Solvent free catalytic C–H functionalisation†‡

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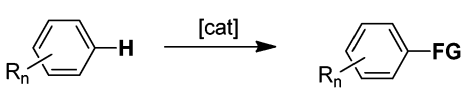
Received 12th February 2010, Accepted 12th March 2010
First published as an Advance Article on the web 30th March 2010
DOI: 10.1039/c003074k

Solvent-free reaction conditions facilitate a range of aromatic C–H functionalisations that traditionally require acidic or disfavoured solvents. These reactions include selective *ortho*- and *meta*-arylation of aryl carbamates and anilides and selective halogenation reactions.

The direct transition metal-catalysed C–H functionalisation of aromatic compounds (Scheme 1) is rapidly growing in importance, due in no small part to the greater step-economy and sustainability engendered compared with more traditional aromatic modifications.[1,2] While highly desirable, such reactions can be exacting, not least with regards to the choice of solvent. For instance many palladium-catalysed functionalisations are conducted in acidic media, such as acetic or trifluoroacetic acid, which can be deleterious to acid-sensitive functionality, or else require the use of industrially disfavoured solvents such as 1,2-dichloroethane (DCE).

We recently reported the palladium-catalysed *ortho*-arylation of arylcarbamates with aryl iodides or diaryliodonium salts.[3] The reactions require the use of acetic or trifluoroacetic acid as solvent, hampering activity with acid-sensitive functional groups. A brief examination of alternative solvents proved unsuccessful, as did an attempt to run reactions 'on water' (see ESI‡),[4,5] but we were delighted to discover that the reaction of aryl *N*,*N*-diethyl carbamates with diaryliodonium salts, [ArI(mes)][OTf], proceeded with excellent selectivity for the mono-arylated free phenol products, **1**,§ *in the absence of solvent* (Table 1, entries 1–8). The preparation of the reaction mixtures proved to be very simple: the starting materials were ground using a pestle and mortar for about 30 seconds to one minute until homogeneous, transferred to a tube and heated *under air* for the requisite time. Stirring was not necessary. The isolated yields of the phenols **1** were higher than those achieved previously in acetic acid.[3] Steric hindrance in the *ortho* position of the aryl carbamate prevented loss of the carabamate function (entry 7) while the reaction using mesityl-(2-(methoxycarbonyl)phenyl)iodonium triflate with 4-(*tert*-butyl)phenyl diethylcarbamate yielded the dibenzopyranone **3** (entry 8) *via* direct arylation followed by lactonisation.



Scheme 1 Catalytic aromatic C–H functionalisation.

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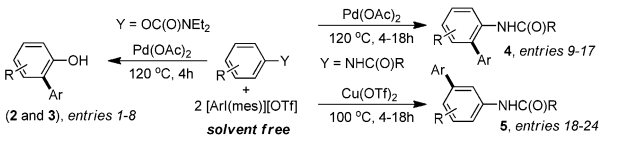
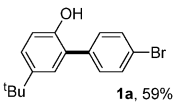
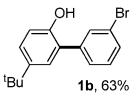
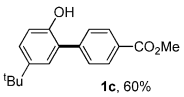
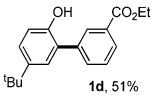
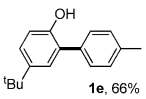
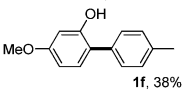
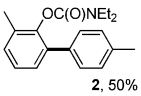
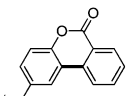
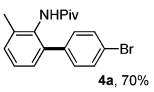
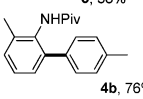
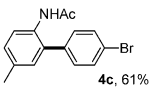
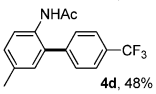
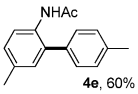
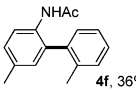
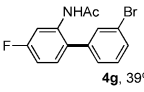
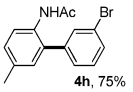
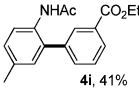
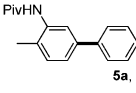
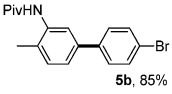
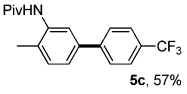
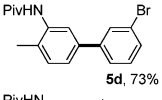
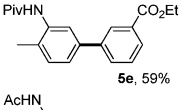
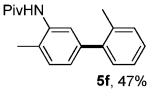
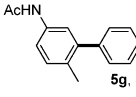
† Dedicated to the memory of Professor Keith Fagnou.
‡ Electronic supplementary information (ESI) available: Experimental details and spectroscopic data. See DOI: 10.1039/c003074k

