Palladium-catalysed *ortho*-arylation of carbamate-protected phenols†

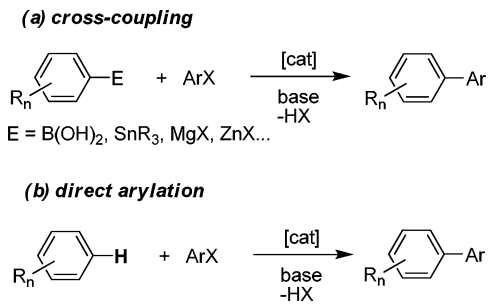
Robin B. Bedford,*[a] Ruth L. Webster[a] and Charlotte J. Mitchell[b]

Received 10th July 2009, Accepted 17th August 2009
First published as an Advance Article on the web 30th September 2009
DOI: 10.1039/b916724m

The carbamate ($-O_2CNR_2$) function is an excellent directing group for palladium-catalysed direct arylation reactions giving both protected or free mono- or di-substituted phenols, as well as an example of a dibenzopyranone, depending on coupling partners (aryl iodides or diaryliodonium salts) and conditions.

Introduction

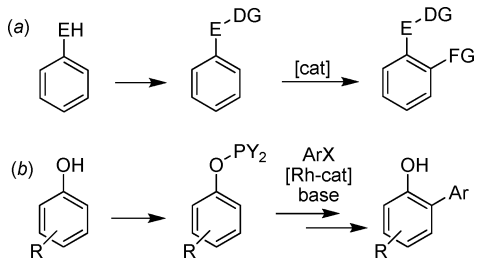
The construction of a biaryl subunit is a key transformation in the synthesis of many important compounds including natural products, polymers, liquid crystals and ligands for homogenous catalysis. Cross-coupling reactions (Scheme 1(a)), particularly the Suzuki reaction (E = $B(OH)_2$, $B(OR)_2$), are routinely employed in biaryl synthesis,[1] but recently much attention has focused on direct arylation reactions where aromatic C–H activation circumvents the synthesis and use of an organometallic nucleophilic coupling partner (Scheme 1(b)).[2,3]



Scheme 1 Biaryl bond-formation by catalytic (a) cross-coupling or (b) direct arylation.

One method frequently employed in intermolecular arylation is to modify the substrate with a 'directing group' that not only protects what may otherwise be a reactive centre, but also facilitates and selectively directs C–H activation (Scheme 2(a)). A recent elegant example of this is the use of ureas as surrogates for anilines in *ortho*-functionalisation reactions under very mild conditions employing palladium catalysis.[4] In a similar manner anilides have been used extensively in place of anilines.[5]

We have an ongoing interest in the *ortho*-arylation of phenols and have described a variety of rhodium-catalysed reactions wherein the directing group is a phosphinite or phosphoramidite ligand: $(ArO)PY_2$, Y = R, NR_2 respectively (Scheme 2(b)).[6,7] An advantage here is that the $(ArO)PY_2$ function is formed *in situ* from a phosphinite, chlorophosphine or aminophosphine all of which can be used in catalytic quantities as a consequence of *in situ* transesterification of the resultant 2-arylphosphinite (or phosphoramidate) with the free phenol.



Scheme 2 (a) Directed intermolecular C–H activation and (b) the rhodium-catalysed *ortho*-arylation of phenols.

There are, however, significant drawbacks with the current methodology. Firstly the reactions require the use of rhodium which is considerably more expensive than palladium. Secondly, optimum product yield is obtained from substrates with a bulky substituent, typically a *tert*-butyl group, in the *ortho*′ position. Unsubstituted or 4-substituted phenols give lower rates and only ever yield the *ortho*, *ortho*′-diarylated products. Fortunately the *tert*-butyl group can be removed, which allows for the construction of unsymmetrical terphenyls,[6d] but its introduction and subsequent loss is far from atom or step economical. A final consideration is that the reactions need to be performed under an inert atmosphere.

