Ye, M. Lautens, *Nat. Chem.* 2015, *7*, 863-870; (g) N. Della Ca', M. Fontana, E. Motti, M. Catellani, *Acc. Chem. Res.* 2016, *49*, 1389-1400; (h) Q. Li, E. M. Ferreira, *Chem. Eur. J.* 2017, *23*, 11519-11523; (i) J. Wang, R. Li, Z. Dong, P. Liu, G. Dong, *Nat. Chem.* 2018, *10*, 866-872; (j) R. Li, G. Dong, *Angew. Chem. Int. Ed.* 2018, *57*, 1697-1701; (k) J. Wang, R. Li, Z. Dong, P. Liu, G. Chen, 2018, *10*, 866-872; (j) G. Qian, M. Bai, S. Gao, H. Chen, S. Zhou, H.-G. Chen, W. Yan, Q. Zhou, *Angew. Chem. Int. Ed.* 2018, *57*, 10980-10984; (m) Z. S. Liu, Q. Gao, Q. Zhou, Angew. Chem. Int. Ed. 2018, 57, 10980-10984; (m) Z.-S. Liu, Q. Gao,

H.-G. Cheng, Q. Zhou, *Chem. Eur. J.* **2018**, *24*, 15461-15476; (n) J. Wang, G. Dong, *Chem. Rev.* **2019**, 119, 7478-7528; (o) H.-G. Cheng, S. Chen, R. Chen, Q. Zhou, Angew. Chem. Int. Ed. 2019, 58, 5832-5844; (p) Q. Gao, Y. Shang, F. Song, F. J. Ye, Z.-S. Liu, L. Li, H.-G. Cheng, Q. Zhou, J. Am. Chem. Soc. 2019, 141, 15986-15993; (q) S. Chen, P. Wang, H.-G. Cheng, C. Yang, Q. Zhou, Chem. Sci. 2019, 10, 8384-8389; (r) J. Wang, Y. Zhou, X. Xu, P. Liu, G.

Zhon, Grenn, Sol. 2019, 10, 0007-0005, (1) a. transfer tr Li, K. M. Engle, J.-Q. Yu, Nature 2015, 519, 334-338; (d) H. Shi, A. N. Herron, Y. Shao, Q. Shao, J.-Q. Yu, *Nature* **2018**, *558*, 581-586. 17. (a) D. S. Surry, S. L. Buchwald, *Chem. Sci.* **2011**, *2*, 27-50; (b) W. Tang, X.

Zhang, *Chem. Rev.* 2003, *108*, 3029-3070.
18. (a) W. S. Wadsworth, W. D. Emmons, *J. Am. Chem. Soc.* 1961, *83*, 1733-1738; (b) J. Boutagy, R. Thomas, *Chem. Rev.* 1974, *74*, 87-99.

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Directing group assisted regioselective C-H functionalization at distal position has drawn significant attention in recent years. Palladium-norbornene cooperative catalysis, typically known as Catellani reaction, was recently investigated to effectuate distal *meta-* and *para-*C-H functionalization. In the present report, we demonstrated *para-*selective arylation of sulfonates, phosphonates and phenols derivatives bearing 2,6-disubstitutions with the help of a suitable *meta-*directing group in association with Pd and norbornene cooperative catalysis. The present protocol allows to synthesize hexa-substituted arenes easily *via* sequential regioselective C-H functionalization.