Chemical Science

An Organic Cation as a Silver(I) Analogue for the Arylation of sp2 and sp3 C–H Bonds with Iodoarenes

Journal:	*Chemical Science*
Manuscript ID:	SC-EDG-04-2014-001215.R1
Article Type:	Edge Article
Date Submitted by the Author:	30-May-2014
Complete List of Authors:	Arroniz, Carlos; Queen Mary University of London, School of Biological and Chemical Sciences Denis, Gabriel; Queen Mary University of London, School of Biological and Chemical Sciences Rassias, Gerasimos; University of Patras, Department of Chemistry Ironmonger, Alan; GlaxoSmithKline, Department of Chemistry Larrosa, Igor; Queen Mary University London, School of Biological and Chemical Sciences

Cite this: DOI: 10.1039/c0xx00000x

www.rsc.org/xxxxxx

ARTICLE TYPE

An Organic Cation as a Silver(I) Analogue for the Arylation of sp^2 and sp^3 C–H Bonds with Iodoarenes

Carlos Arroniz,[a,b] J. Gabriel Denis,[a] Alan Ironmonger,[b] Gerasimos Rassias[b,‡] and Igor Larrosa*[a]

Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX

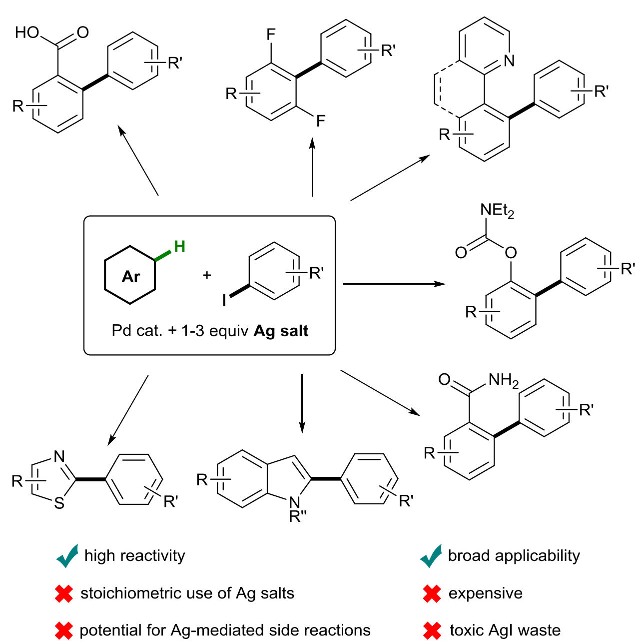
DOI: 10.1039/b000000x

Reactions promoted by stoichiometric amounts of silver salts suffer from high cost, limited availability and raise environmental concerns. This manuscript describes studies leading to the discovery of a general replacement for silver with an inexpensive and convenient organic salt in palladium catalysed direct C(sp^2)–H and C(sp^3)–H arylation reactions.

One of the fundamental goals in chemical research is the development of broadly applicable, cost-effective, practical and sustainable synthetic methods. In this context, the development of C–H bond arylation processes has attracted significant interest as more environmentally-friendly alternatives to traditional cross-couplings. These new transformations use readily available starting materials, thus avoiding the preparation and use of organometallic reagents as coupling partners and the associated generation of stoichiometric amounts of metallic waste.[1]

In 2005, Daugulis and Zaitsev developed a method for the direct arylation of anilides with iodoarenes using a catalytic system involving $Pd(OAc)_2$ in combination with stoichiometric AgOAc.[2] This powerful system and its various modifications have since been successfully applied to a great variety of C–H arylation processes involving iodoarene coupling partners (Scheme 1).[3,4] However, to date one of the major drawbacks of these methodologies is the requirement for stoichiometric silver additives.[5] Silver(I) salts are a uniquely appropriate partner for Pd, Au, Cu, Rh, Ru and Pt catalysts, particularly when halide abstraction is required in the catalytic process.[6] However, due to the ability of silver salts to also act as oxidants and Lewis acids, sometimes undesired side reactions are observed.[7] Furthermore, when used as stoichiometric reagents, these expensive silver salts considerably increase the overall cost of the process and generate significant amounts of metal waste. Therefore those transformations are prohibitively expensive for industry. Importantly, whereas there are alternatives to Ag salts in their role of oxidants, the only other well-known halide scavengers (Pb, Tl and Hg salts) are highly toxic and rarely used for this purpose.

