ORGANIC LETTERS

2013
Vol. 15, No. 6
1410–1413

Palladium-Catalyzed Arylation of Simple Arenes with Iodonium Salts

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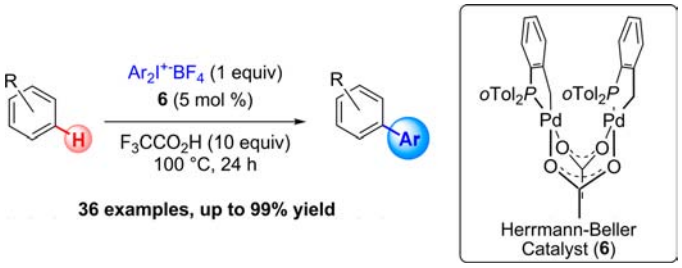
Received February 12, 2013

ABSTRACT



The development of an arylation protocol for simple arenes with diaryliodonium salts using the Herrmann–Beller palladacycle catalyst is reported. The reaction takes simple aromatic feedstocks and creates valuable biaryls for use in all sectors of the chemical industry.

Biaryls are important motifs in pharmaceuticals, agrochemicals, and natural products.[1] Their construction using transition metal (TM) mediated coupling has become a major research area in synthesis,[2] with a rich heritage dating back over a century to reactions such as the Pschorr cyclization[3] and Ullmann coupling.[4] The importance of biaryl synthesis drives continual efforts at improving reaction efficiency and atom economy, with the area of C–H arylation representing a significant recent development toward these two goals.[5] Harnessing unfunctionalized C–H components as reactants for biaryl synthesis avoids multistep syntheses of activated precursors, enhancing efficiency and opening up new substrate classes for value-added synthesis.

Recent work has identified aryliodanes and aryliodonium salts as powerful reagents for C–H arylation, offering new reaction pathways and conditions relative to their aryl halide congeners.[6] Their enhanced reactivity, including the facility to access higher oxidation states of TM catalysts (e.g., Pd and Cu), has enabled a variety of C–H bond arylations on otherwise intractable substrates.[7] We were interested in using these compounds to develop a C–H arylation system for simple arene feedstocks.

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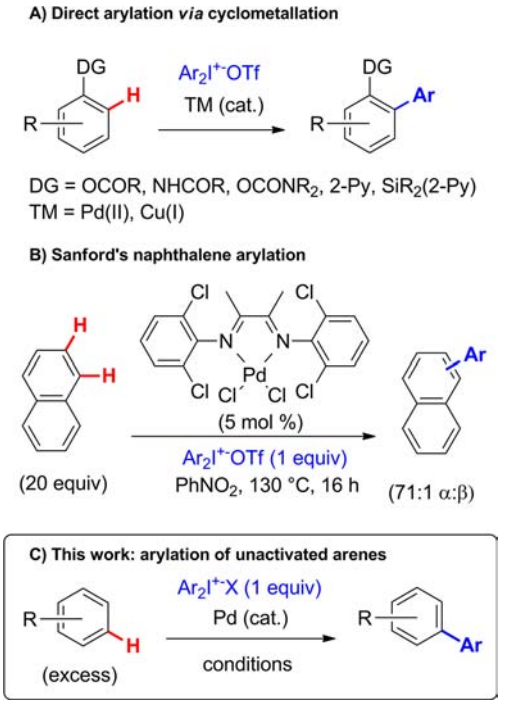
10.1021/ol400412z
Published on Web 03/05/2013

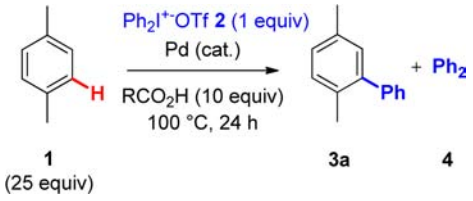
Scheme 1. Arylation Protocols Using Diaryliodonium Salts