Table 1 Solvent free catalytic *ortho*- and *meta*-arylation of carbamates and anilides



Entry	Product	Entry	Product
1[a]	 **1a**, 59%	2[a]	 **1b**, 63%
3[a]	 **1c**, 60%	4[a]	 **1d**, 51%
5[a]	 **1e**, 66%	6[a]	 **1f**, 38%
7[a]	 **2**, 50%	8[a,b]	 **3**, 58%
9[c]	 **4a**, 70%	10[d]	 **4b**, 76%
11[c]	 **4c**, 61%	12[d]	 **4d**, 48%
13[d]	 **4e**, 60%	14[d]	 **4f**, 36%
15[d]	 **4g**, 39%	16[c]	 **4h**, 75%
17[c]	 **4i**, 41%	18[e]	 **5a**, 91%
19[f]	 **5b**, 85%	20[e]	 **5c**, 57%
21[f]	 **5d**, 73%	22[f]	 **5e**, 59%
23[e]	 **5f**, 47%	24[e]	 **5g**, 38%

[a] $ArOC(O)NEt_2$ (0.18 mmol), $Pd(OAc)_2$ (5 mol%), 120 °C, 4 h. [b] From mesityl(2-(methoxycarbonyl)phenyl)iodonium triflate. [c] Anilide (0.18 mmol), $Pd(OAc)_2$ (5 mol%), 120 °C, 4 h. [d] 0.5 mmol scale, 18 h. [e] Anilide (0.5 mmol), $Cu(OTf)_2$ (10 mol%) 100 °C, 18 h. [f] 0.18 mmol scale, 4 h.

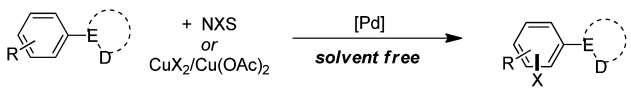
Such solvent-free *ortho*-C–H functionalisation reactions are very rare[6] and we were thus keen to widen the scope of this arylation reaction beyond aryl carbamates. Accordingly we found that anilide substrates were also well tolerated (entries 9–17). In these cases we again observed high mono-selectivity,§ in stark contrast to an equivalent reaction reported by Daugulis and Zaitsev who obtained a di-arylated product when using acetic acid as solvent.[7]

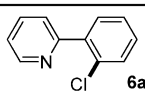
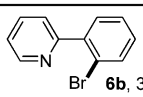
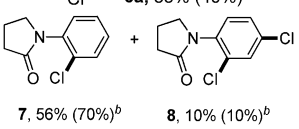
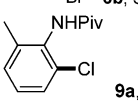
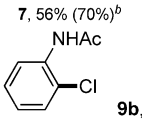
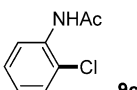
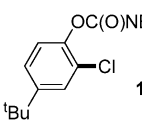
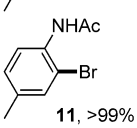
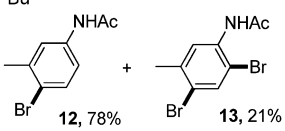
The solvent free approach is not limited to *ortho*-functionalisation. Recently Phipps and Gaunt reported an elegant, copper-catalysed *meta*-arylation of anilides using diaryliodonium salts in DCE.[8] Gratifyingly, we found that these unusual reactions were also amenable to solvent free conditions (Table 1, entries 18–24). Solvent-free C–H functionalisation is not limited to direct arylation reactions but can also be extended to halogenation (Table 2).

