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Synthesis of Quaternary Aryl Phosphonium Salts: Photoredox-Mediated Phosphine Arylation

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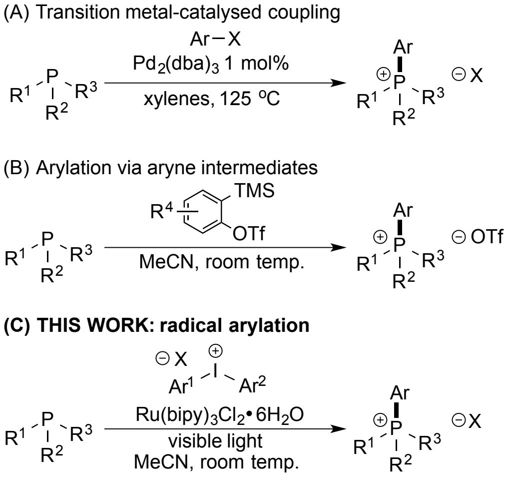
We report a synthesis method for the construction of quaternary aryl phoshonium salts at ambient temperature. The regiospecific reaction invovles the coupling of phosphines with aryl radicals derived from diaryliodonium salts under photoredox conditions.

Quaternary phosphonium salts are a fundamentally important class of organophosphorus compounds, which have been applied as synthesis reagents[i] phase-transfer catalysts,[ii] ionic liquids,[iii] anti-cancer agents[iv] as well as in drug delivery.[v] More recently, phosphonium salts have begun to be explored as Lewis acids[vi] as a result of their low lying σ* orbitals, opening up an exciting new class of organocatalysts.

Despite this diverse range of applications methods for the construction of aryl-substituted phosphonium salts are limited. Transition metal-mediated couplings of phosphines[vii] and aryl halides, such as the palladium-catalysed reactions reported by Charette and co-workers (Scheme 1A),[viib,c] are known but typically take place at high temperatures. An important alternative method was recently reported by Juge and co-workers (Scheme 1B) and involves the interception of *in situ*-generated arynes with phosphines at room temperature.[viii] This method is limited somewhat by the availability of 2-(trimethylsilyl)aryl triflates and poor the regioselectivities obtained during the coupling of unsymmetrical arynes with phosphines.

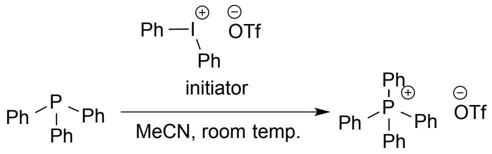
With these limitations in mind we sought a method that could be conducted at ambitent temperature and was regiospecific with respect to carbon-phosphorus bond formation. We reasoned that the arylation of tervalent organophosphorus compounds with iodonium salts,[ix] first reported by Reutov and co-workers in 1965[x] and subsequently revisited by Kampmeier,[xi] could meet the above criteria. The latter non-preparative[xii] mechanistic study corroborated a redox radical chain process involving aryl and phosphoranyl radicals[xiii] and, despite being overlooked since,[xiv] suggested that a synthetically useful phosphine arylation reaction could be developed. Herein we report a photoredox-initiated arylation reaction between aryliodonium salts and phosphines under ambient reaction conditions (Scheme 1C).



Scheme 1.

We began by establishing a new method for the initiation of the putative radical chain at ambient temperature under photoredox conditions.[xv] To this end the combination of visible light with $Ru(bpy)_3Cl_2$ was explored (Table 1). Gratifyingly, the photo-redox initiated arylation of triphenylphosphine with diphenyliodonium triflate (entry 1) gave the corresponding phosphonium salt in good conversion. Next, the analogous reaction without the 10W lamp was investigated (entry 2) and gave a much-reduced 23% conversion. The arylation reaction did proceed in the presence of visible light without $Ru(bpy)_3Cl_2$, albeit more slowly (12% conversion after 20 mins, entry 3).

Table 1. Survey of initiation methods.



