ChemComm
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View Article Online
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Palladium-catalyzed *para*-selective arylation of phenols with aryl iodides in water†

Cite this: DOI: 10.1039/c3cc44345k

Received 9th June 2013,
Accepted 3rd July 2013

DOI: 10.1039/c3cc44345k

www.rsc.org/chemcomm

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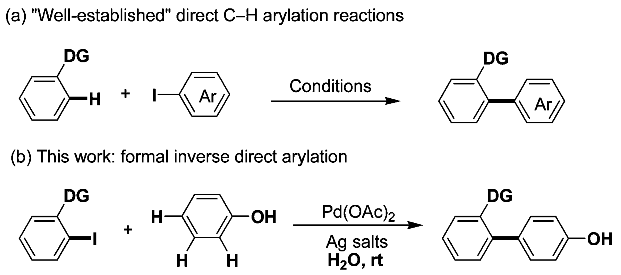
Highly *para*-selective palladium-catalyzed direct arylation of phenols with aryl iodides was demonstrated by taking advantage of the formal inverse direct arylation strategy. A series of 4-aryl phenols were synthesised by employing water as a "green" solvent under mild reaction conditions.

Transition-metal-catalyzed direct aromatic C–H arylation has recently emerged as a versatile strategy for the synthesis of biaryl compounds.[1] The direct transformation of C–H bonds avoids the use of one or both of the prefunctionalized coupling partners, leading to a more atom-economical and environmentally friendly process than traditional cross-coupling reactions. Although tremendous progress has been made in this field, these direct arylations usually suffer from harsh reaction conditions, large excess of arene coupling partners and the regioselectivity problems. The use of directing groups, such as amides, oximes, pyridines, and acetanilides, has become the most common strategy to enhance the reactivity and control the regioselectivity, which results in *ortho* functionalized biaryl products (Scheme 1a).[2] Nevertheless, the *meta* or *para*-selective C–H arylation of mono-substituted benzenes remains largely unexplored and has attracted growing attention.[3]



Scheme 1 Pd-catalyzed direct C–H arylations.

Phenols are common and important structural motifs in natural products, pharmaceuticals, agrochemicals, and polymers.[4] Therefore, the direct functionalization of phenol derivatives has attracted much attention recently. In 2003, Bedford and coworkers disclosed a method for rhodium-catalyzed *ortho* C–H arylation of 2-substituted phenols.[5] Daugulis and coworkers reported that phenols could be *ortho* arylated by aryl chlorides *via* the benzyne mechanism.[6] Moreover, the *ortho*-arylation of phenols can be circumvented by the introduction of a directing group, such as phenolic esters and *O*-phenylcarbamates.[7] By contrast, the direct *meta* or *para*-selective arylation of phenol or its derivatives is still a great challenge. Notably, Gaunt and coworkers have reported an appealing protocol for copper-catalyzed arylation of phenol ethers by diaryliodonium salts with high *para*-selectivity.[8] Recently, an alternative approach to the *meta* and *para*-arylated phenols by using cyclohexenone as a phenol surrogate through a palladium-catalyzed tandem process was demonstrated by the groups of Stahl and Imahori.[9] To the best of our knowledge, direct intermolecular *para*-arylation of unprotected phenols with aryl halides has not yet been disclosed.

From the perspective of green chemistry, water is regarded as an ideal reaction medium because of its natural, inexpensive, nontoxic, and environmentally friendly characteristics.[10] As part of our continuous interest in aqueous catalysis,[11] herein we describe a novel method for palladium-catalyzed *para*-selective arylation of unprotected phenols with aryl iodides in water under mild conditions. It was envisioned that aryl iodide bearing an *ortho* coordination group would accelerate the transition metal oxidative addition to provide a thermodynamically stable intermediate and facilitate the activation of phenol, which is formally opposite to the well-established direct C–H arylations (Scheme 1b).[12]

At first, we began with the reaction between the commercially available 2-iodobenzoic acid (**1a**) and phenol (**2a**), because the carboxyl group was proven to be a versatile functionality for further transformations.[13] To our delight, 85% yield of *para*-selective arylated product **3a** was obtained by utilizing the Pd(OAc)$_2$/AgTFA catalyst in water (see ESI† for details). The excellent reactivity of aryl