Recent studies on the use of Ag salts as additives in Au-catalyzed reactions have shown that, in addition to abstracting a halogen, Ag may play additional roles essential to the catalytic process and form mixed Au-Ag active species.[8] In the case of C–H arylation reactions, it is possible that Ag salts may also be acting as terminal oxidants, assisting in the oxidative addition step or facilitating the C–H activation. A recent mechanistic study on the role of additives in palladium acetate-catalyzed *ortho*-C–H bond functionalizations suggested that Ag interacts with Pd in a cooperative manner for an enhanced heterobimetallic C–H activation.[9] We now report studies that demonstrate that the role of silver salts in several C–H arylation processes with iodoarenes is exclusively that of iodide capture. Furthermore, we have identified that in these processes silver salts can be conveniently replaced with a more redox stable and inexpensive quaternary ammonium salt while maintaining the high reactivity and broad substrate class scope displayed by the previous Pd/Ag systems. To the best of our knowledge, this is the first example of a silver replacement of general applicability to a wide range of C–H arylation processes.

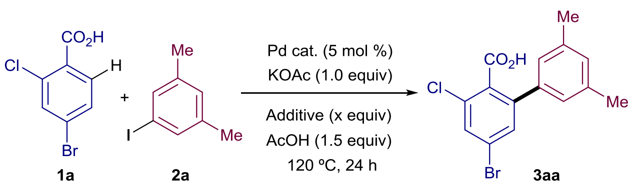


Scheme 1 Selected Examples of the General Scope of Current Protocols for C–H Arylation Using Iodoarenes and Stoichiometric Silver Salts.

Our initial efforts were directed at assessing the role of Ag salts in a common C–H arylation methodology: the ortho-arylation of benzoic acid **1a** with iodoarene **2a** (Table 1). Reaction under standard, Ag salt-mediated, conditions led to formation of biaryl product **3aa** in 87% yield (entry 1).[4ac]

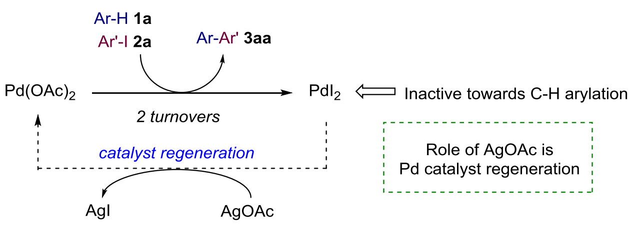
Replacement of AgOAc with KOAc led to a reduction in yield to 9%, roughly consistent with two turnovers of the Pd catalyst (entry 2). A qualitative colorimetric test suggested the presence of PdI_2 in the reaction mixture.[10] Replacing $Pd(OAc)_2$ with PdI_2 led to no reaction (entry 3). Finally, using PdI_2 in combination with AgOAc fully restored the high reactivity of the system (entry 4). These results suggest that in these reactions $Pd(OAc)_2$ is a competent catalyst for the C–H arylation process, but is poisoned by iodide after two turnovers (Scheme 2). Thus, the silver salt is required for regenerating catalytically active $Pd(OAc)_2$ from inactive PdI_2 via the formation and precipitation of the highly insoluble AgI salts, and not for the C–H arylation itself.

Table 1 Mechanistic studies on the role of Ag salt additives [a]



entry	Pd cat.	additive (equiv)	**3aa** (%)[b]
1	$Pd(OAc)_2$	AgOAc (1)	87
2	$Pd(OAc)_2$	KOAc (1)	9
3	PdI_2	KOAc (1)	0
4	PdI_2	AgOAc (1)	84

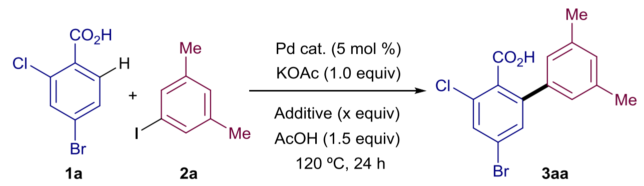
[a] Reactions were carried out using 0.5 mmol of **1a** and 3 equiv of **2a**. [b] Yields were determined by ^{1}H NMR analysis using an internal standard.



Scheme 2 Poisoning and Regeneration of Pd Catalyst in C–H Arylation.

Having established that Ag salts are not intrinsically required for the C–H arylation process, we hypothesised that a more benign acetate salt could equally facilitate regeneration of the Pd catalyst if the acetate counter-cation produced a highly insoluble iodide salt within the reaction medium. To examine the validity of this hypothesis we investigated the replacement of AgOAc with a variety of acetate salts (Table 2). The addition of NaOAc, CsOAc or $Cu(OAc)_2$ proved to be ineffective for the regeneration of the catalyst (entries 1-3).[11] To our delight, a survey of quaternary ammonium salts (entries 4-7) revealed that tetra*methyl*ammonium acetate could be used to regenerate the catalyst (entry 5), leading to the product in 45% yield (*ca* 9 catalyst turnovers). Further, NMe_4OAc could be formed *in situ* by the equimolar combination of the more readily available and inexpensive NMe_4Cl and KOAc (entry 8). An experiment using unreactive PdI_2 demonstrated that, like AgOAc, NMe_4OAc salts are able to regenerate catalytically active Pd species *in situ* (entry 9). Increasing the equivalents of base and iodide abstractor gave an improved yield (entries 10 and 11), with 2.05 equiv of NMe_4Cl affording similar yields of product to those obtained using AgOAc (compare entry 11 with entry 1 in Table 1).[12]