Entry	Initiator	Time	Conversion^{a}		
	(mol%)	(min)	PPh_3	PPh_3O	PPh_4
1	10 W lamp $Ru(bpy)_3Cl_2$ 2 mol%	20	19	10	73
2	$Ru(bpy)_3Cl_2$ 2 mol%	20	71	6	23
3	10 W lamp	20	84	6	12
4	None	120	100	0	0
5	AIBN (80 °C) 10 mol%	240	0	50	50

^{a}Determined *via* ^{31}P NMR analysis of the crude the reaction mixture.

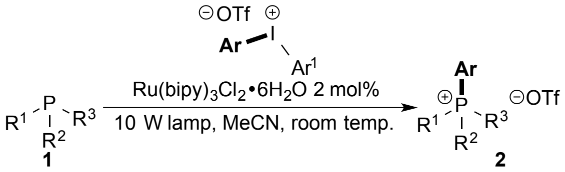
Finally, in the absence of both ruthenium and visible light (entry 4) no conversion to phosphonium salt was obtained after 120 minutes. These experiments demonstrate that $Ru(bpy)_3Cl_2$ in combination with visible light from a 10 W lamp serve as an effective radical initiator in this system at ambient temperature.[xvi] For comparison initiation using AIBN proved to be less efficient (entry 5) giving 23% conversion at 80 °C after two hours. Having established that the combination of $Ru(bpy)_3Cl_2$ and visible light was effective for initiating a radical-based coupling reaction we proceeded to examine the scope of this room temperature arylation protocol.

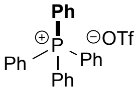
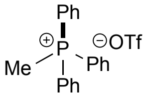
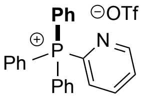
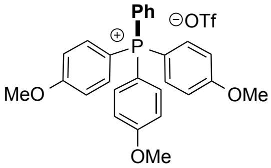
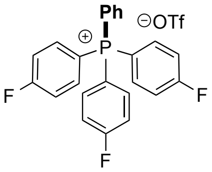
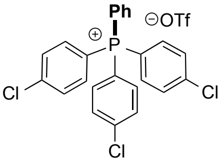
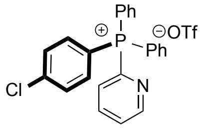
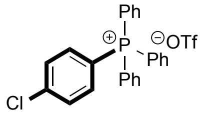
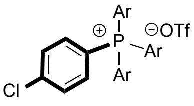
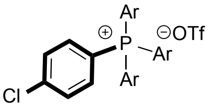
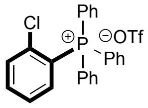
We began by arylating a range of triarylphosphines with diphenyliodonium triflate (Table 2, entries 1,3,4,5 and 6) to afford the corresponding phosphonium salts **2** in moderate to excellent isolated yield following flash chromatography and recrystallization. The arylation of methyldiphenylphosphine (entry 2) was also efficient.

Next we sought to prepare further phosphonium salts bearing functional groups that would facilitate further transformations after arylation. To this end we prepared two chlorophenyl(mesityl)iodonium triflates and carried out arylation reactions with a range of phosphines (entries 7-11). The phosphonium salt products were obtained in good to moderate yields and are suitable for further functionalization *via* cross coupling.[viib] In each case selective transfer of the chlorophenyl group over the mesityl group was observed.[xvii]