In contrast to arene substrates containing heteroatoms, where directed approaches to C−H arylation are well developed (Scheme 1A),[8] C−H arylation of nonactivated arenes continues to present a challenge.[9] No effective general protocols for the arylation of simple unactivated arenes with iodonium salts have been disclosed, with only the singular case of naphthalene having being studied by several groups.[10] Sanford and co-workers have reported a notable example in this area, developing a naphthalene arylation protocol that is highly α-selective using a palladium(II) diimine precatalyst (Scheme 1B). There remains the need, however, for more general approaches to this fundamental class of chemical building block. In this communication we wish to disclose a palladium(II)-catalyzed protocol for the arylation of simple arenes with symmetrical diaryliodonium salts (Scheme 1C).

We began with a broad screening effort using *para*-xylene, **1**, as substrate with a range of diaryliodonium salts under a variety of conditions. As nonfunctionalized arenes are cheap and readily available (often employed as solvents) from petrochemical sources, the arene was used in excess with the iodonium salt as the limiting reagent. Moderate yields of a *ca.* 1:1 mixture of the desired product **3a** and biphenyl **4** were obtained from a reaction with 25 equiv of *para*-xylene, **1**, at 100 °C in the presence of 10 equiv of acetic acid and 10 mol % palladium(II) acetate (Table 1, entry 2).[11] With this lead result in hand, an assessment of reaction conditions and the acid promoter was performed in an attempt to gain greater reaction selectivity (Table 1).

Table 1. Palladium Catalyzed Phenylation of *para*-Xylene with Diphenyliodonium Triflate



entry	Pd cat.[a]	R	yield **3a** (%)[b]	yield **4** (%)[b]
1	$Pd(OAc)_2$	none	26	24
2	$Pd(OAc)_2$	Me	62	58
3	$Pd(OAc)_2$	H	10	15
4	$Pd(OAc)_2$	^{i}Pr	74	35
5	$Pd(OAc)_2$	^{n}Bu	52	37
6	$Pd(OAc)_2$	^{t}Bu	41	29
7	$Pd(OAc)_2$	$(CH_2)_2CH$	31	26
8	$Pd(OAc)_2$	$(CH_2)_4CH$	42	34
9	$Pd(OAc)_2$	$(CH_2)_5CH$	48	34
10	$Pd(OAc)_2$	2,4,6-$Me_3(C_6H_2)$	28	31
11	$Pd(OAc)_2$	CCl_3	37	6
12[c]	$Pd(OAc)_2$	CF_3	48	<5
13[d]	$Pd(OAc)_2$	CF_3	70	16
14[c]	**6**[e]	CF_3	83	trace
15[c,d]	**6**[e]	CF_3	96	trace

[a] 10 mol % of palladium(II) acetate. [b] Yield based upon isolated mixture of **3a** and **4**, as determined by ^{1}H NMR. [c] Average isolated yield of four experiments. [d] Experiment carried out with $Ph_2I^{+-}BF_4$ as the coupling partner. [e] 5 mol % of **6**.

In general, diphenyl iodonium triflate, **2**, could be cross-coupled with **1** in the presence of alkanoic acids (entries 2−6) and cyclic alkanoic acids (entries 7−9) in varying yields (up to 74%) but with poor selectivity.[12] Reaction selectivities of 7:1 and 12:1 (**3a:4**) were observed using

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(9) Selected examples of nonactivated arene C−H functionalization: (a) Lafrance, M.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 16496–16497. (b) Wen, J.; Zhang, J.; Chen, S.-Y.; Li, J.; Yu, X.-Q. *Angew. Chem., Int. Ed.* **2008**, *47*, 8897–8900. (c) Sun, C.-L.; Li, H.; Yu, D.-G.; Yu, M.; Zhou, X.; Lu, X.-Y.; Huang, K.; Zheng, S.-F.; Li, B.-J.; Shi, Z.-J. *Nat. Chem.* **2010**, *2*, 1044–1049. (d) Vallée, F.; Mousseau, J. J.; Charette, A. B. *J. Am. Chem. Soc.* **2010**, *132*, 1514–1516. (e) Shirakawa, E.; Itoh, K.-i.; Higashino, T.; Hayashi, T. *J. Am. Chem. Soc.* **2010**, *132*, 15537–15539. (f) Liu, W.; Cao, H.; Zhang, H.; Zhang, H.; Chung, K. H.; He, C.; Wang, H.; Kwong, F. Y.; Lei, A. *J. Am. Chem. Soc.* **2010**, *132*, 16737–16740. (g) Tan, Y.; Hartwig, J. F. *J. Am. Chem. Soc.* **2011**, *133*, 3308–3311.