Table 2 Selected Optimization Results [a]

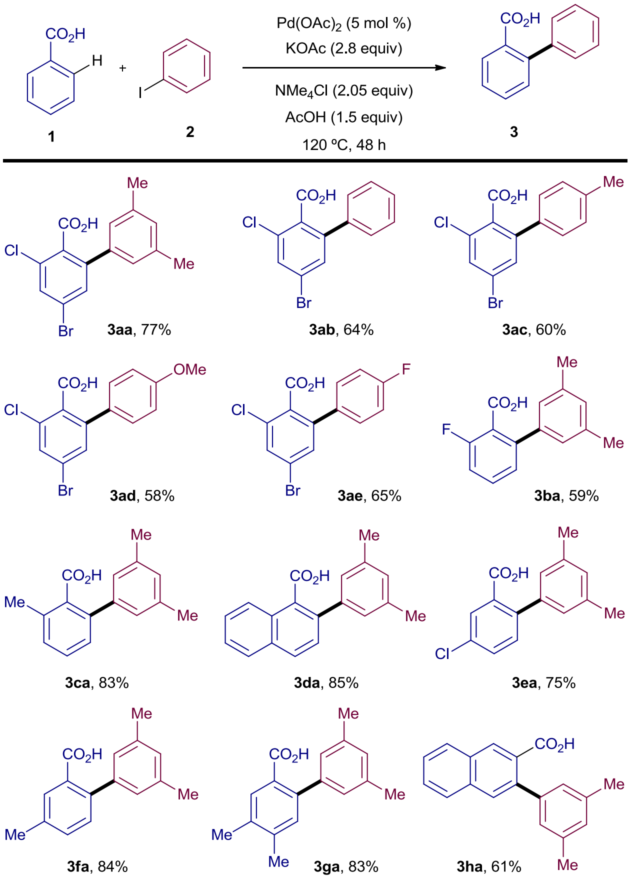


entry	Pd cat.	additive (equiv)	**3aa** (%)[b]
1	$Pd(OAc)_2$	NaOAc (1)	9
2	$Pd(OAc)_2$	$Cu(OAc)_2$ (1)	9
3	$Pd(OAc)_2$	CsOAc (1)	10
4	$Pd(OAc)_2$	NH_4OAc (1)	4
5	$Pd(OAc)_2$	NMe_4OAc (1)	45
6	$Pd(OAc)_2$	NEt_4OAc (1)	9
7	$Pd(OAc)_2$	NBu_4OAc (1)	12
8	$Pd(OAc)_2$	NMe_4Cl (1)+KOAc (1)	44
9	PdI_2	NMe_4Cl (1)+KOAc (1)	42
10	$Pd(OAc)_2$	NMe_4Cl (1.25)+KOAc (1.25)	62
11 [c]	$Pd(OAc)_2$	NMe_4Cl (2.05)+KOAc (1.8)	85

[a] Unless otherwise noted, all reactions were carried out using 0.5 mmol of **1a** and 3 equiv of **2a**. [b] Yields were determined by ^{1}H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard. [c] Reaction run for 48 h. NMe_4Cl and KOAc added in two portions.

The effect of NMe_4 salts on the catalytic activity is remarkable, in particular when compared with the ineffective ammonium salts bearing much larger (NBu_4 and NEt_4) or smaller (NH_4) cations. This may be due to a more favourable cation/anion radii ratio, leading to a more effective crystal packing of the corresponding iodide salt.[13] The solubility of NMe_4I in AcOH was determined to be lower than 0.3 mg per mL, which compares favourably to the higher solubilities of NH_4I (4.7 mg per mL), NEt_4I (6.5 mg per mL) and NBu_4I (647 mg per mL).