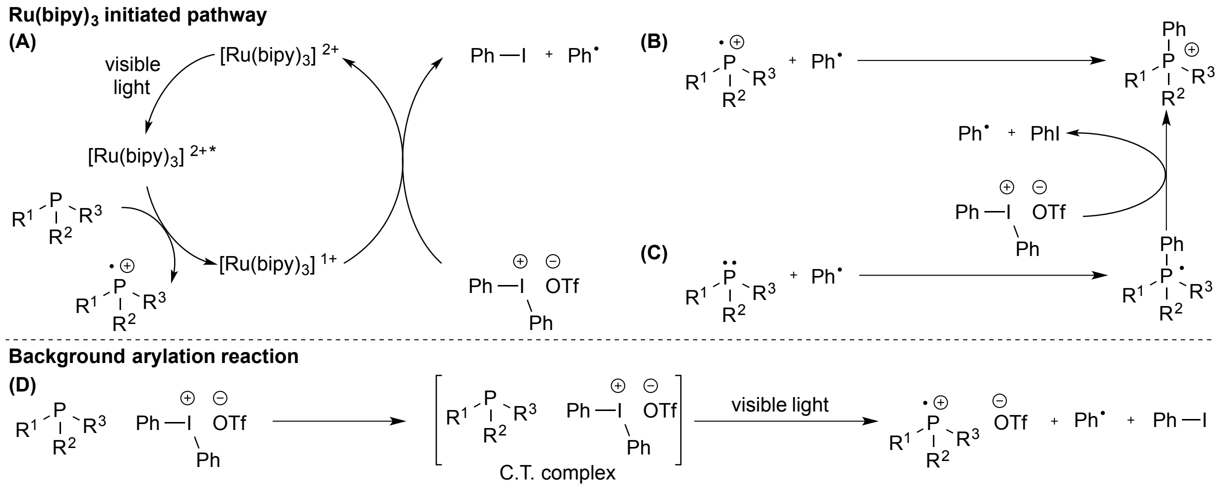
In summary the arylation protocol provides access to a range of functionalised aryl phosphonium salts under ambient conditions.

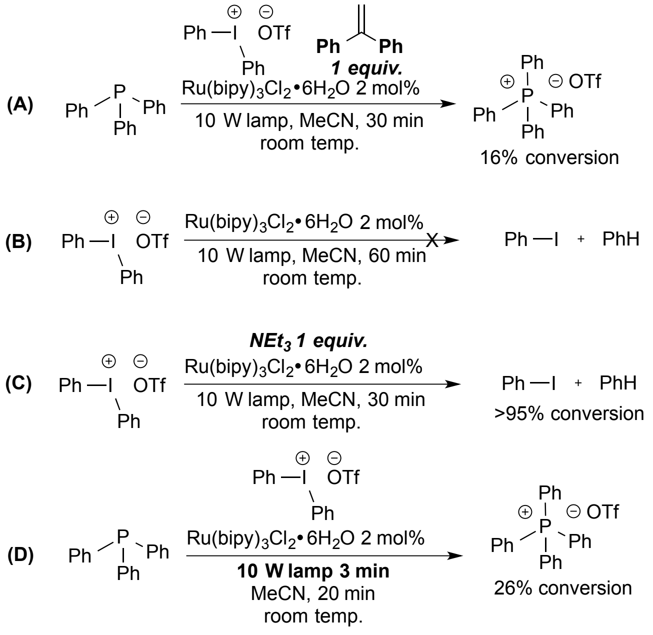
Table 2. Scope of the arylation reaction.



Entry		Product	Isolated yield (%)
1	**2a**		85
2	**2b**		74
3	**2c**		82
4	**2d**		57
5	**2e**		69
6	**2f**		51
7	**2g**		63
8	**2h**		65
9	**2i**	 Ar=4-fluorophenyl	71
10	**2j**	 Ar=4-methoxyphenyl	57
11	**2k**		46

[a]Typical procedure: iodonium salt (1.0 equiv, 0.7-0.8 mmol), phosphine (1.5 equiv) and Ru(bpy)$_3$Cl$_2$•6H$_2$O (10 mol%). Yields are for isolated phosphonium salts following normal phase flash chromatography and recrystalisation.





Scheme 1 (top) Scheme 2 (right)