In order to address all of these shortcomings we decided to examine the use of carbamates as protecting/directing groups in the unprecedented palladium-catalysed *ortho*-arylation of phenols. The choice of aryl carbamates was made as they are readily prepared, easy to convert back to free phenols, show interesting biological properties in their own right[8] and the 2-arylated products are useful precursors for dibenzopyranones *via* Snieckus–Fries rearrangements.[9]

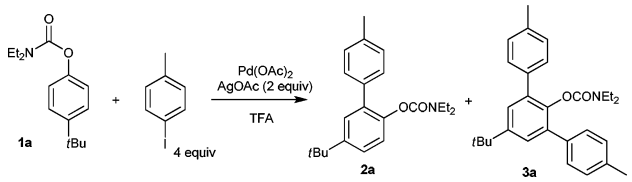
Results and discussion

Table 1 outlines selected results from the optimisation of the *ortho*-arylation of diethyl carbamate **1a** with 4-iodotoluene.†[10] As a starting point we used the catalyst and solvent system employed by Daugulis and co-workers for the *ortho*-arylation of anilides, although we found that less forcing reaction conditions and/or shorter reaction times were typically required.[11] In all cases reactions were performed under air using solvents as received; a significant operational advantage.

[a]*School of Chemistry, University of Bristol, Cantock's Close, Bristol, BS8 1TS, UK. E-mail: r.bedford@bristol.ac.uk*
[b]*GlaxoSmithKline, Stevenage, SG1 2NY, UK*

† Electronic supplementary information (ESI) available: Table of optimisation data, spectroscopic data, ^1H and ^{13}C NMR spectra. See DOI: 10.1039/b916724m

Table 1 Reaction optimisation (selected results).[a]



Entry	Mol% Pd	Temp./°C	Time/h	Spec. yield (%) [b] 2a	3a	Total
1	10	50	48	45	44	99
2	5			46	41	87
3[c]	10			46.5	14	60.5
4[d]				27.5	0	27.5
5		90	18	43.5	17	60.5
6		110		<5	0	<5
7[e]	5	100	2	39	45	84
8[e]			1	51	31	82
9[d,e]				22.5	0	22.5

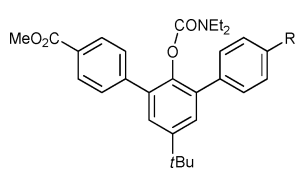
[a] Conditions: **1a** (0.241 mmol), 4-IC_6H_4Me (0.963 mmol), AgOAc (0.482 mmol) and TFA (1 ml). [b] Determined by ^{1}H NMR (1,3,5-$C_6H_3(OMe)_3$ internal standard). [c] 1 equiv. AgOAc. [d] 1 equiv. ArI. [e] Microwave heating.

At 50 °C within 48 h good to excellent conversions to *ortho*-arylated products were seen, but with no selectivity between the mono- and di-arylated compounds **2a** and **3a** respectively (entries 1 and 2). Lowering either the silver acetate or aryl iodide loadings gave significant improvements in selectivity for **2a** at the expense of overall yield (entries 3 and 4). Mono-selectivity could also be increased by raising the temperature and lowering the reaction time (entry 5) but at higher temperature catalyst decomposition occurred (entry 6). Gratifyingly, good activity was observed under microwave heating conditions within much shorter reaction times.

Using the microwave heating conditions, with a 1–2 h reaction time, we next examined the scope of the reaction and these results are summarised in Table 2.† Varying the carbamate function proved deleterious to the overall yield compared with diethylcarbamate, although both dimethyl and diisopropyl carbamates gave enhanced mono-arylation selectivity (entries 1 and 3). Both electron-withdrawing and donating groups were tolerated in the *para*-position of the aryl iodide (entries 5–9) including a bromide which opens the possibility of further catalytic functionalisation.