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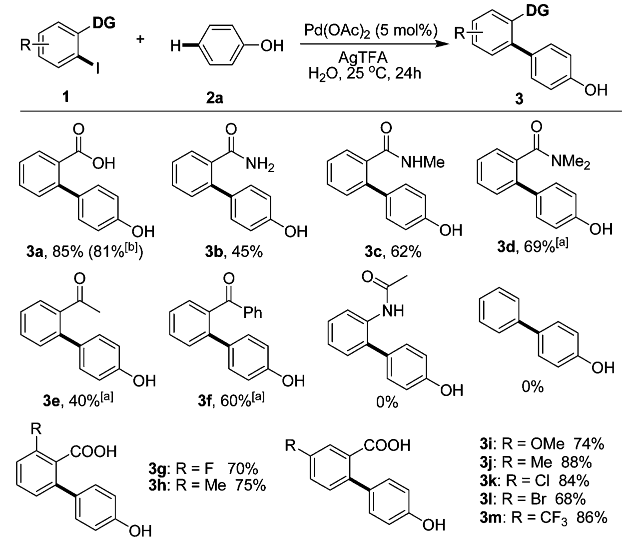
† Electronic supplementary information (ESI) available. See DOI: 10.1039/c3cc44345k

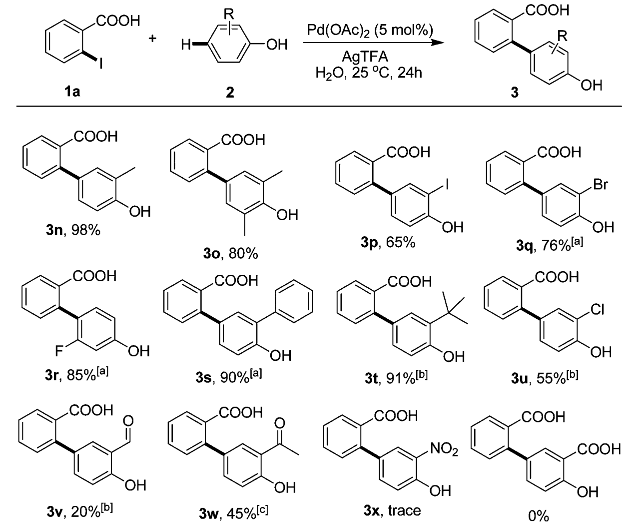


Scheme 2 Standard reaction conditions: **1** (0.4 mmol), **2a** (1 mmol), $Pd(OAc)_2$ (0.02 mmol), AgTFA (0.44 mmol), H_2O (0.8 mL), rt, 24 h. The yield of isolated product is reported. [a] 60 °C. [b] **1a** (10 mmol), **2a** (25 mmol).

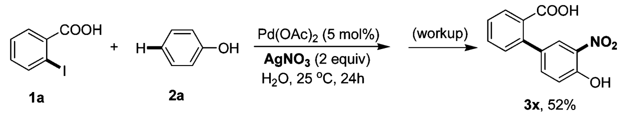
iodide containing a carboxyl group aroused our interest in the examination of other functional groups. As summarized in Scheme 2, various amides including primary, secondary, or even tertiary amides were investigated under the optimized reaction conditions and resulted in the formation of desired corresponding *para*-arylated products **3b**, **3c**, **3d** in moderate yields ranging from 45% to 69%. Furthermore, the ketones also succeeded in this reaction as a coordination group to give the desired products **3e** and **3f**. As expected, the use of iodobenzene bearing no coordination group failed to give the arylated product. A variety of 2-iodobenzoic acids bearing diverse substituents were also applicable to the arylation reaction. With either electron-donating or withdrawing groups, for example methoxyl (**3i**), bromo (**3l**), fluoro (**3g**), and trifluoromethyl groups (**3m**), the reactions proceeded smoothly and resulted in moderate to excellent yields ranging from 68% to 88%. It is worthy to note that the aqueous catalysis can be readily scaled-up to gram-scale synthesis. For example, 1.72 g (81%) of product **3a** could be obtained when the reaction was performed on the 10 mmol scale.

Subsequently, we investigated the scope of various phenols to survey the generality of this reaction, and the results are summarized in Scheme 3. Satisfyingly, a series of substituted phenols were converted to give only *para*-arylated products in all cases with high efficiency. Furthermore, addition of a catalytic amount of acid substantially improved the reactivity of the electron-deficient phenols.[14] Importantly, the phenols containing iodo, bromo, and chloro substituents were all compatible with the reaction, enabling further synthetic manipulations (**3p**, **3q**, and **3u**). 3-Fluorophenol also readily worked under the reaction conditions, and afforded the corresponding product in 85% yield (**3r**). However, salicylic acid completely inhibited this transformation, which supposedly resulted from the chelating ability of the substrate.