In terms of the mechanism our experimental observations, as well as those of others[xviii] are consistent with the pathways depicted in Scheme 1. Visible light-induced excitation of $Ru(bpy)_3Cl_2$ results in population of the excited state, which is reductively quenched by the phosphine resulting in the corresponding phosphoniumyl radical cation.[xix] The derived ruthenium (I) species now reduces the iodonium salt, resulting in fragmentation to afford an aryl radical and iodobenzene as a by-product. Formation of the product phosphonium salt can now occur through two pathways. Either, the phosphoniumyl radical cation combines with the phenyl radical (Scheme 1B), or a radical chain process intervenes (Scheme 1C). The radical chain reaction involves addition of a phenyl radical to triphenylphosphine to afford an intermediate phosphoranyl radical.[xiii] Subsequent oxidation of this radical by the iodonium salt affords the phosphonium salt product and propagates the radical chain. Support for above proposal comes the following experiments depicted in Scheme 2. An arylation reaction conducted in the presence of 1,1-diphenylethylene resulted in significantly reduced conversion to the product phosphonium salt (16% compared to 73% under standard conditions, entry 1 Table 1). This is consistent with covalent trapping of phenyl radicals, as is the production of increased amounts of triphpenylphosphine oxide from the reaction of the intermediate phosphoniumyl radical cation with water.[xx] Secondly, diphenyliodonium triflate is stable with respect to reductive fragmentation in the presence of $Ru(bpy)_3Cl_2$ and visible light (Scheme 2B). This rules out an alternative photoredox initiation involving oxidative quenching of excited ruthenium(II) by the iodonium salt. In a third experiment (Scheme 2C) diphenyliodonium triflate was converted into iodobenzene and benzene in the presence of $Ru(bpy)_3Cl_2$ and triethylamine. These two observations are congruent with the Ru(I)-mediated reduction of the iodonium salt depicted in Scheme 1A. Finally, an arylation reaction in which irradiation was stopped after 3 minutes resulted in 26% conversion. This suggests that the arylation process is weighted more towards Scheme 1B than the radical chain process (Scheme 1C) .[xxi]

The reaction also proceeds in the presence of visible light but absence of $Ru(bipy)_3$ (Table 1, entry 3). We speculate that this arylation proceeds through a charge transfer complex[ixf] (Scheme 1D) from which electron transfer from phosphine to iodonium salt may occur in the presence of visible light to provide the phosphoniumyl radical cation and phenyl radical.

In conclusion we have developed synthesis method for the construction of aryl-substituted phosphonium salts under mild conditions. This protocol opens up a valuable new route to functionalised aryl phosphonium salts and demonstrates the utility of photoredox-mediated arylation reactions[xxii] in the area of organophosphorus chemistry.

Notes and references

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[i] (a)R.W. Hoffman, *Angew. Chem. Int. Ed*. 2001, **50**, 1411; (b) L.K. Hwang, Y. Na, J. Lee, Y. Do, S. Chang, *Angew. Chem. Int. Ed.* 2005, **44**, 6166.

[ii] For a recent reviews, see (a) D. Enders, T.V. Nguyen, *Org. Biomol. Chem.* 2012, **10**, 5327; (b) K. Manabe, *Tetrahedron Lett*., 1998, **39**, 5807; (c) R. He, K. Maroua, *Synthesis,* 2009, **13**, 2289; (d) C.-L. Zhu, F.-G. Zhang, W. Meng, J. Nie, D. Cahard, J.-A. Ma, *Angew. Chem. Int. Ed.* 2011, **50**, 5869; (e) S. Shirakawa, A. Kasai, T. Tokuda, K. Maruoka, *Chem. Sci.* 2013, **4**, 2248; (f) S. Shirakawa, T. Tokuda, A. Kasai, K. Marouka, *Org. Lett.* 2013, **15**, 3350; (g) B. Wang, Y. Liu, C. Sun, Z. Wei, J. Cao, D. Liang, Y. Lin, H. Duan, *Org. Lett.* 2014, **16**, 6432.

[iii] (a) H. Coa, L. McNamee, H. Apler, *J. Org. Chem.* 2008, **73**, 3530. (b) J. McNulty, A. Capretta, J. Wilson, J. Dyck, G. Adjabeng, A.J.J. Robertson, *Chem. Soc., Chem. Commun.* 2002, 1986; (c) D.A. Gerritsma, A.J. Robertson, J. McNulty, A. Capretta, *Tetrahedron Lett.* 2004, **45**, 7629; (d) J. McNulty, A. Capretta, S. Cheekoori, J.A.C. Clyburne, A. Robertson, *J. Chemica Oggi* 2004, **22**, 13; (e) J. McNulty, S. Cheekoori, J.J. Nair, V. Larichev, A. Capretta, A.J. Robertson, *Tetrahedron Lett.* 2005, **46**, 3641; (f) J. McNulty, J.J. Nair, S. Cheekoori, V. Larichev, A. Capretta, A.J. Robertson, *Chem. Eur. J.* 2006, **12**, 9314; (g) J. McNulty, S. Cheekoori, T.P. Bender, J.A. Coggan, *Eur. J. Org. Chem.* 2007, **9**, 1423; (h) J. McNulty, J.J, Nair, A.J. Robertson, *Org. Lett.* 2007, **9**, 4575.

