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Palladium catalysed cross-coupling reactions of silylamines†‡

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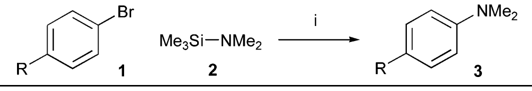
The palladium-catalysed formation of C–N bonds to produce a range of aryl amines in supercritical carbon dioxide is reported; carbamic acid formation is avoided in part by the use of *N*-silylamines as surrogates for the free amine.

Palladium-catalysed C–N bond forming reactions have attracted much interest recently owing to the key role played by these products in a number of fields *e.g.* pharmaceuticals, xerography, electronic materials. The pioneering work of Buchwald and Hartwig in this area has been confined to conventional organic solvents.[1,2] Supercritical carbon dioxide ($scCO_2$) has emerged as an environmentally benign alternative to volatile organic solvents.[3] Our studies[4–7] and subsequently those of others[8,9] have shown that a range of palladium catalysed processes (Heck, Suzuki, Sonogashira and Stille couplings) can be carried out as efficiently (or better) in $scCO_2$ as in conventional solvents using both homogeneous conditions and solid supported reagents and substrates. Extension to include C–N bond formation then became a natural objective.

Typically primary and secondary amines exist in equilibrium with their carbamic acid ammonium salts in $scCO_2$, dramatically affecting their solubility and reactivity.[10] *In situ* carbamic acid formation has been elegantly employed by Fürstner and Leitner to temporarily protect an N–H group during a ring closing metathesis reaction in carbon dioxide.[11] Bulky substituents can inhibit carbamic acid formation[12] although concomitant reduction in reactivity of the amine can be expected. Therefore, if a palladium-catalysed aromatic amination reaction is to be accomplished effectively it is necessary to develop methodology which avoids the use of a free NH functionality. Transmetallation of amine groups from tin to palladium is known.[13] However, the toxicity of organotin compounds makes this route unfavourable. In this Communication we report the results of preliminary investigations into the use of a silylamine as a surrogate for the free amine.

Initial studies looked at the coupling of trimethylsilyldimethylamine **2** with aryl bromides in toluene (Table 1). Employing 5 mol% $Pd(OAc)_2$, 10 mol% $P(t\text{-}Bu)_2$(biphen) and 1.4 equivalents of Cs_2CO_3, aromatic amination of electron poor aryl halides was observed in reasonable yield (Table 1, entries 1–3). Stronger bases were not used to avoid potential reaction with CO_2. The results for electron rich (Table 1, entry 5) and electronically neutral (Table 1, entry 4) aryl halides were less satisfactory and reaction times of 64 h were required before good conversion was observed. No success was realised on transferring these processes to $scCO_2$.

Table 1 Aromatic amination with trimethylsilyldimethylamine in toluene[a]

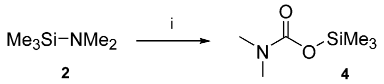


Entry	R	Time[a]	Yield (%)
1	COOMe	64	78
2	COMe	64	73
3	NO_2	64	58
4	H	40	27
5	OMe	64	0

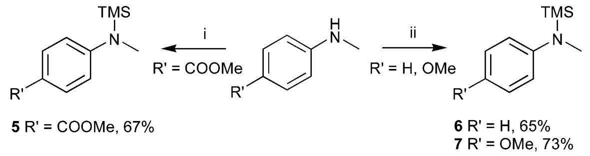
[a] *Reagents and conditions*: (i) 5 mol% $Pd(OAc)_2$, 10 mol% $P(t\text{-}Bu)_2$(*o*-biphen), 1.4 equiv. Cs_2CO_3, toluene, 60 °C.

On subjecting trimethylsilyldimethylamine **2** alone to $scCO_2$ under the reaction conditions, complete conversion to the silylcarbamate **4** was observed (Scheme 1). This result led us to believe that in addition to employing a surrogate for the free amine we must also consider the availability of the lone pair electrons on the nitrogen to react with the carbon dioxide. Aromatic amines are much less basic and less nucleophilic than their aliphatic analogues (pK_a $C_6H_5NH_3^+$ 4.70 *cf.* $MeNH_3^+$ 10.65)[14] owing to the delocalisation of the nitrogen lone pair into the π-system of the aromatic ring. We therefore investigated the arylation of aromatic silylamines. Aromatic silylamines **5–7** were synthesised from the free amine and chlorotrimethylsilane, and purified by vacuum distillation (Scheme 2). Once purified, the silylamines were handled under nitrogen at all times and stored at −20 °C for periods of up to three months without noticeable degradation.