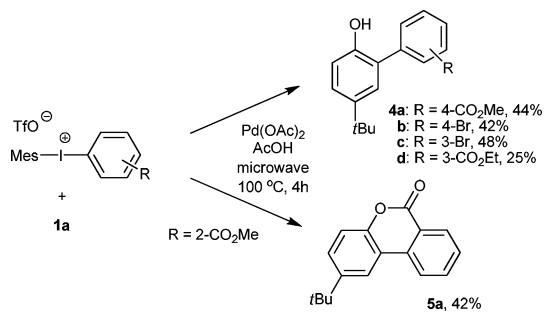
meta-Substitution was also well tolerated (entries 10–12) but poor activity was seen with *ortho*-substituted aryl iodides (entries 13 and 14). The introduction of *meta*-substitution on the phenoxide residue led to selective mono-arylation with no diarylated products observed (entries 15–20).

The isolated mono-arylated carbamates **2** could be used as substrates in further arylation reactions to generate symmetrical or unsymmetrical terphenyls; thus subjecting **2c** to the same conditions as those used in Table 2 for 2 h with 4-iodo methylbenzoate, 4-iodobromobenzene and 4-iodotoluene yielded the diarylated arylcarbamates **3c**, **l** and **m** respectively.



3c: R = CO_2Me, 44%
l: R = Br, 61%
m: R = OMe, 56%

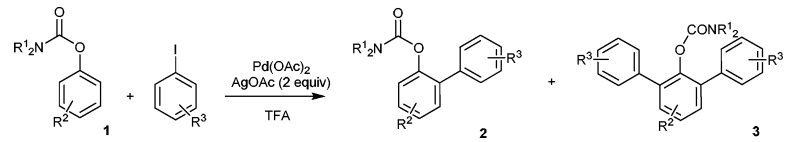
In order to improve mono-selectivity with unsubstituted or *para*-substituted phenols, we examined briefly the coupling of carbamates with diaryliodonium salts (Scheme 3).[12,13] We were pleased to find that in these cases, the reactions proceeded with complete mono-selectivity. Under these reaction conditions, loss of the carbamate occurred yielding the free phenols **4a–d**. By contrast, when the synthesis of **4a** was performed at 80 °C then ^{1}H NMR analysis of the crude product mixture indicated ~40% **4a** along with ~20% of the corresponding carbamate **2c** and ~18% of the diarylated carbamate **3c**. This, combined with the observation that free 4-*tert*-butylphenol does not react with diaryliodonium salts under the reaction conditions, suggests that the observed mono-selectivity at higher temperature results from the rate of deprotection of the products **4** being competitive with secondary arylation at elevated temperature.



Scheme 3 Conditions: **1a** (0.06 g, 0.241 mmol), diaryliodonium triflate (0.482 mmol), $Pd(OAc)_2$ (10 mol%), AcOH (1 ml).

Reaction of **1a** with a 2-methylbenzoate-containing iodonium salt yielded the dibenzopyranone **5a** *via* a novel tandem arylation–deprotection–lactonisation pathway. Dibenzopyranones are an important class of natural products that display a range of biological properties and consequently such a compact synthesis is desirable.

Table 2 *ortho*-Arylation of carbamates under microwave heating.[a]