Interestingly, during the workup process, we discovered that compound **3a** is ready to be nitrified and converted to product **3x** by replacing the silver trifluoroacetate with silver nitrate (Scheme 4).



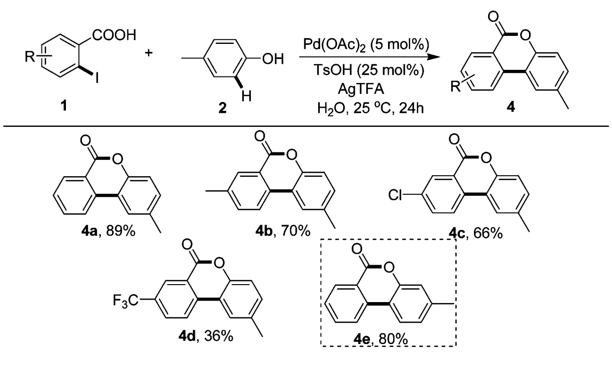
Scheme 3 Standard reaction conditions: **1a** (0.4 mmol), **2** (1 mmol), $Pd(OAc)_2$ (0.02 mmol), AgTFA (0.44 mmol), H_2O (0.8 mL), rt, 24 h. The yield of isolated product is reported. [a] TsOH (0.1 mmol) was added, 60 °C. [b] TsOH (0.1 mmol) was added, 70 °C. [c] 70 °C.



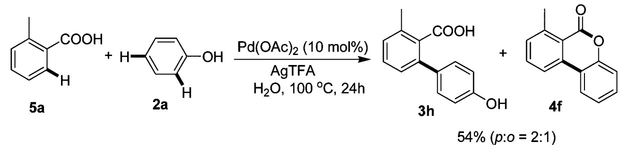
Scheme 4 Tandem C–H arylation/nitrification.

This tandem reaction might provide an alternative method for the synthesis of **3x**, which is particularly difficult to be achieved through direct arylation by employing high electron-deficient 2-nitrophenol as shown in Scheme 3.

Moreover, it is notable that the *para*-substituted phenols could be *ortho* arylated and followed by an intramolecular condensation process *in situ*, resulting in the formation of dibenzopyranones, which are common structural motifs existing in many natural products and biologically active molecules (Scheme 5).[15] To our surprise, 3-methylphenol also provided the dibenzopyranone product *via ortho*-arylation, suggesting that the steric bulkiness of the methyl group plays an important role in this transformation (**4e**).



Scheme 5 Standard reaction conditions: **1** (0.4 mmol), **2** (1 mmol), $Pd(OAc)_2$ (0.02 mmol), AgTFA (0.44 mmol), TsOH (0.1 mmol), H_2O (0.8 mL), rt, 24 h.



Scheme 6 Oxidative C–H/C–H cross-coupling reaction.

The detailed mechanism of this *para*-arylation reaction is not clear at this stage. Based on the previous investigations of the palladium-catalyzed C–H arylation with aryl iodides,[16] the reaction might involve electrophilic metalation of the C–H bond of phenol (a KIE of 1.3 was observed, see ESI†), and then followed by oxidative addition of ArI to a high-valent palladium species that is stabilized by the presence of a coordination group.[17] The reductive elimination would result in the arylated product **3**.

Stimulated by the recent success in direct oxidative C–H/C–H cross-coupling reactions,[18] we envisioned that a considerable improvement of step economy would be constituted by the direct use of phenol and aromatic acid. We were pleased to find that the aqueous catalytic system was able to promote the oxidative C–H/C–H cross-coupling reaction in acceptable yield with the increase in the reaction temperature to 100 °C (Scheme 6). However, poor selectivity was observed ($p:o = 2:1$), suggesting that the oxidative coupling process might go through a radically different pathway.[19] Further studies to improve the selectivity, as well as to elucidate the mechanism are currently underway and will be published in due course.