Initial studies focused on the palladium-catalysed cross coupling of silylamines **5–7** with the activated aryl bromide methyl 4-bromobenzoate **8**. Treatment of the aromatic silylamines under the reaction conditions described (Table 2) afforded a range of coupled products (Table 2). Although arylation took place at 60 °C, conversion was incomplete in all cases but could be improved by reaction at 100 °C. At a $scCO_2$ pressure of 3000 psi, the reaction between the activated aryl bromide **8** and the electron poor silylamine **5** (R′ = COOMe) gave the diaryl amine product **9** in excellent yield (84%).§ This is, to the best of our knowledge, the first example of an aromatic amination to be observed in $scCO_2$. Electron rich (**11**, R′ = OMe) and neutral (**10**, R = H) silylamines gave disappointingly low yields of 40% or less (Table 2, entries 2 and 3) with a decrease in yield being observed after extended reaction time at a $scCO_2$ pressure of 3000 psi. The solvent properties of $scCO_2$ are known to vary greatly with temperature and pressure. By lowering the reaction pressure to 1800 psi and extending the reaction times to 48 h, yields of 77 and 76% respectively (Table 2, entries 5 and 6) were obtained. Repeating the reaction in the absence of palladium catalyst resulted in no product (1H NMR analysis of the reaction mixture), verifying the need for involvement of palladium in the catalytic process.



Scheme 1 *Reagents and conditions*: (i) $scCO_2$, 60 °C, 1800 psi.



Scheme 2 *Reagents and conditions*: (i) a. *n*-BuLi, THF, −78 °C, 2 h, b. TMSCl, rt, 17 h; (ii) TMSCl, NEt_3, CH_2Cl_2, 17 h.

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† We would like to dedicate this paper to the memory of Professor Ian Rothwell.

‡ Electronic supplementary information (ESI) available: experimental procedures and spectroscopic data for compounds **3–7**, **9–11** and **14–17**. See http://www.rsc.org/suppdata/cc/b4/b406868h/.

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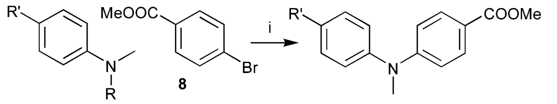
Table 2 Aromatic amination in $scCO_2$[a]



5 R' = COOMe, R = TMS
6 R' = H, R = TMS
7 R' = OMe, R = TMS

9 R' = COOMe
10 R' = H
11 R' = OMe

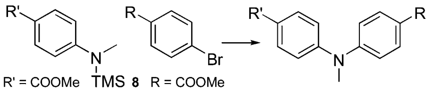
Entry	R	R′	Pressure/psi	Time	Yield (%)
1	**TMS**	**COOMe**	**3000**	**17**	**84**
2	TMS	OMe	3000	17	40
3	TMS	H	3000	17	28
4	TMS	COOMe	1800	17	69
5	**TMS**	**OMe**	**1800**	**48**	**77**
6	**TMS**	**H**	**1800**	**48**	**76**
7	H	COOMe	1800	17	35
8	H	H	1800	48	34
9	H	OMe	1800	48	55

[a] Reagents and conditions: (i) 2.5 mol% $Pd(OAc)_2$, 5 mol% $P(t\text{-}Bu)_2$(*o*-biphen), 1.4 equiv. Cs_2CO_3, $scCO_2$, 100 °C.

In order to verify the necessity to use a silylamine as a surrogate for the free amine, control reactions were carried out with the free amine (Table 2, entries 7–9). In all cases incomplete conversion was observed and yields of the amination product were considerably lower. From these results we can conclude that in order to understand the efficacy of the palladium-catalysed amination processes in $scCO_2$ we must consider both the nucleophilicity of the free amine and the role of the silylamine as a surrogate for the protio-analogue.

Table 3 shows the results of extending this methodology to a range of aryl bromides (**8**, **12** and **13**). Good to excellent results for the coupling of electron-deficient, -neutral and -rich silylanilines **5–7** with electron-deficient **8** and electron-neutral **12** aryl bromides were obtained (Table 3). The electron-rich aryl bromide **13** showed average yield when coupling with an electron-deficient silylaniline **5**, but the results for coupling to electron-neutral **6** and electron-rich silylaniline **7** were less satisfactory (Table 3).

Table 3 Palladium-catalysed aromatic amination in $scCO_2$[a]



5 R' = COOMe
6 R' = H
7 R' = OMe

8 R = COOMe
12 R = H
13 R = OMe

9 R' = COOMe, R = COOMe
10 R' = COOMe, R = H
11 R' = COOMe, R = OMe
14 R' = H, R = H
15 R' = H, R = OMe
16 R' = OMe, R = H
17 R' = OMe, R = OMe

Silylamines	Aryl bromides		
	8, R = COOMe	**12**, R = H	**13**, R = OMe
5, R′ = COOMe	84[b]	77[c]	57[c]
6, R′ = H	76	55	25
7, R′ = OMe	77	66	25

[a] *Reagents and conditions*: 2.5 mol% $Pd(OAc)_2$, 5 mol% $P(t\text{-}Bu)_2$(*o*-biphen), 1.4 equiv. Cs_2CO_3, $scCO_2$, 100 °C, *ca.* 1800 psi, 48 h unless otherwise indicated. [b] 3000 psi for 17 h. [c] 1800 psi for 17 h.

