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Synthesis of Polycyclic Molecules by Double $C(sp^2)-H/C(sp^3)-H$ Arylations with a Single Palladium Catalyst

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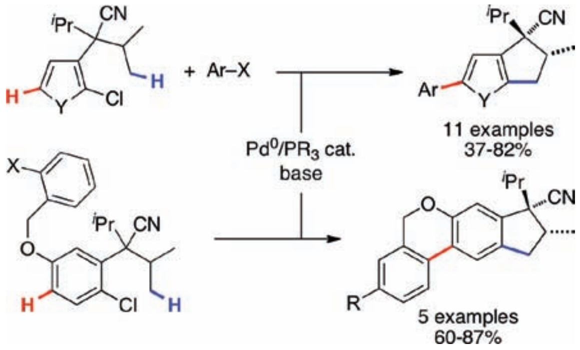
ABSTRACT



Polycyclic molecules were obtained in good yields by double $C(sp^2)-H/C(sp^3)-H$ arylations mediated by a single palladium/phosphine catalyst. Both double intermolecular/intramolecular and intramolecular/intramolecular C−C couplings were performed successfully, which indicates that this concept has a broad applicability for the rapid construction of molecular complexity.

In recent years, transition-metal-catalyzed C−H bond functionalization has emerged as a powerful tool to transform otherwise unreactive C−H bonds into carbon −carbon or carbon−heteroatom bonds.[1,2] In particular, C−H arylation has become an attractive alternative to traditional C−C cross-coupling reactions due to the minimization of stoichiometric metallic waste and the costs associated with the preparation of starting materials.[3] Efforts by our group[4] and others[5,6] in the context of alkane $C(sp^3)-H$ arylation under palladium(0) catalysis have led to a greater scope for intramolecular reactions, generating

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(1) *Handbook of C−H Transformations*; Dyker, G., Ed.; Wiley-VCH: Weinheim, 2005.

(2) *Topics in Current Chemistry*, Vol. 292; Yu, J.-Q., Shi, Z., Eds.; Springer: Heidelberg, 2010.

(3) Selected recent reviews: (a) Campeau, L.-C.; Fagnou, K. *Chem. Commun.* **2006**, 1253. (b) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174. (c) McGlacken, G. P.; Bateman, L. M. *Chem. Soc. Rev.* **2009**, *38*, 2447. (d) Bellina, F.; Rossi, R. *Tetrahedron* **2009**, *65*, 10269. (e) Ackermann, L.; Vicente, R.; Kapdi, A. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 9792.

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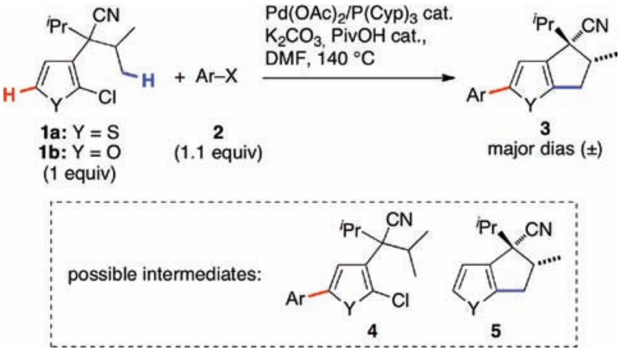
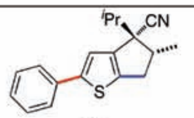
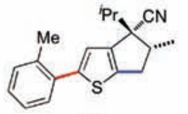
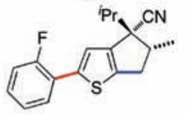
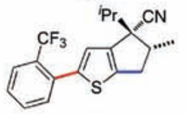
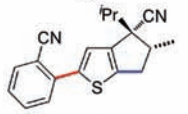
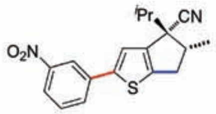
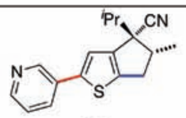
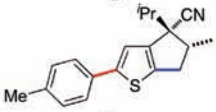
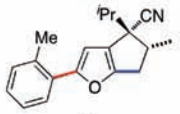
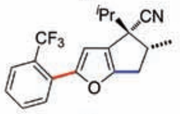
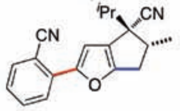
Table 1. Double Intermolecular C(sp^2)−H/Intramolecular C(sp^3)−H Arylation of Thiophenes and Furans[a]