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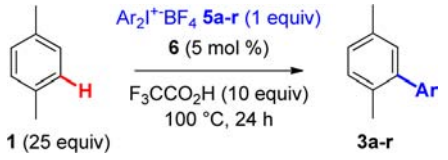
(11) This side reaction could proceed via the reductive elimination of the iodine(III) reagent or via the palladium mediated coupling of the 'waste' iodoarene with the aryliodonium salt.

(12) Sulfonic acids, diacids, and amino acids were also found to be ineffective; see Supporting Information for details.

trichloroacetic acid and trifluoroacetic acid respectively, but the isolated yield remained moderate (entries 11 and 12). Altering the iodonium salt counterion demonstrated that less coordinating anions, $-OTf$ and $-BF_4$, performed best. Further reaction optimization altering stoichiometries, temperature, reaction times, reaction set up, and the use of additives and oxidants were all assessed with little improvement to the reaction selectivity or yield (see Supporting Information for full details of reaction optimization). Finally, a wide range of palladium precatalysts and ligand systems were screened, and it was noted that the addition of ligands was generally detrimental, and very few palladium precatalysts were productive. Pleasingly, however, the Herrmann–Beller palladacycle, **6**, was effective in the reaction (entries 14 and 15), enabling almost exclusive formation of the desired **3a** with only trace amounts of **4** detected (entry 14) at 5 mol % loading. The use of diphenyliodonium tetrafluoroborate as the coupling partner further improved the yield of the product and its selective formation (entries 13 and 15).[13]

Table 2. Palladium Catalyzed Arylation of *para*-Xylene with Symmetrical Diphenyliodonium Tetrafluoroborates