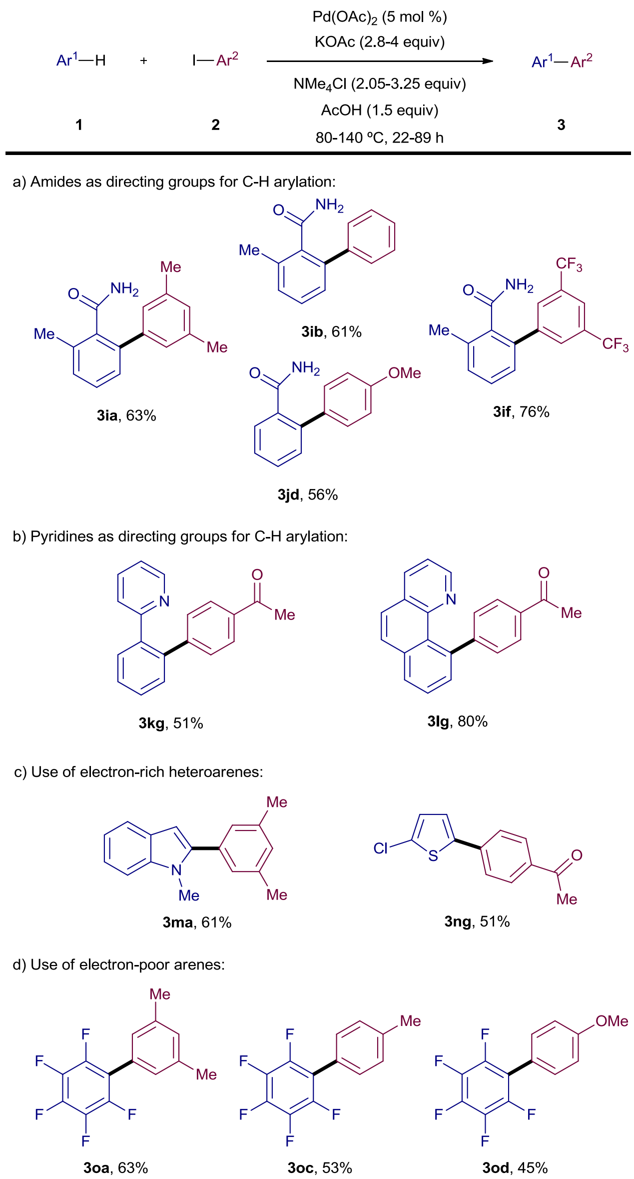
Having found a suitable cheap and benign replacement for Ag(I) salts, we explored the effects of substitution in both the benzoic acid and the iodoarene coupling partners (Scheme 3). Gratifyingly, both electron-poor and electron-rich iodoarenes led to the corresponding biaryl products in yields similar to, or higher than, those reported for the same AgOAc mediated process (**3ab**-**3ae**).[4ac] Varied substitution was also possible on the benzoic acid coupling partner, with high yields observed for *ortho*, *meta* and/or *para* substituted benzoic acids (**3ba**-**3ha**).



Scheme 3 Scope of the silver-free C–H arylation of benzoic acids with iodoarenes. All reactions were carried out on 0.5 mmol scale. Yields are of the isolated pure material.

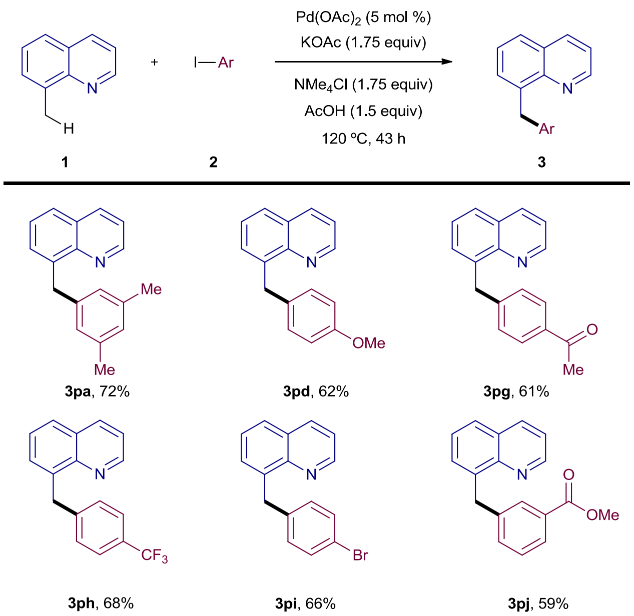
We envisaged that formation of unreactive PdI_2 may be a common intermediate in the majority of Pd(II)-catalysed C–H arylation reactions with iodoarene coupling partners. Therefore, we explored the general applicability of NMe_4OAc as an organic analogue for Ag(I)-salts to a wide variety of C–H arylation reactions (Scheme 4). It is noteworthy that simply by adjusting a few reaction parameters the system could be applied to other classes of substrates. Using free amides instead of carboxylic acids as the directing group, the NMe_4-mediated protocol furnished the biaryl products in good yield (**3ia-3jd**). Other common directing groups for C–H arylation, pyridine and benzoquinoline, were also successfully used under silver-free conditions (**3kg-lg**). We then explored the application of our arylation protocol to other heteroarenes in the absence of a directing group. Remarkably, this protocol also allowed the arylation of *N*-methylindole and 2-chlorothiophene in good yields (**3ma-3ng**). These reactions proceeded with high C2 and C5 regioselectivity, respectively (>95:5 by ^{1}H NMR). Finally, the C–H arylation of electron-poor arenes was also tested and, to our delight, silver-free couplings with pentafluorobenzene could be successfully achieved (**3oa-3od**).