entry	X	product	yield (%)[b]	dr[c]
1	Br	 **3a**	37	>95:5
2	Br	 **3b**	82	16:1
3	Cl		60	4:1
4	Br	 **3c**	65	7:1
5	Br	 **3d**	79	6:1
6	Br	 **3e**	80	5:1
7	Br	 **3f**	72	17:1
8	Cl	 **3g**	62	4:1
9	Br	 **3h**	0[d]	–
10	Br	 **3i**	65	7:1
11	Br	 **3j**	78	6:1
12	Br	 **3k**	50	5:1

[a] Reaction conditions: heteroaryl chloride (1 equiv), aryl halide (1.1 equiv), Pd(OAc)$_2$ (5 mol %), P(Cyp)$_3$•HBF$_4$ (20 mol %), K$_2$CO$_3$ (2 equiv), PivOH (30 mol %), DMF, 140 °C, 6−24 h. [b] Yield of the isolated product. [c] Determined by ^{1}H NMR analysis of the crude reaction mixture. [d] 1:1 ratio of **1a**/**4** after 14 h.

various motifs of synthetically useful fused carbocycles and heterocycles.[7] We report herein that intramolecular C(sp^3)−H arylations can be combined with inter- or intramolecular C−H arylations in the presence of the same palladium catalyst. These new types of double C−H arylations[8] allow the rapid construction of molecular complexity and provide an efficient access to original polycyclic molecules.

The double intermolecular C(sp^2)−H/intramolecular C(sp^3)−H arylation of chlorothiophene **1a** with aryl halides **2** was first investigated (Table 1). Individual C−H arylations at play in this reaction are known,[3,4f,9] but we wondered if a single batch of catalyst was able to perform both operations in one pot without undergoing deactivation intermediately. This was observed to be the case, and

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(7) Review: Jazzar, R.; Hitce, J.; Renaudat, A.; Sofack-Kreutzer, J.; Baudoin, O. *Chem.—Eur. J.* **2010**, *16*, 2654.

(8) For recent examples of multiple C(sp^2)−H arylations: (a) Huang, Q.; Fazio, A.; Dai, G.; Campo, M. A.; Larock, R. C. *J. Am. Chem. Soc.* **2004**, *126*, 7460. (b) Wakui, H.; Kawasaki, S.; Satoh, T.; Miura, M.; Nomura, M. *J. Am. Chem. Soc.* **2004**, *126*, 8658. (c) Kamikawa, K.; Takemoto, I.; Takemoto, S.; Matsuzaka, H. *J. Org. Chem.* **2007**, *72*, 7406. (d) Ohno, H.; Iuchi, M.; Fujii, N.; Tanaka, T. *Org. Lett.* **2007**, *9*, 4813. (e) Majumdar, K. C.; Chakravorty, S.; De, N. *Tetrahedron Lett.* **2008**, *49*, 3419. (f) Join, B.; Yamamoto, T.; Itami, K. *Angew. Chem., Int. Ed.* **2009**, *48*, 3644. (g) Della Ca', N.; Maestri, G.; Catellani, M. *Chem.—Eur. J.* **2009**, *15*, 7850. (h) Thirunavukkarasu, V. S.; Parthasarathy, K.; Cheng, C.-H. *Chem.—Eur. J.* **2010**, *16*, 1436. (i) Shibahara, F.; Yamaguchi, E.; Murai, T. *Chem. Commun.* **2010**, *46*, 2471.

the best results were obtained using the $Pd(OAc)_2$/tricyclopentylphosphine [$P(Cyp)_3$] catalyst previously developed for intramolecular arylation,[4f] in the presence of catalytic pivalic acid[10] and K_2CO_3 in DMF at 140 °C. Remarkably, only 1.1 equiv of aryl halide was sufficient to achieve complete conversion under these conditions. The reaction proceeded more efficiently with aryl halides **2** bearing an *ortho* or *meta* electron-withdrawing or neutral group (entries 2−8), whereas other aryl bromides such as bromobenzene (entry 1) and *p*-bromotoluene (entry 9) gave mixtures of unreacted **1a**, mono-C(sp^2)−H arylation (**4**), and bis-arylation (**3**) products.