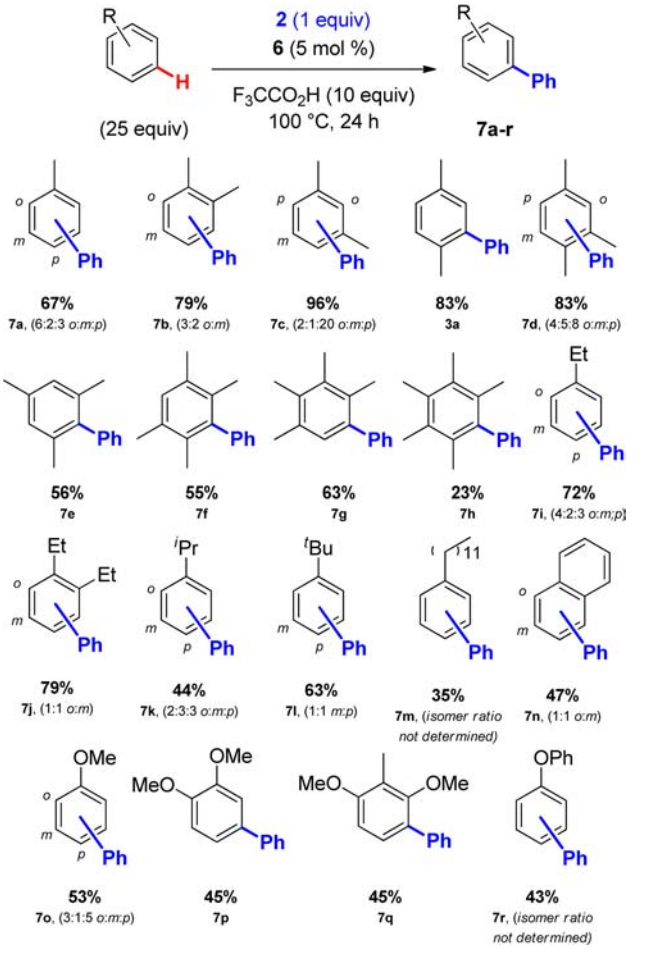
entry	Ar	compound	yield (%)[a]
1	*p*-$MeOC_6H_4$ (**5b**)	**3b**	42
2	*p*-MeC_6H_4 (**5c**)	**3c**	63
3	*m*-MeC_6H_4 (**5d**)	**3d**	48
4	*o*-MeC_6H_4 (**5e**)	**3e**	19
5	*m*-,*p*-$Me_2C_6H_3$ (**5f**)	**3f**	42
6[b]	C_6H_5 (**5a**)	**3a**	96
7	*p*-FC_6H_4 (**5g**)	**3g**	60
8	*m*-FC_6H_4 (**5h**)	**3h**	39
9	*o*-FC_6H_4 (**5i**)	**3i**	42
10	*p*-ClC_6H_4 (**5j**)	**3j**	99
11	*m*-ClC_6H_4 (**5k**)	**3k**	93
12	*m*-,*p*-$Cl_2C_6H_3$ (**5l**)	**3l**	74
13	*p*-BrC_6H_4 (**5m**)	**3m**	56
14	*m*-BrC_6H_4 (**5n**)	**3n**	68
15	*o*-BrC_6H_4 (**5o**)	**3o**	<5
16	*m*-IC_6H_4 (**5p**)	**3p**	23
17[c]	*p*-$CO_2MeC_6H_4$ (**5q**)	**3q**	53
18[c]	*m*-$NO_2C_6H_4$ (**5r**)	**3r**	40

[a] Isolated yield. [b] Average isolated yield of four experiments. [c] Product contaminated with the respective iodoarene byproduct.

With optimized conditions in hand, a variety of substituted symmetrical diaryliodonium tetrafluoroborate salts were coupled with *para*-xylene (Table 2). The reaction proceeded in moderate-to-excellent yields with both electron-donating (entries 1–5) and electron-withdrawing groups (entries 7–18) on the iodonium salt, although the latter tended to perform better. Substitutions on the *para*- and *meta*-positions were well tolerated, but substrates with *ortho*-substituents were somewhat lower yielding (entries 4, 9, and 15). The coupling of a wide range of haloaryl substituents was possible (entries 7–16), affording halo-biaryls containing versatile handles for subsequent molecular elaboration. These haloaryl couplings are exemplified by the incorporation of *para*- and *meta*-chlorophenyl, *meta*,*para*-dichlorophenyl, and *para*- and *meta*-bromophenyl units in 99, 93, 74, 56, and 68% yields respectively (entries 10–14). It was even possible to couple a *meta*-iodophenyl moiety, albeit in a modest yield of 23% (entry 16). The resilience of haloarenes indicates that reactive palladium(0) species are not likely to be formed under the reaction conditions and demonstrates the orthogonality of this methodology compared to traditional cross-coupling chemistries.[14]

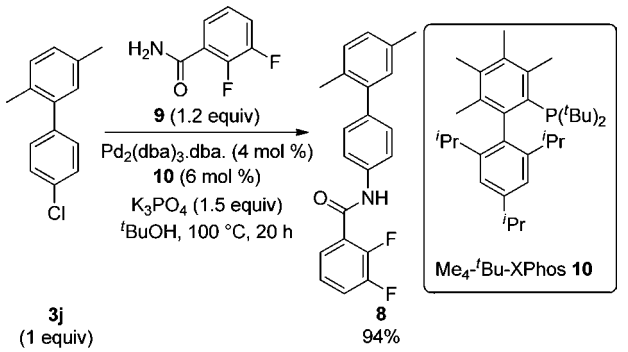
The reaction scope of the arene component was investigated using diphenyliodonium triflate, **2**, a salt readily synthesized on a large scale using the method of Olofsson

Scheme 2. Phenylation of Electron-Rich Arenes with Diphenyliodonium Triflate



(13) Unsymmetrical diaryliodonium salts containing a bulky, nontransferable arene were considerably less effective in the reaction under the optimized conditions. Aryl iodides were also ineffective under the reaction conditions.