The solvent free *ortho*-chlorination and -bromination of 2-phenylpyridine and *N*-phenylpyrrolidin-2-one with *N*-halo-succinimides (entries 1–3) works comparably or better than similar reactions in acetic acid reported by Sanford and co-workers.[9] In the reaction of *N*-phenylpyrrolidin-2-one with *N*-chlorosuccinimide some competitive electrophilic *para*-chlorination is observed (entry 3). The solvent free *ortho*-chlorination of anilides using a mixture of copper acetate and copper chloride produced good to excellent yields of the desired products **9** in 2 h (entries 4–6), by contrast Shi and co-workers reported that equivalent reactions in DCE require heating for two days.[10] The *ortho*-chlorination reaction also worked well with an aryl carbamate substrate (entry 7).

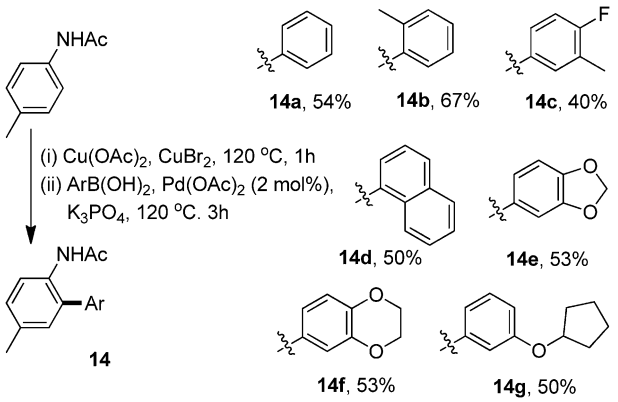
Solvent-free bromination proceeded with high yields (entries 8–10) and good scalability—the reaction can be readily performed with ~0.1 mol starting material—however the observed selectivity is somewhat different to that in the chlorination reactions. While *N*-(*p*-tolyl)acetamide yielded the *ortho*-brominated product **10** (entry 8), *N*-(*m*-tolyl)acetamide gave a mixture of *para*-bromo (major) and *ortho*,*para*-dibromo products **12** and **13** respectively (entry 9). When the reaction was repeated in the absence of palladium (entry 10) little *ortho*-bromination occurred. This implies that in the latter case, simple electrophilic bromination alone occurred, while in the former there was a competitive C–H functionalisation process operative. Such disparity in the mechanisms of halogenation with copper chloride or bromide salts has very recently been reported by Stahl and co-workers for reactions in solution.[11] It is interesting to note that in Shi and co-workers' original publication,[10] the only substrate with a free *para*-position employed in the bromination reactions was *N*-(*m*-tolyl) acetamide. When we reproduced this reaction under Shi's conditions (entry 11) we actually obtained the *para*-substituted product **12** in 80% yield, along with trace amounts of **13**, and not the *ortho*-bromo product claimed. The spectroscopic data for **12** are essentially identical to those claimed by Shi for the *ortho* product. We suggest that the products of their brominations, although not their chlorinations, are in fact derived from simple electrophilic substitution rather than

Table 2 Solvent free, palladium-catalysed direct halogenations



Entry	Product(s)	Entry	Product(s)
1[a]	 **6a**, 35% (40%)[b]	2[a]	 **6b**, 33% (50%)[b]
3[a]	 **7**, 56% (70%)[b] **8**, 10% (10%)[b]	4[c]	 **9a**, 98%
5[c]	 **9b**, 57%	6[c]	 **9c**, 93%
7[c]	 **10**, 60%	8[d]	 **11**, >99% (78%)[e]
9[d]	 **12**, 78% **13**, 21%	10[d,f]	**12**, 82% + **13**, trace
		11[g]	**12**, 80% + **13**, trace
		12[g,f,b]	**12**, 80% + **13**, trace