To further highlight the applicability and significance of the new catalytic system, we then examined C(sp^3)–H bond arylation reactions (Scheme 5). Importantly, functionalization at the benzylic position of 8-methylquinoline proceeded well under silver-free conditions for iodoarenes containing both electron-donating and electron-withdrawing groups (**3pa-3pj**).



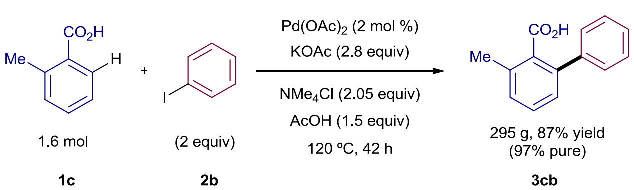
Scheme 4 Generality of the silver-free C–H arylation of arenes with iodoarenes. All reactions were carried out on 0.5 mmol scale. Yields are of the isolated pure material.

The development of NMe_4-promoted reactions offers major economical and practical advantages over existing Ag-mediated methods. Firstly, the method provides a new avenue to reduce the cost of a number of chemical processes; NMe_4Cl is *ca*. 50 times cheaper than AgOAc,[14] and is produced in large scale (>5,000 tons/year). Secondly, the synthetic advancement is also favourable from an environmental point of view; while AgOAc and AgI are both classed as very toxic to the aquatic environment, NMe_4OAc and its by-product NMe_4I[15] are only classed as irritants. Moreover, the tolerance of the system covers a broad range of chemical motifs and the procedure is operationally trivial; the reaction proceeds smoothly under air with no special precautions needed. Overall, the methodology greatly increases the potential for C–H bond direct arylations to be exploited in pharmaceutical and agrochemical industries, where the value of a synthetic process is mainly assessed by the viability in terms of cost and environmental impact.



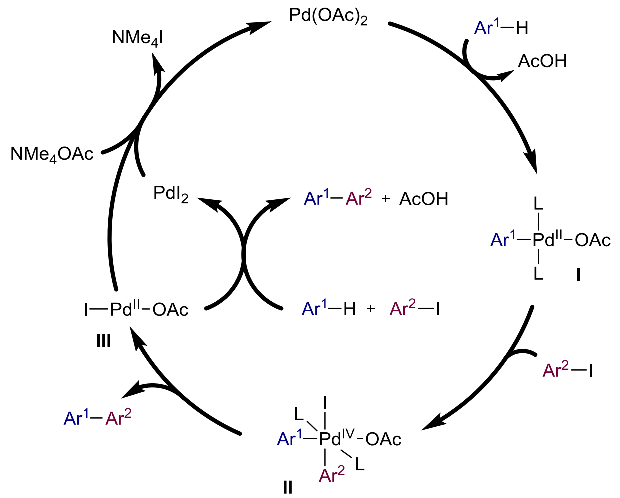
Scheme 5 Scope of the C(sp[3])–C(sp[2]) coupling. All reactions were carried out on 0.5 mmol scale. Yields are of the isolated pure material.

In order to demonstrate the utility of the new silver-free coupling for process chemistry, we scaled-up the reaction more than 3,000 times in a 5 L reactor. Further optimization of the method allowed the arylation of 1.6 mol (218 g) of *o*-toluic acid **1c** with 2 equiv of iodobenzene (**2b**) and 2 mol % $Pd(OAc)_2$ (Scheme 6). After an acid–base work-up, the reaction afforded 295 g of product **3cb** in 87% yield with a 97% a/a purity by HPLC suitable for most applications. The purity could be upgraded to >99.9% if required by a simple re-slurry process in *n*-heptane.[10] The analogous reaction using AgOAc would have required 267 g of the silver salt, worth £840, and would have generated 376 g of waste in the form of AgI.[16] Excluding costs associated with waste streams, this new process represents savings of *ca*. 70%. We are confident that our NMe_4-promoted methodology could be readily carried out on multi-kilogram scale.



Scheme 6 Scale-up of the silver-free arylation reaction. See ESI for full details.†

Our study helps to define the mechanism of previously reported Ag-promoted systems.[3,4] The comparable reactivity, and required reaction times, observed between the NMe_4-mediated method and those using silver salts suggests that the role of Ag(I) is purely that of a halophile in the catalyst regeneration step. Therefore, other functions attributed to Ag(I) such as terminal oxidant, activator of iodoarenes or assistant in the C–H activation step can most likely be ruled out for this type of arylation processes. Based on these results, a proposed general catalytic cycle for the reactions here reported is depicted in Scheme 7. We postulate a Pd(II/IV) cycle where the C–H activation of the arene would take place first to form an aryl Pd(II) complex **I**. This intermediate may then undergo oxidative addition to Pd(IV) species **II** which, after reductive elimination, would release the biaryl product and the catalyst in the form of PdIOAc (**III**). This intermediate could undergo ligand exchange with NMe_4OAc to form $Pd(OAc)_2$, disproportionate to PdI_2 and $Pd(OAc)_2$ or could also initiate a second catalytic cycle which would result in unreactive PdI_2. Finally, PdI_2 would react with NMe_4OAc, regenerating catalytically active $Pd(OAc)_2$.