A proposed catalytic cycle for the process is shown in Fig. 1. Oxidative addition of the aryl bromide **19** is followed by transmetallation of the amino functionality from silicon to palladium to give the palladium(II) species **23**. Subsequent reductive elimination furnishes the coupled product **24** and regenerates the Pd(0) catalyst **18**. It is interesting to note that transmetallation is observed without the need for a fluoride source which is often required for the transfer of carbon functionality from silicon to palladium.[15] We believe this can be explained by the enhanced nucleophilicity of nitrogen compared with carbon. Further experiments are in hand to clarify the proposed mechanism.

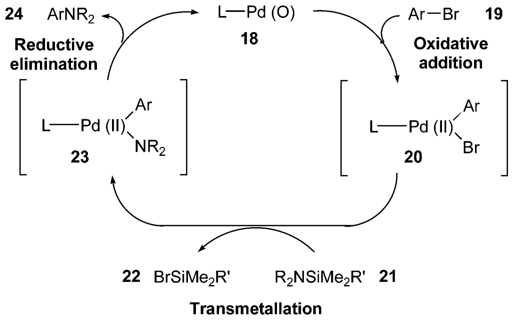


Fig. 1 Proposed catalytic cycle.

In summary, novel methodology for the synthesis of a wide variety of aromatic amines in supercritical carbon dioxide has been developed. Work is underway to extend the scope of this methodology to include non-aromatic amines and alternative aryl halides. We thank the EPSRC for financial support and provision of the National Mass Spectrometry Service, Swansea. We thank AstraZeneca (Dr Ian McConvey), The Isaac Newton Trust, Cambridge and the Cambridge-MIT Institute (CMI) for generous financial support. We thank Ms M. W. S. Tsang and Professors R. L. Danheiser and J. W. Tester for collaboration and helpful discussion under the CMI collaboration.

Notes and references

§ General procedure for catalytic amination of aryl bromides with silylamines in $scCO_2$. Flame dried cesium carbonate (228 mg, 0.7 mmol, 1.4 equiv.), aryl bromide (0.5 mmol), palladium acetate (2.8 mg, 0.012 mmol, 2.5 mol%) and di-*tert*-butyl biphenylphosphine (7.5 mg, 0.025 mmol, 5 mol%) were placed in a 10 cm^3 stainless steel cell and the cell sealed. The cell was evacuated and refilled with nitrogen (three cycles). The silylamine (1.2 equiv.) was injected through the inlet port and the cell connected to the CO_2 line and charged with CO_2 (99.9995%—further purified over an Oxisorb® catalyst) to approximately 760 psi (volume *ca.* 1 cm^3 liquid carbon dioxide). The cell was heated to 100 °C and the pressure adjusted to *ca.* 1800 psi by the addition of further CO_2. The reagents were maintained at this temperature and pressure for 17 h before the cell was allowed to cool to room temperature. The contents of the cell were vented into ethyl acetate (50 cm^3), and once atmospheric pressure had been reached, the cell was opened and washed with further aliquots of ethyl acetate (3×10 cm^3). The combined organic fractions were filtered and concentrated *in vacuo* to furnish the crude material which was purified by flash column chromatography over silica.

1 A. R. Muci and S. L. Buchwald, in *Topics in Current Chemistry: Cross-Coupling Reactions*, Springer-Verlag, Berlin, 2002, **vol. 219**.
2 J. F. Hartwig, *Angew. Chem. Int. Ed. Engl.*, 1998, **37**, 2046.
3 P. G. Jessop and W. Leitner, *Chemical Synthesis Using Supercritical Fluids*, Wiley-VCH, Weinheim, 1999.
4 S. V. Ley, C. Ramarao, R. S. Gordon, A. B. Holmes, A. J. Morrison, I. F. McConvey, I. M. Shirley, S. C. Smith and M. D. Smith, *Chem. Commun.*, 2002, 1134.
5 R. S. Gordon and A. B. Holmes, *Chem. Commun.*, 2002, 640.
6 T. R. Early, R. S. Gordon, M. A. Carroll, A. B. Holmes, R. E. Shute and I. F. McConvey, *Chem. Commun.*, 2001, 1966.
7 M. A. Carroll and A. B. Holmes, *Chem. Commun.*, 1998, 1395.
8 N. Shezad, R. S. Oakes, A. A. Clifford and C. M. Rayner, *Tetrahedron Lett.*, 1999, **40**, 2221.
9 D. K. Morita, D. R. Pesiri, S. A. David, W. H. Glaze and W. Tumas, *Chem. Commun.*, 1998, 1397.
10 P. G. Jessop, Y. Hsiao, T. Ikariya and R. Noyori, *J. Am. Chem. Soc.*, 1996, **118**, 344.
11 A. Fürstner, L. Ackermann, K. Beck, H. Hori, D. Kock, K. Langermann, M. Liebl, C. Six and W. Leitner, *J. Am. Chem. Soc.*, 2001, **123**, 9000.
12 H. Fischer, O. Gyllenhaal, J. Vessman and K. Albert, *Anal. Chem.*, 2003, **75**, 622.
13 M. Kosugi, M. Kameyama and T. Migita, *Chem. Lett.*, 1983, 927.
14 *The Merck Index*, Merck and Co., Inc., Whitehouse Station, NJ, 13th edn., 2001.
15 Y. Hatanaka and T. Hiyama, *Synlett*, 1991, 845.