In conclusion, we have presented the first example of highly *para*-selective palladium-catalyzed direct C–H arylation of unprotected phenols with aryl iodides. In particular, this reaction employs inexpensive, environmentally benign, and nontoxic water as the solvent under extremely mild conditions (room temperature for most of the cases). Moreover, this methodology provides a novel method for the synthesis of valuable dibenzopyranones. Further studies and applications of this formal inverse direct arylation strategy are currently underway in our laboratory.

We are grateful to the Natural Science Foundation of China (No. 21072132 and 21272161) and the Ministry of Education of China (No. 20120181110050) for financial support. We also acknowledge the Key Laboratory of Green Chemistry and Technology of Ministry of Education for HRMS analysis.

Notes and references

1 (*a*) I. V. Seregin and V. Gevorgyan, *Chem. Soc. Rev.*, 2007, **36**, 1173; (*b*) L. Ackermann, R. Vicente and A. R. Kapdi, *Angew. Chem., Int. Ed.*, 2009, **48**, 9792; (*c*) O. Daugulis, H. Q. Do and D. Shabashov, *Acc. Chem. Res.*, 2009, **42**, 1074; (*d*) C.-L. Sun, B.-J. Li and Z.-J. Shi, *Chem. Commun.*, 2010, **46**, 677; (*e*) J. Wencel-Delord, T. Droge, F. Liu and F. Glorius, *Chem. Soc. Rev.*, 2011, **40**, 4740.

2 (*a*) T. W. Lyons and M. S. Sanford, *Chem. Rev.*, 2010, **110**, 1147; (*b*) K. M. Engle, T.-S. Mei, M. Wasa and J.-Q. Yu, *Acc. Chem. Res.*, 2012, **45**, 788.

3 (*a*) G. Brasche, J. Garcia-Fortanet and S. L. Buchwald, *Org. Lett.*, 2008, **10**, 2207; (*b*) R. J. Phipps and M. J. Gaunt, *Science*, 2009, **323**, 1593; (*c*) C. S. Yeung, X. Zhao, N. Borduas and V. M. Dong, *Chem. Sci.*, 2010, **1**, 331; (*d*) H. A. Duong, R. E. Gilligan, M. L. Cooke, R. J. Phipps and M. J. Gaunt, *Angew. Chem., Int. Ed.*, 2011, **50**, 463; (*e*) C.-L. Ciana, R. J. Phipps, J. R. Brandt, F.-M. Meyer and M. J. Gaunt, *Angew. Chem., Int. Ed.*, 2011, **50**, 458; (*f*) X. Wang, D. Leow and J.-Q. Yu, *J. Am. Chem. Soc.*, 2011, **133**, 13864; (*g*) L. T. Ball, G. C. Lloyd-Jones and C. A. Russell, *Science*, 2012, **337**, 1644.

4 (*a*) J. H. P. Tyman, *Synthetic and Natural Phenols*, Elsevier, New York, 1996; (*b*) Z. Rappoport, *The Chemistry of Phenols*, Wiley-VCH, Weinheim, 2003.

5 R. B. Bedford, S. J. Coles, M. B. Hursthouse and M. E. Limmert, *Angew. Chem., Int. Ed.*, 2003, **42**, 112.

6 T. Truong and O. Daugulis, *Chem. Sci.*, 2013, **4**, 531.

7 (*a*) C. Huang and V. Gevorgyan, *J. Am. Chem. Soc.*, 2009, **131**, 10844; (*b*) B. Xiao, Y. Fu, J. Xu, T.-J. Gong, J.-J. Dai, J. Yi and L. Liu, *J. Am. Chem. Soc.*, 2010, **132**, 468; (*c*) X. Zhao, C. S. Yeung and V. M. Dong, *J. Am. Chem. Soc.*, 2010, **132**, 5837; (*d*) L. Ackermann, E. Diers and A. Manvar, *Org. Lett.*, 2012, **14**, 1154.

8 Only one example of the selective *para* C–H arylation of unprotected phenol has been reported. See ref. 3*e*.

9 (*a*) T. Imahori, T. Tokuda, T. Taguchi and H. Takahata, *Org. Lett.*, 2012, **14**, 1172; (*b*) Y. Izawa, C. Zheng and S. S. Stahl, *Angew. Chem., Int. Ed.*, 2013, **52**, 3672.