Interestingly, intermolecular C(sp^2)−H arylation occurred before intramolecular C(sp^3)−H arylation with aryl bromides, as shown by the observation of compound **4** and the absence of compound **5** at incomplete substrate conversion. In addition, the diastereoselectivity observed for products **3** that were obtained in the presence of aryl bromides was usually higher (dr ≥ 5:1) than that observed for product **5** that was obtained in the absence of aryl bromide (dr = 4:1). When *o*-chlorotoluene was employed as the coupling partner (entry 3) instead of *o*-bromotoluene (entry 2), intramolecular C(sp^3)−H arylation occurred first, as shown by the observation of compound **5** and the absence of compound **4** at incomplete substrate conversion. The 4:1 diastereoselectivity observed for **3b** in this case (entry 3) is also consistent with this analysis. With the studied aryl bromides **2**, oxidative addition of the C−Br bond to Pd seems to occur first and the Pd catalyst is thus committed first to the intermolecular C(sp^2)−H arylation. In contrast, with *o*-chlorotoluene, oxidative addition seems to occur first from the more electron-deficient heteroarene C−Cl bond and thus intramolecular C(sp^3)−H arylation is taking place first. Additional factors such as the accelerating effect of the heteroarene chlorine atom on the intermolecular C(sp^2)−H arylation[11] and the difference in C(sp^3)−H and C(sp^2)−H bond strengths may also be at play in this double C−H arylation process. Interestingly, furan **1b** could be arylated successfully, similar to thiophene **1a** (entries 10−12), although longer reaction times were required due to the lower reactivity of the furan motif toward intermolecular C(sp^2)−H arylation. Major diastereoisomers **3** obtained from this double arylation process all possessed the *cis* configuration, as determined by NOESY experiments and by X-ray diffraction analysis for compound **3f** (Figure 1). The latter revealed a highly planar biaryl structure, indicating that the difference in diastereoselectivities observed with the various aryl bromides arise from electronic factors rather than from steric ones.

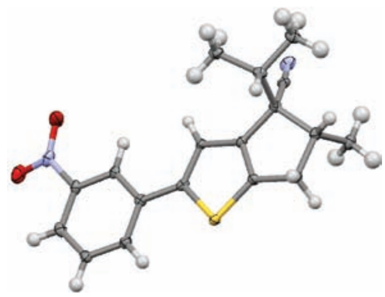
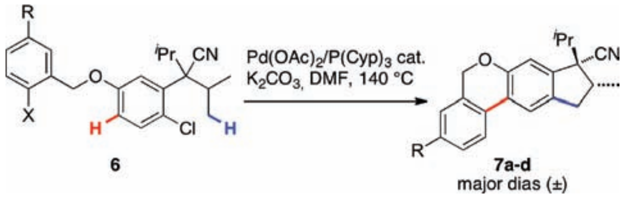


Figure 1. X-ray crystal structure of compound **3f** (30% probability ellipsoids plot).

A double intramolecular C(sp^2)−H/C(sp^3)−H arylation was next investigated, and dihalogenated substrates **6**, synthesized in five steps from commercially available compounds (see the Supporting Information), were studied as a proof of concept (Table 2). The same reaction conditions as those in the mixed inter/intramolecular arylation (Table 1) were employed, with the exception of pivalic acid which was not required to obtain optimal yields in this case.[12] Under these conditions, fused tetracyclic compounds **7a−d** were obtained in good yields and with comparable diastereoselectivities, regardless of the electron-withdrawing/-donating nature of the R substituent on the haloarene ring. Monitoring these reactions at incomplete conversion revealed that intramolecular C(sp^2)−H arylation preceded intramolecular C(sp^3)−H arylation with X = Br, which again results probably from the faster initial oxidative addition of the C−Br bond to the Pd catalyst. The same reactivity trend was observed with X = Cl (entry 2), for which the first oxidative addition probably occurs at the least sterically hindered C−Cl