Scheme 3. Synthesis of the Immunosuppressant, **8**



and co-workers (Scheme 2).[15] It was found that electron-rich arenes were phenylated relatively easily, but electron-poor arenes could not be coupled in any appreciable yield. The effect of the arene substitution pattern was fully assessed with a range of di-, tri-, tetra-, and pentamethylbenzenes. Good-to-excellent yields were obtained in most cases (**7a**–**7g**), although selectivities were generally low. A drop in yield was noted when the product is di-*ortho*-substituted (**7e** and **7f**) or when the number of C–H bonds available for arylation is limited (e.g., pentamethylbenzene **7h**). A selection of alkylbenzenes (**7i**–**7m**) and naphthalene (**7n**) were likewise productive in the reaction. We were pleased to see that heteroatom-substituted arenes could be incorporated into the reaction, with several methoxybenzenes undergoing phenylation (**7o**–**7r**). Yields were lower than the analogous methylbenzenes, but selectivity was improved with single isomers exclusively obtained for the dimethoxybenzene substrates **7p** and **7q**.

In order to demonstrate the value of the developed methodology, the synthesis of the immunosuppressant **8** was completed in two simple, high-yielding palladium-catalyzed steps. Compound **8** has been reported as an inhibitor of interleukin-2, a cytokine that modulates numerous immunological responses within the cell.[16] Arylation of *para*-xylene with *para*-chlorophenyl iodonium salt **5j** gave biaryl **3j** in 99% yield (Table 2, entry 10), with the chloro group untouched under the arylation conditions. A Buchwald–Hartwig amination with amide **9**, utilizing the highly electron-rich Buchwald ligand tetramethyl-*tert*-butyl-XPhos, **10**, then introduced the difluorobenzamide moiety at the *para*-position of the biaryl unit in 94% yield (Scheme 3).[17]

In summary, the development of a new palladium(II)-catalyzed arylation protocol for the coupling of simple, unactivated arenes with diaryliodonium salts has been achieved. The key factors influencing reaction success were the use of the Herrmann–Beller palladacycle as a precatalyst and stoichiometric trifluoroacetic acid to enhance the electrophilicity of the palladium catalyst.[18] The reaction employs the more expensive iodonium salt as the limiting reagent, a significant advantage for simple chemical feedstocks, and one that compares favorably to other C–H arylation protocols of arenes where the iodine(III) reagent is used in excess.[7b–f] The arenes used in this study are cheap, readily available, and recoverable via distillation, sublimation, or column chromatography from the crude reaction mixtures. The reaction was tolerant of halogen functionality, a feature exemplified in the highly efficient synthesis of biologically active amide **8** in two steps from simple building blocks. Further applications of this work are underway in our laboratory.

Acknowledgment. We thank the EPSRC (Leadership Fellowship to M.F.G.) and the University of Manchester (postdoctoral fellowship to T.E.S.). Gabriele Fumagalli (University of Manchester) is acknowledged for the synthesis of a number of iodonium salts.

Supporting Information Available. Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(14) The benchmark reaction with diphenyliodonium tetrafluoroborate and di(*para*-chlorophenyl)iodonium tetrafluoroborate were scaled up to 2.5 mmol scale with little drop off in product yield (95 and 96%, respectively).

(15) Bielawski, M.; Zhu, M.; Olofsson, B. *Adv. Synth. Catal.* **2007**, *349*, 2610. Using this protocol, it was possible to make diphenyliodonium triflate from iodobenzene and benzene on a 100 mmol scale with the product obtained in a 96% yield (41 g).

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(17) Ikawa, T.; Barder, T. E.; Biscoe, M. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 13001.

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The authors declare no competing financial interest.