Scheme 7 Proposed general catalytic cycle.

Conclusions

In summary, we have described the discovery of an organic analogue of silver(I)-salts, and develop reaction conditions that allow the Pd-catalysed C–H coupling reaction of a variety of classes of substrates: benzoic acids, benzamides, 2-phenylpyridines, benzoquinolines, indoles, thiophenes, polyfluorobenzenes and 8-methylquinolines with diverse substituted iodoarenes under silver-free conditions. The new method is easily scalable and benefits from the use of inexpensive and readily available reactants, an operationally simple procedure, high functional group tolerance and low-toxicity waste. We believe that this discovery will provide a pathway for facilitating application of numerous existing, and new, direct C–H bond functionalizations to industry, in addition to opening the door to other novel silver-free transition metal catalysed processes.

Acknowledgments

We gratefully acknowledge GlaxoSmithKline and the Engineering and Physical Sciences Research Council for generous support via ImpactQM KTA, the European Research Council for a Starting Research Grant (to I.L.) and MINECO-Spain for a FPI Fellowship (to J.G.D.).

Notes and references

[a] *School of Biological and Chemical Sciences, Queen Mary University of London, Joseph Priestley Building, Mile End Road, E1 4NS, London (UK)*
Tel: +44 (0) 20 7882 8404; E-mail: i.larrosa@qmul.ac.uk
[b] *GlaxoSmithKline Medicines Research Centre,Gunnels Wood Road, Stevenage, SG1 2NY, Hertfordshire (UK)*
† Electronic Supplementary Information (ESI) available: complete experimental procedures, characterization data and NMR spectra. See DOI: 10.1039/b000000x/
‡ Present address: Department of Chemistry, University of Patras. 26500, Patras, Greece.