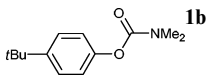
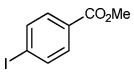
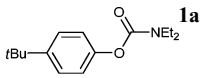
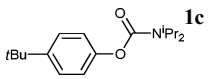
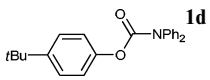
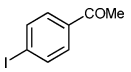
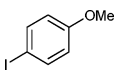
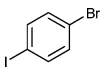
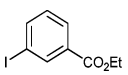
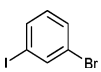
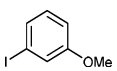
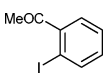
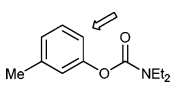
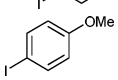
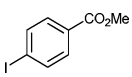
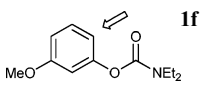
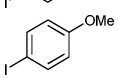
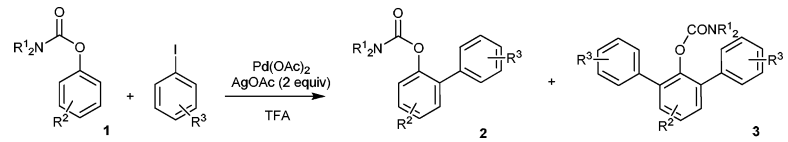
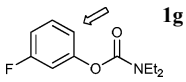
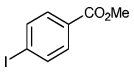
Entry	Carbamate[b]	Aryl iodide	Time/ h	Spec. Yield (%) [c](isolated)
1	 **1b**		2	**2b**, 37.5 (20)
				3b, 4 (3)
2	 **1a**			**2c**, 60 (59)
				3c, 24 (22)
3	 **1c**			**2d**, 22 (14)[d]
				3d, 0
4	 **1d**			0
5	**1a**			**2a**, 39 (30)
				3a, 45 (41)
6				**2e**, 43 (32)
				3e, 35 (34)
7				**2f**, 40 (37)
				3f, 42.5 (36)
8			1	**2g**, 27 (23)
				3g, 65 (64)
9			2	**2h**, 57.5 (53)
				3h, 22.5 (14)
10			1	**2i**, 53 (30)
			2	**3i**, 33
				2i, 30
				3i, 70 (70)
11			2	**2j**, 42 (40)
				3j, 8[f]
12				**2k**, 20 (16)[g]
				3k, 0
13				0[e]
14	 **1e**			**2l**, 89 (77)
15				**2m**, 33 (27)
16	 **1f**			**2n**, 74 (67)

Table 2 *(Contd.)*



Entry	Carbamate[b]	Aryl iodide	Time/ h	Spec. Yield (%) [c](isolated)
17				**2o**, 64 (62) **2p**, 33 (32)
18	 **1g**			
19				**2p**, 20 (17)

[a] Conditions: **1** (0.241 mmol), ArI (0.963 mmol), AgOAc (0.482 mmol), $Pd(OAc)_2$ (5 mol%) and TFA (1 ml), microwave heating, 100 °C. [b] Site of arylation indicated where ambiguous. [c] Spectroscopic yield determined by ^{1}H NMR (1,3,5-$C_6H_3(OMe)_3$ internal standard). [d] Isolated after 1 h reaction. [e] GC-MS reveals significant homocoupling of the aryl iodide. [f] Not isolated. [g] Not isolated pure.

Conclusions

In summary, we have developed two complementary palladium-catalysed *ortho*-arylation reactions of carbamate-protected phenols with either aryl iodides or diaryliodonium salts. The former gives both mono- and di-arylated products, whilst the latter method favours mono-arylation. These processes represent a significant improvement on the previously reported rhodium-catalysed reactions in that palladium is substantially cheaper, the reactions can be performed under air and small phenolic precursors without 2-substitution are well tolerated. The use of diaryliodonium salts as the arylating reagent leads to deprotection of the phenol which can in turn be exploited in the one-pot synthesis of a dibenzopyranone *via* a novel sequential arylation–deprotection–lactonisation process, an area that we are currently investigating further.

Experimental

General experimental conditions

Chemical reagents were used as supplied from commercial sources unless otherwise specified. Melting points were uncorrected. Microwave reactions were carried out with an Emrys Optimiser Microwave (0-20 bar pressure range, 15–300 W power range from a magnetron operating at 2.45 GHz). The reactions were carried out in a 5 mL sealed microwave vial equipped with magnetic stirrer, heating at a rate of 2 to 5 °C s^{-1}, then held for the stated time period. The temperature was monitored by an internal IR sensor.