10 For selected examples of transition-metal-catalyzed C–H arylation in or on water, see: (*a*) G. L. Turner, J. A. Morris and M. F. Greaney, *Angew. Chem., Int. Ed.*, 2007, **46**, 7996; (*b*) E. F. Flegeau, M. E. Popkin and M. F. Greaney, *Org. Lett.*, 2008, **10**, 2717; (*c*) S. A. Ohnmacht, P. Mamone, A. J. Culshaw and M. F. Greaney, *Chem. Commun.*, 2008, 1241; (*d*) S. A. Ohnmacht, A. J. Culshaw and M. F. Greaney, *Org. Lett.*, 2010, **12**, 224; (*e*) P. B. Arockiam, C. Fischmeister, C. Bruneau and P. H. Dixneuf, *Angew. Chem., Int. Ed.*, 2010, **49**, 6629; (*f*) L. Ackermann, J. Pospech and H. K. Potukuchi, *Org. Lett.*, 2012, **14**, 2146.

11 For selected examples: (*a*) Y. Qu, F. Ke, L. Zhou, H. Xiang, D. Wu and X. Zhou, *Chem. Commun.*, 2011, **47**, 3912; (*b*) H. Deng, Z. Li, F. Ke and X. Zhou, *Chem.–Eur. J.*, 2012, **18**, 4840.

12 J. J. Mousseau, F. Vallée, M. M. Lorion and A. B. Charette, *J. Am. Chem. Soc.*, 2010, **132**, 14412.

13 (*a*) L. J. Gooßen, N. Rodríguez and K. Gooßen, *Angew. Chem., Int. Ed.*, 2008, **47**, 3100; (*b*) N. Rodríguez and L. J. Gooßen, *Chem. Soc. Rev.*, 2011, **40**, 5030; (*c*) J. Cornella and I. Larrosa, *Synthesis*, 2012, 653.

14 The $Pd(OAc)_2$ precatalyst might be converted to the cationic species such as $[Pd(OTs)]^+$, which is significantly more electrophilic than the $Pd(OAc)_2$. See: C. Jia, T. Kitamura and Y. Fujiwara, *Acc. Chem. Res.*, 2001, **34**, 633.

15 K. Koch, J. Podlech, E. Pfeiffer and M. Metzler, *J. Org. Chem.*, 2005, **70**, 3275.

16 (*a*) O. Daugulis and V. Zaitsev, *Angew. Chem., Int. Ed.*, 2005, **44**, 4046; (*b*) R. Giri, N. Maugel, J.-J. Li, D.-H. Wang, S. P. Breazzano, L. B. Saunders and J.-Q. Yu, *J. Am. Chem. Soc.*, 2007, **129**, 3510; (*c*) H. A. Chiong, Q. N. Pham and O. Daugulis, *J. Am. Chem. Soc.*, 2007, **129**, 9879; (*d*) N. Lebrasseur and I. Larrosa, *J. Am. Chem. Soc.*, 2008, **130**, 2926; (*e*) C. He and G. Chen, *Angew. Chem., Int. Ed.*, 2011, **50**, 5192; (*f*) J. Vicente, A. Arcas, F. Julia-Hernandez and D. Bautista, *Angew. Chem., Int. Ed.*, 2011, **50**, 6896; (*g*) L. D. Tran and O. Daugulis, *Angew. Chem., Int. Ed.*, 2012, **51**, 5188.

17 The palladium-catalyzed C–H arylations with Ag(I)/ArI have been proposed to proceed *via* a Pd(IV) intermediate (see ref. 16*c*), however, the intermediacy of Pd(III) complexes cannot be excluded; (*a*) D. C. Powers, M. A. L. Geibel, J. E. M. N. Klein and T. Ritter, *J. Am. Chem. Soc.*, 2009, **131**, 17050; (*b*) N. R. Deprez and M. S. Sanford, *J. Am. Chem. Soc.*, 2009, **131**, 11234.

18 (*a*) C. S. Yeung and V. M. Dong, *Chem. Rev.*, 2011, **111**, 1215; (*b*) C. Liu, H. Zhang, W. Shi and A. Lei, *Chem. Rev.*, 2011, **111**, 1780.

19 The previous reports of palladium-catalyzed oxidative C–H/C–H couplings using silver salts as the terminal oxidant were proposed *via* a Pd(0/II) mechanism. For selected examples: (*a*) K. L. Hull and M. S. Sanford, *J. Am. Chem. Soc.*, 2007, **129**, 11904; (*b*) H. Li, J. Liu, C.-L. Sun, B.-J. Li and Z.-J. Shi, *Org. Lett.*, 2011, **13**, 276.