Table 2. Double Intramolecular C(sp^2)−H/C(sp^3)−H Arylation[a]



entry	X	R	product	yield (%)[b]	dr[c]
1	Br	H	**7a**	68	4.5:1
2	Cl	H	**7a**	83	4.5:1
3	Br	F	**7b**	72	5:1
4	Br	CF_3	**7c**	87	5:1
5	Br	OMe	**7d**	60	5:1

[a] Reaction conditions: $Pd(OAc)_2$ (5 mol %), $P(Cyp)_3$•HBF_4 (20 mol %), K_2CO_3 (2 equiv), DMF, 140 °C, 24−36 h. [b] Yield of the isolated product. [c] Determined by ^1H NMR analysis of the crude reaction mixture.

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(9) For similar conditions developed for intermolecular C−H arylations of heteroarenes: Liégault, B.; Lapointe, D.; Caron, L.; Vlassova, A.; Fagnou, K. *J. Org. Chem.* **2009**, *74*, 1826.

(10) Lafrance, M.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 16496.

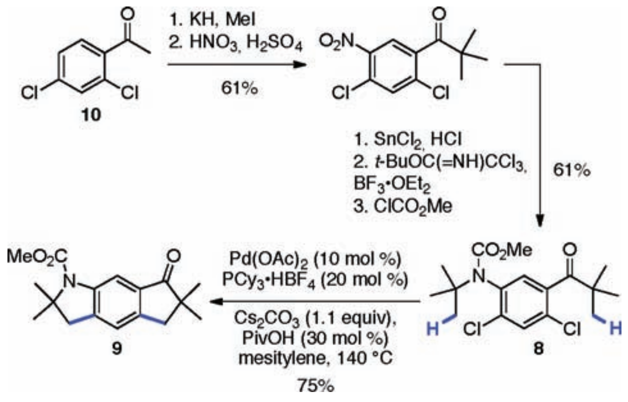
(11) Liégault, B.; Petrov, I.; Gorelsky, S. I.; Fagnou, K. *J. Org. Chem.* **2010**, *75*, 1047.

(12) For similar conditions developed for intramolecular C(sp^2)−H arylations: (a) Campeau, L.-C.; Parisien, M.; Leblanc, M.; Fagnou, K. *J. Am. Chem. Soc.* **2004**, *126*, 9186. (b) Campeau, L.-C.; Parisien, M.; Jean, A.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 581.

bond. This order of arylation events may explain why a complete regioselectivity was observed for the intramolecular C(sp^2)−H arylation, which occurred as expected at the most sterically accessible C(sp^2)−H bond *para* to the quaternary benzylic carbon.[12]

Finally, we examined the feasibility of a double intramolecular C(sp^3)−H/C(sp^3)−H arylation under the same guidelines.[5b,c] As in previous examples, the corresponding individual C−H arylations are known,[4f] but we again wondered if a single batch of catalyst could perform both operations. To this purpose, we chose to study the reactivity of dichloride **8** (Scheme 1), which was synthesized in five steps, 37% overall yield, from 2,4-dichloroacetophenone **10**. We considered as well other dihalogenated substrates, but **8** turned out to be the most accessible. Gratifyingly, compound **8** furnished original fused tricyclic product **9** in 75% yield, under conditions previously optimized for individual C−H arylations, i.e. with tricyclohexylphosphine as the Pd ligand, Cs_2CO_3/pivalic acid as the base/additive, and mesitylene as the solvent.[4f]

Scheme 1. Double Intramolecular C(sp^3)−H/C(sp^3)−H Arylation



In conclusion, we have synthesized original polycyclic molecules in good yields and diastereoselectivities by double C−H arylations mediated by a single palladium/phosphine catalyst. Both double intermolecular/intramolecular and intramolecular/intramolecular C−C couplings were performed successfully, which indicates that this concept may be broadly used for the rapid construction of molecular complexity.

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Supporting Information Available. Full characterization of all new compounds, detailed experimental procedures, copies of NMR spectra for target molecules, and X-ray crystal structure data (CIF) for compound **3f**. This material is available free of charge via the Internet at http://pubs.acs.org.