[a] Substrate (1 mmol), NCS or NBS (1.2 equiv.), $Pd(OAc)_2$ (5 mol%), 120 °C, 2 h. [b] Spectroscopic yield (NMR, 1,3,5-$MeOC_6H_3$ internal standard). [c] Substrate (1 mmol), $Cu(OAc)_2$ (2 equiv.), $CuCl_2$ (2 equiv.), $Pd(OAc)_2$ (5 mol%), 120 °C, 2 h. [d] Substrate (0.5 mmol), $Cu(OAc)_2$ (2 equiv.), $CuBr_2$ (2 equiv.), $Pd(OAc)_2$ (5 mol%), 120 °C, 1 h. [e] 0.089 mol anilide scale. [f] Pd-free. [g] Substrate (0.5 mmol), $Cu(OAc)_2$ (2 equiv.), $CuBr_2$ (2 equiv.), $Pd(OAc)_2$ (10 mol%), DCE (4 ml), 90 °C, 48 h.



Scheme 2 Sequential solid-state bromination/Suzuki coupling.

palladium-catalysed C–H functionalisation. Indeed, when the reaction is repeated in solution *in the absence of palladium* (entry 12) similar results are obtained.

In order to extend the utility of the solvent free methodology, we briefly examined sequential solid-phase bromination/Suzuki couplings of *N*-(*p*-tolyl)acetamide (Scheme 2). This two step methodology again proved very simple: the powder obtained from the solid-phase bromination was reground with the appropriate arylboronic acid, K_3PO_4 and palladium acetate and then heated. Such solid-phase Suzuki reactions are rare.[12]

In summary, we have developed a range of highly expedient solvent-free aromatic CH functionalisation reactions. In most cases these proceed with comparable or higher yields and better selectivity than the equivalent reactions in solution, which require acidic or toxic solvents. Most, but not all of the arylation reactions occur in the melt phase, while many of the halogenation reactions occur in the solid state, yielding the products as powders, and we are currently exploring these phase effects further as well as expanding the scope of the solvent free reactions.

We thank EPSRC and GSK for funding.

Notes and references

§ In all cases, no diarylated product was observed in crude product mixtures, only unreacted starting material.

1 For recent overviews, see: (*a*) Selective Functionalization of C–H Bonds (thematic issue), *Chem. Rev.*, 2010, **110**, 575–1211; (*b*) Catalytic Aromatic C–H Activation (Symposium in Print), *Tetrahedron*, 2008, **64**, 5963–6138; (*c*) *Handbook of C–H Transformations*, ed. G. Dyker, Wiley-VCH, Weinheim, 2005.
2 (*a*) X. Chen, K. M. Engle, D.-H. Wang and J.-Q. Yu, *Angew. Chem., Int. Ed.*, 2009, **48**, 5094; (*b*) D. Alberico, M. E. Scott and M. Lautens, *Chem. Rev.*, 2007, **107**, 174; (*c*) I. V. Seregin and V. Gevorgyan, *Chem. Soc. Rev.*, 2007, **36**, 117; (*d*) K. Godula and D. Sames, *Science*, 2006, **312**, 67.
3 R. B. Bedford, R. L. Webster and C. J. Mitchell, *Org. Biomol. Chem.*, 2009, **7**, 4853.
4 For recent examples of C–H functionalisation reactions run 'on water' see: G. L. Turner, J. A. Morris and M. F. Greaney, *Angew. Chem., Int. Ed.*, 2007, **46**, 7996.
5 For a recent example of arylation of ureas in water see: T. Nishikata, A. R. Abela and B. H. Lipshutz, *Angew. Chem., Int. Ed.*, 2010, **49**, 781.
6 Selected examples of solvent free, catalytic C–H activation reactions: (*a*) C. M. Rao Volla and P. Vogel, *Org. Lett.*, 2009, **11**, 1701; (*b*) V. G. Zaitsev, D. Shabashov and O. Daugulis, *J. Am. Chem. Soc.*, 2005, **127**, 13154; (*c*) Z. Shi and C. He, *J. Org. Chem.*, 2004, **69**, 3669.
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