1 For recent reviews on direct arylation reactions and Pd-catalysed C–H activation methodologies, see: (a) D. Alberico, M. E. Scott and M. Lautens, *Chem. Rev.*, 2007, **107**, 174; (b) L. Ackermann, R. Vicente and A. R. Kapdi, *Angew. Chem. Int. Ed.*, 2009, **48**, 9792; (c) X. Chen, K. M. Engle, D.-H. Wang and J.-Q. Yu, *Angew. Chem. Int. Ed.*, 2009, **48**, 5094; (d) T. W. Lyons and M. S. Sanford, *Chem. Rev.*, 2010, **110**, 1147; (e) J.-Q. Yu and Z. Shi, Ed. *Topics in Current Chemistry: C-H Activation*, 1st ed.; Springer: Berlin Heidelberg, 2010; (f) J. Wencel-Delord, T. Dröge, F. Liu and F. Glorius, *Chem. Soc. Rev.*, 2011, **40**, 4740; (g) C. S. Yeung and M. V. Dong, *Chem. Rev.*, 2011, **111**, 1215; (h) C.-L. Sun, B.-J. Li and Z.-J. Shi, *Chem. Rev.*, 2011, **111**, 1293; (i) L. Ackermann, *Chem. Rev.*, 2011, **111**, 1315; (j) L. McMurray, F. O. O'Hara and M. Gaunt, *Chem. Soc. Rev.*, 2011, **40**, 1885; (k) J. Yamaguchi, A. D. Yamaguchi and K. Itami, *Angew. Chem. Int. Ed.*, 2012, **51**, 8960.
2 O. Daugulis and V. G. Zaitsev, *Angew. Chem. Int. Ed.*, 2005, **44**, 4046.
3 For reviews: (a) O. Daugulis, H.-Q. Do and D. Shabashov, *Acc. Chem. Res.*, 2009, **42**, 1074; (b) O. Daugulis, *Top. Curr. Chem.*, 2010, **292**, 57; (c) K. M. Engle, T.-S. Mei, M. Wasa, M. and J.-Q. Yu, *Acc. Chem. Res.*, 2012, **45**, 788.
4 (a) V. G. Zaitsev, D. Shabashov and O. Daugulis, *J. Am. Chem. Soc.*, 2005, **127**, 13154; (b) D. Shabashov and O. Daugulis, *Org. Lett.*, 2005, **7**, 3657; (c) K. Kobayashi, A. Sugie, M. Takahashi, K. Masui and A. Mori, *Org. Lett.*, 2005, **7**, 5083; (d) D. Shabashov and O. Daugulis, *Org. Lett.*, 2006, **8**, 4947; (e) A. Lazareva and O. Daugulis, *Org. Lett.*, 2006, **8**, 5211; (f) K. Kobayashi, M. S. M. Ahmed and A. Mori, *Tetrahedron*, 2006, **62**, 9548; (g) 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; (h) G. L. Turner, J. A. Morris and M. F. Greaney, *Angew. Chem. Int. Ed.*, 2007, **46**, 7996; (i) H. A. Chiong, Q.-N. Pham and O. Daugulis, *J. Am. Chem. Soc.*, 2007, **129**, 9879; (j) D. Shabashov and O. Daugulis, *J. Org. Chem.*, 2007, **72**, 7720; (k) N. Arai, T. Miyaoku, S. Teruya and A. Mori, *Tet. Lett.*, 2008, **49**, 1000; (l) N. Lebrasseur and I. Larrosa, *J. Am. Chem. Soc.*, 2008, **130**, 2926; (m) E. F. Flegeau, M. E. Popkin and M. F. Greaney, *Org. Lett.*, 2008, **10**, 2717; (n) C. Qin and W. Lu, *J. Org. Chem.*, 2008, **73**, 7424; (o) D. Shabashov, J. R. M. Maldonado and O. Daugulis, *J. Org. Chem.*, 2008, **73**, 7818; (p) V. S. Thirunavukkarasu, K. Parthasarathy and C.-H. Cheng, *Angew. Chem. Int. Ed.*, 2008, **47**, 9462; (q) F, Yang, Y. Wu, Z. Zhu, J. Zhang and Y. Li, *Tetrahedron*, 2008, **64**, 6782; (r) R. B. Bedford, R. L. Webster and C. J. Mitchell, *Org. Biomol. Chem.*, 2009, **7**, 4853; (s) M. P. Huestis and K. Fagnou, *Org. Lett.*, 2009, **11**, 1357; (t) T. Nishikata, A. R. Abela and B. H. Lipshutz, *Angew. Chem. Int. Ed.*, 2010, **49**, 781; (u) S. A. Ohnmacht, A. J. Culshaw and M. F. Greaney, *Org. Lett.*, 2010, **12**, 224; (v) O. René and K. Fagnou, *Org. Lett.*, 2010, **12**, 2116; (w) G.-W. Wang, T.-T. Yuan and D.-D. Li, *Angew. Chem. Int. Ed.*, 2011, **50**, 1380; (x) W. Li, Z. Xu, P. Sun, X. Jiang and M. Fang, *Org. Lett.*, 2011, **13**, 1286; (y) J. Cornella, M. Righi and I. Larrosa, *Angew. Chem. Int. Ed.*, 2011, **50**, 9429; (z) F. Chen, Q.-Q. Min and X. Zhang, *J. Org. Chem.*, 2012, **77**, 2992; (aa) D.-D. Li, T.-T. Yuan and G.-W. Wang, *J. Org. Chem.*, 2012, **77**, 3341; (ab) M. Wasa, K. S. L. Chan, X.-G. Zhang, J. He, M. Miura and J.-Q. Yu, *J. Am. Chem. Soc.*, 2012, **134**, 18570; (ac) C. Arroniz, A. Ironmonger, G. Rassias and I. Larrosa, *Org. Lett.*, 2013, **15**, 910; (ad) J.-C. Wan, J.-M. Huang, Y.-H. Jhan and J.-C. Hsieh, *Org. Lett.*, 2013, **15**, 2742; (ae) R. Feng, J. Yao, Z. Liang, Z. Liu and Y. Zhang, *J. Org. Chem.*, 2013, **78**, 3688; (af) P. Ricci, K. Kraemer, X. C. Cambeiro and I. Larrosa, *J. Am. Chem. Soc.*, 2013, **135**, 13258; (ag) S. Islam and I. Larrosa, *Chem. Eur. J.*, 2013, **19**, 15093; (ah) Z. Huang and G. Dong, *J. Am. Chem. Soc.*, 2013, **135**, 17747; (ai) W. R. Gutekunst and P. S. Baran, *J. Org. Chem.*, 2014, **79**, 2430; (aj) J. Luo, S. Preciado and I. Larrosa, *J. Am. Chem. Soc.*, 2014, **136**, 4109; (ak) L. C. M. Castro and N. Chatani, *Chem. Eur. J.*, 2014, **20**, 4548; (al) J. He, S. Li, Y. Deng, H. Fu, B. N. Laforteza, J. E. Spangler, A. Homs and J.-Q. Yu, *Science*, 2014, **343**, 1216.