General methodology for the preparation of 4-*tert*-butylphenyl-*N*,*N*-dialkyl carbamates & 4-*tert*-butylphenyl diphenylcarbamate

To a solution of 4-*tert*-butylphenol (3.00 g, 20 mmol) in MeCN (40 ml) was added K_2CO_3 (5.53 g, 40 mmol) followed by carbamoyl chloride (2.8 ml, 22 mmol). The reaction mixture was heated at 85 °C for 18 h. The reaction mixture was then diluted with water (30 ml) and washed with Et_2O (3 × 50 ml). The organic extracts were washed with NaOH solution (80 ml, 1 M) followed by water (80 ml), then brine (80 ml). The organic extracted were then dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was subjected to column chromatography to yield the carbamate.

General methodology for the preparation of *meta*-substituted phenyl-*N*,*N*-dialkyl carbamates

To a solution of the appropriate phenol (0.81 mmol) in MeCN (15 ml) was added K_2CO_3 (2.23 g, 16.11 mmol) followed by carbamoyl chloride (1.10 ml, 0.87 mmol). The reaction mixture was heated at 85 °C for 18 h. The reaction mixture was then diluted with water (20 ml) and washed with Et_2O (3 × 30 ml). The organic extracts were then washed with NaOH solution (50 ml, 1 M) followed by water (50 ml), then brine (50 ml). The organic extracted were then dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was subjected to column chromatography to yield the carbamate.

Optimisation for the palladium-catalysed *ortho*-arylation of 1a with 4-iodotoluene

To a Schlenk tube, sealed Young's tube or microwave vial was added the appropriate catalyst, ligand, additive, **1a** (0.060 g, 0.241 mmol), 4-iodotoluene (0.210 g, 0.963 mmol) and solvent (1 ml). The mixture was stirred at the appropriate temperature for the designated time period and then allowed to cool to room temperature. H_2O was added (5 ml) followed by $NaHCO_3$ (saturated solution, 10 ml) and the organic phase was extracted into dichloromethane (3 × 10 ml). The combined organic extracts were dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. 1,3,5-Trimethoxybenzene (0.040 g, 0.241 mmol) was added and the mixture dissolved in ~1 ml $CDCl_3$, an aliquot was removed and the spectroscopic yield was determined by ^{1}H NMR spectroscopy.

General methodology for the *ortho*-arylation of *N*,*N*-dialkyl carbamates & 4-*tert*-butylphenyl diphenylcarbamate using $Pd(OAc)_2$

To a microwave vial was added the appropriate carbamate (0.241 mmol), aryl iodide (0.963 mmol), silver acetate (0.080 g, 0.482 mmol), $Pd(OAc)_2$ (0.003 g, 0.012 mmol) and trifluoroacetic acid (1 ml), the vial was sealed and the vessel subjected to microwave heating at 100 °C for the appropriate time. H_2O was added (5 ml) followed by $NaHCO_3$ (saturated solution, 10 ml) and the

organic phase was extracted into dichloromethane (3 × 10 ml). The combined organic extracts were dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. The crude mixture was purified on silica gel to afford the product.

General methodology for the preparation of unsymmetrical diaryl phenyl carbamates 3c, 3k and 3l

To a microwave vial was added $Pd(OAc)_2$ (0.7 mg, 0.003 mmol) as a standard solution in TFA (0.25 M), **2c** (0.025 g, 0.065 mmol), aryl iodide (0.26 mmol) and trifluoroacetic acid (0.5 ml). The mixture was subjected to microwave heating for 2 h at 100 °C. H_2O was added (5 ml) followed by $NaHCO_3$ (saturated solution, 10 ml) and the organic phase was extracted into dichloromethane (3 × 10 ml). The combined organic extracts were dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. The crude mixture was purified on silica gel to afford the product.