[iv] (a) D.C. Rideout, T. Calogeropoulou, J.S. Jworksi, R. Dagnino, R.M. McCarthy, *Anti-Cancer Drug Des.* 1989, 4, 265; (b) D.C. Rideout, A. Bustmante, J. Patel, *Int. J. Cancer*, 1994, **57**, 247.

[v] R.A.J. Smith, C.M. Porteous, A.M. Gane, M.P. Murphy, *Proc. Natl. Acad. Sci. USA*, 2003, **100**, 5407.

[vi] For reviews, see: (a) T. Werner, *Adv. Synth. Catal.* 2009, **351**, 1469; (b) J.M. Bayne and D.W. Stephan, *Chem. Soc. Rev*., DOI:10.1039/C5CS00516G. For recent examples, see (c) N. Dunn , M.Ha and A. Radosevich, *J. Am. Chem. Soc*. 2012, **134**, 11330; (d) L. J. Hounjet, C. B. Caputo and D. W. Stephan, *Angew. Chem. Int. Ed.* 2012, **51**,4714; (e) C. B. Caputo, L. J. Hounjet, R. Dobrovetsky and D.W.Stephan, *Science* 2013, **341**,1374; (f) M. Pérez, L. J. Hounjet, C. B. Caputo, R. Dobrovetsky and D.W.Stephan, *J.Am. Chem. Soc*. 2013 , **135**, 18308; (g) M. Perez, C. B. Caputo, R. Dobrovetsky and D.W.Stephan, Proc. Natl. Acad. Sci. 2014, **111**, 10917; (h) M. Pérez, T. Mahdi, L.J. Hounjet and D.W. Stephan, *Chem. Comm.,* 2015**, 51**, 11301; (i) T. vom Stein, M. Pérez, R. Dobrovetsky, D. Winkelhaus, C.B. Caputo and D.W. Stephan, *Angew. Chem. Int. Ed.,* 2015 **54**, 10178; (j) J.M. Bayne, M.H. Holthansen and D.W. Stephan, *Dalton Trans.* 2015, 44, 12256-12264

[vii] For a recent review on transition-metal catalyzed C-P cross coupling, see (a) F.M.J. Tappe, V.T. Trepohl, M. Oestreich, *Synthesis,* 2010, **18**, 3037; (b) D. Marcoux, A.B. Charette, *J. Org. Chem.* 2008, **73**, 590; (c) D. Marcoux, A.B. Charette, *Adv. Synth. Catal.* 2008, **350**, 2967. For Ni-mediated coupling, see (d) L. Horner, G. Mummenthey, H. Moser, and P. Beck, *Chem. Ber.* 1966, **99**, 2782.

[viii] E. Redmund, A.R. Leroux, J. Bayardon, S. Juge, *Org. Lett.* 2010, **12**, 1568.

[ix] For reviews, see (a) M.S. Yusubov, A.V. Maskaev, V.V. Zhdankin, *Arkivoc*, 2011, 380; (b) V. V. Zhdankin and P.J. Stang, *Chem. Rev*. 2008, **108**, 5299; (c) E. A. Merritt and B. Olofsson, *Angew. Chem., Int. Ed*. 2009, **48**, 9052. For relevant examples, see (d) S.R. Neufeldt, M.S. Sanford, *Adv. Synth. Catal*. 2012, **354**, 3517; (e) Y.-X. Liu, D. Xue, J.-D. Wang, C.-J. Zhao, Q-Z. Zou, C. Wang and J. Xiao, *Synlett* 2013, **24**, 507; (f) M. Tobisu, T. Furukawa and N. Chatani, *Chem. Lett*. 2013, **42**, 1203; (g) J. Heng, Y. Cheng, R. Wang, Y. Zhang and S. Yu, *Chem. Commun.* 2014, **50**, 6164; (h) G. Fumagalli, S. Boyd, and M. F. Greaney, *Org. Lett.*, 2013, **15**, 4398.