5 Some success has been achieved in avoiding silver salts for specific substrates via bidentate-chelation assistance: (a) D. Shabashov and O. Daugulis, *J. Am. Chem. Soc.*, 2010, **132**, 3965; (b) M. Ye, G.-L. Gao, A. J. F. Edmunds, P. A. Worthington, J. A. Morris and J.-Q. Yu, *J. Am. Chem. Soc.*, 2011, **133**, 19090; (c) L. Huang, Q. Li, C. Wang and C. Qi, *J. Org. Chem.*, 2013, **78**, 3030; (d) M. Ye, A. J. F. Edmunds, J. A. Morris, D. Sale, Y. Zhang and J.-Q. Yu, *Chem. Sci.*, 2013, **4**, 2374; (e) D. S Roman and A. B. Charette, *Org. Lett.*, 2013, **15**, 4394.
6 (a) M. Naodovic and H. Yamamoto, *Chem. Rev.*, 2008, **108**, 3132; (b) J.-M. Weibel, A. Blanc and P. Pale, *Chem. Rev.*, 2008, **108**, 3149; (c) M. Alvarez-Corral, M. Muñoz-Dorado and I. Rodríguez-García, *Chem. Rev.*, 2008, **108**, 3174; (d) Y. Yamamoto, *Chem. Rev.*, 2008, **108**, 3199; (e) J.-M. Weibel, A. Blanc and P. Pale, *Silver in Organic Chemistry*, (Ed: M. Hamata), Wiley, New Jersey, 2010.
7 (a) C. Nevado and A. M. Echavarren, *Chem. Eur. J.*, 2005, **11**, 3155; (b) E. M. Beccalli, G. Broggini, M. Martinelli and S. Sottocornola, *Chem. Rev.*, 2007, **107**, 5318; (c) G. Rassias, N. G. Stevenson, N. R. Curtis, J. M. Northall, M. Gray, J. C. Prodger and A. J. Walker, *Org. Process Res. Dev.*, 2010, **14**, 92; (d) M. Vellakkaran, M. M. S. Andappanb and N. Kommu, *Green Chem.*, 2014, DOI: 10.1039/C3GC42504E.
8 (a) D. Weber and M. R. Gagné, *Org. Lett.*, 2009, **11**, 4962. (b) D. Wang, R. Cai, S. Sharma, J. Jirak, S. K. Thummanapelli, N. G. Akhmedov, H. Zhang, X. Liu, J. L. Petersen, and X. Shi, *J. Am. Chem. Soc.*, 2012, **134**, 9012. (c) A. Homs, I. Escofet and A. M. Echavarren, *Org. Lett.*, 2013, **15**, 5782.
9 M. Anand, R. B. Sunoj and H. F. Schaefer III, *J. Am. Chem. Soc.*, 2014, **136**, 5535.
10 See ESI for details.†
11 Recently, Yu and co-workers have identified a viable alternative for catalyst regeneration in iodination reactions by the effective combination of a specific amide auxiliary and CsOAc as iodide scavenger, see: (a) X.-C. Wang, Y. Hu, S. Bonacorsi, Y. Hong, R. Burrell and J.-Q. Yu, *J. Am. Chem. Soc.*, 2013, **135**, 10326. Earlier studies on halogenation of C–H bonds showed that $Pd(OAc)_2$ can be obtained from PdI_2 with IOAc. This iodonium(I) reagent is not suitable for silver-free arylations as it has to be preformed from AgOAc or $PhI(OAc)_2$ *in situ*, see: (b) D.-H. Wang, X.-S. Hao, D.-F. Wu and J.-Q. Yu, *Org. Lett.*, 2006, **8**, 3387; (c) T.-S. Mei, R. Giri, N. Maugel and J.-Q. Yu, *Angew. Chem. Int. Ed.*, 2008, **47**, 5215; (d) T.-S. Mei, D.-H. Wang and J.-Q. Yu, *Org. Lett.*, 2010, **12**, 3140.
12 The reaction performed best under neat conditions but some organic solvents are also tolerated. For example, running the reaction 1 M in dioxane, EtOAc or PhCl led to 64%, 53% and 46%, respectively. See Table S1 in the ESI for more details.†
13 J. Palomo and P. N. Pintauro, *J. Membrane Sci.*, 2003, **215**, 103.
14 Based on Sigma-Aldrich catalogue prices (April 2014), NMe_4Cl costs £10.5/mol whereas AgOAc costs £526/mol.
15 NMe_4I was isolated from the reaction mixture by filtration and characterized, see ESI.†
16 In addition, work-up of reaction mixtures is more difficult when silver is present in the system due to its poor filtration properties. Also, recycling of metal catalysts is hampered by the presence of other metals in the waste, see: (a) E. Jimenez-Nuñez and A. M. Echavarren, *Chem. Rev.*, 2008, **108**, 3326; (b) H. Schmidbaur and A. Schier, *Z. Naturforsch.*, 2011, **66b**, 329.