General methodology for synthesis of mono-aryl substituted phenols, 4 and chromenone 5a

To a microwave vial was added **1a** (0.06 g, 0.241 mmol), hypervalent iodine reagent (0.482 mmol), $Pd(OAc)_2$ (5.4 mg, 0.024 mmol) and acetic acid (1 ml). The vial was sealed and the solution heated at 100 °C for 4 h. H_2O was added (15 ml) and the organic phase was extracted into dichloromethane (3 × 10 ml). The combined organic extracts were dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. The crude mixture was purified on silica gel to afford the product.

Acknowledgements

We thank EPSRC and GSK for funding and Johnson Matthey for the loan of palladium acetate.

Notes and references

1 (*a*) *Metal-Catalyzed Cross-Coupling Reactions*, ed. F. Diederich, and P. J. Stang, Wiley-VCH, Weinheim, Germany, 1998; (*b*) N. Miyaura, Ed., *Cross-Coupling Reactions (Topics in Current Chemistry)*, vol. 219, Springer, New York, 2002.
2 For a recent review see: D. Alberico, M. E. Scott and M. Lautens, *Chem. Rev.*, 2007, **107**, 174.
3 For recent overviews, see: (*a*) *Catalytic Aromatic C–H Activation (Symposium in Print) Tetrahedron*, vol. 64, 2008, pp. 5963–6138; (*b*) *Handbook of C–H Transformations*, ed. G. Dyker, Wiley-VCH, Weinheim, 2005.
4 C. E. Houlden, M. Hutchby, C. D. Bailey, J. G. Ford, S. N. G. Tyler, M. R. Gagné, G. C. Lloyd-Jones and K. I. Booker-Milburn, *Angew. Chem., Int. Ed.*, 2009, **48**, 1830.
5 For an overview see: O. Daugulis, H.-Q. Do and D. Shabashov, *Acc. Chem. Res.*, 2009, **42**, 1074.
6 (*a*) R. B. Bedford, S. J. Coles, M. B. Hursthouse and M. E. Limmert, *Angew. Chemie, Int. Ed.*, 2003, **42**, 11; (*b*) R. B. Bedford and M. E. Limmert, *J. Org. Chem.*, 2003, **68**, 8669; (*c*) R. B. Bedford, M. Betham, A. J. M. Caffyn, J. P. H. Charmant, L. C. Lewis-Alleyne, P. D. Long, D. Polo-Ceron and S. Prashar, *Chem. Commun.*, **2008**, 990; (*d*) R. B. Bedford, M. F. Haddow, R. L. Webster and C. J. Mitchell, *Org. Biomol. Chem.*, 2009, **7**, 3119.
7 S. Oi, S. Watanabe, S. Fukita and Y. Inoue, *Tetrahedron Lett.*, 2003, **44**, 8665.
8 For example physostigmine, neostigmine and rivastigmine are acetylcholine esterase inhibitors used variously in the treatment of myasthenia gravis, Alzheimer's and Parkinson's diseases, carbofuran and carbaryl are insecticides used in crop protection.
9 For a recent example and leading references see: C. A. James and V. Snieckus, *J. Org. Chem.*, 2009, **74**, 4080.
10 For full optimisation data see Table S1 in the ESI†.
11 O. Daugulis and V. G. Zaitsev, *Angew. Chem., Int. Ed.*, 2005, **44**, 4046.
12 For selected recent examples of the use of Ar_2I^+ in direct arylation reactions see: (*a*) R. J. Phipps and M. J. Gaunt, *Science*, 2009, **323**, 1593; (*b*) R. J. Phipps, N. P. Grimster and M. J. Gaunt, *J. Am. Chem. Soc.*, 2008, **130**, 8172; (*c*) N. R. Deprez, D. Kalyani, A. Krause and M. S. Sanford, *J. Am. Chem. Soc.*, 2006, **128**, 4972 and ref. 11 above.
13 For an overview of Pd-catalysed Ar_2I^+ coupling reactions, see: N. R. Deprez and M. S. Sanford, *Inorg. Chem.*, 2007, **46**, 1924.