[x] A. Ptitsyna, M.E. Pudwva, A. Reutov, *Dokl. Akad. Nauk SSSR*, 1965, **166**, 582.

[xi] J.A. Kampmeier and T.W. Nalli, *J. Org. Chem*. 1993, **58**, 943.

[xii] This mechanistic study involved two substrates, namely, triphenylphosphine and trimethylphosphite. The reactions were non-preparative and conducted in NMR tubes.

[xiii] For a review on phosphoranyl radicals, see W.G. Bentrude, *Acc. Chem. Res.* 1982, **15**, 117.

[xiv] For recent related coupling reactions involving arylation of P-H and P-OH bonds using iodonium salts, see (a) J. Xu, P. Zhang, Y. Gao, Y. Chen, G. Tang, and Y. Zhao, *J. Org. Chem.*, 2013, **78**, 8176; (b) B. Xiong, X. Feng, L. Zhu, T. Chen, Y. Zhou, C.T. Au and S-F. Yin, *ACS Catal.*, 2015, **5**, 537; (c) M. Fañanás-Mastral and B.L. Feringa, *J. Am. Chem. Soc.* 2014,**136**, 9894; (d) Y. He, H. Wu and F.D. Toste, *Chem. Sci.*, 2015, **6**, 1194.

[xv] For selected reviews, see (a) K.P. Prier, D.A Rankic and D.W.C. MacMillan, *Chem. Rev.,* 2013, *113*, 5322; (b) Y. Xi, H. Yi and A. Lei, *Org. Biomol. Chem.,* 2013, **11**, 2387 and (c) J.W. Tucker and C.R.J. Stephenson, *J. Org. Chem.* 2012, **77,** 1617.

[xvi] Given the proximity of the lamp to the reaction vessel the internal temperature was monitored and found to be 32 °C. A further 1 h control experiment between Ph_3P and Ph_2IOTf at 32 °C resulted in the formation of Ph_3PO (6 %) and Ph_4POTf (3%) with 92% of Ph_3P remaining.

[xvii] The selective transfer of electron deficient aryl groups over the relatively electron rich mesityl group has been observed previously non-catalysed nucleophilic arylation reactions, see (a) J. Malmgren, S, Santoro, N, Jalalian, F. Himo and B. Olofsson, *Chem. Eur. J.* 2013, **19**, 10334; (b) S. K. Sundalam and David R. Stuart , *J. Org. Chem*. 2015, **80**, 6456. We observed no arylation between triphenylphosphine and 4-methoxyphenyl(mesityl)iodonium triflate under the reaction conditions depicted in Table 2.

[xviii] R. Muneer and T.W. Nalli, Macromolecules, 1998, **31**, 7976

[xix] For recent work involving phoshonium radical cations, see K.D. Reichl, D.H. Ess, and A.T. Radosevich, *J. Am. Chem. Soc.* 2013, **135**, 9354.

[xx] For electrochemical generation of the trimesityl phosphoniumyl radical and subsequent reaction with water to afford the corresponding phosphine oxide, see: B. Merzougui, Y. Berchadsky and P. Tordo, G. Gronchi, *Electrochimica Acta* 1997, **42**, 2445.

[xxi] We are grateful to a reviewer for suggesting this experiment.

[xxii] There are several other methods for the generation of aryl radicals under photoredox conditions, for example from diazonium salts, see (a) H. Cano-yelo and A. Deronzier, *J. Chem. Soc., Perkin Trans. 2,* 1984, **16**, 1093; (b) H. Cano-yelo and A. Deronzier, *Tetrahedron Lett.* 1984, ***25,*** 5517; (c) D. Kalyani, K.B. McMurtrey, S.R. Neufeldt and M.S. Sanford, *J. Am. Chem. Soc.,* 2011, **133**, 18566. It is likely that further arylation reactions of tervalent phosphorus compounds will be developed along these lines.