Development of a practical Buchwald–Hartwig amine arylation protocol using a conveniently prepared (NHC)Pd(R-allyl)Cl catalyst†

Mark J. Cawley,[a] F. Geoffrey N. Cloke,[b] Richard J. Fitzmaurice,[a] Stuart E. Pearson,[c] James S. Scott[c] and Stephen Caddick*[a]

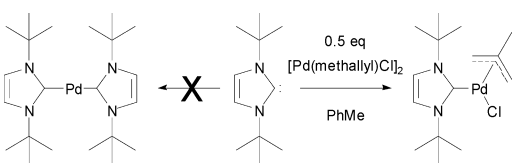
Received 28th January 2008, Accepted 22nd April 2008
First published as an Advance Article on the web 6th June 2008
DOI: 10.1039/b801479e

Continuing efforts to establish a more general "user-friendly" protocol for the palladium-catalysed arylation of amines (Buchwald–Hartwig reaction) are described herein. Significant advances have been made through the use of the versatile (SIPr)Pd(methallyl)Cl complex in conjunction with the reliable base lithium hexamethyldisilazide (LHMDS).

Introduction

In recent years, substantial research has been carried out on N-heterocyclic carbene (NHC) ligands, and the successful replacement of phosphines by NHC ligands has had some notable success in the development of catalysts for palladium chemistry.[1,2] The Buchwald–Hartwig reaction is of considerable importance in modern synthetic chemistry due to the regular occurrence of the aniline moiety in a number of biologically active molecules and dyestuffs.[2,3] Whilst a plethora of Pd-NHC protocols have been developed for this reaction, many are conducted using an inert atmosphere and are often carried out using a glovebox, significantly limiting the broader application of these techniques. Furthermore, many of the studies published have emphasised the range of halides, as opposed to diversity of amines, that undergo the coupling reaction. For these reasons, continuing efforts are being made within our group towards the development of an idealised practical protocol which is efficient at room temperature and can be applied generically across a wide range of amines and halides. We now present a new study on amine arylation using a new isolated Pd-NHC complex, which provides an improvement on our previous reported protocols.[4,5]

Complexes of the type (NHC)Pd(R-allyl)Cl were first reported by Caddick and Cloke in 2000 when (I*t*-Bu)Pd(methallyl)Cl was prepared while attempting the synthesis of the corresponding biscarbene complex Pd(I*t*-Bu)$_2$ (Scheme 1).[6] (NHC)Pd(R-allyl)Cl complexes have since been elegantly shown to be very active in amine arylation, Suzuki coupling and ketone arylation.[7–10] Their activity appears to stem from the fact that they offer more facile access to the mono-ligated species than previously reported protocols using imidazolium salts.[11]



Scheme 1 First example of an (NHC)Pd(R-allyl)Cl complex.

As (NHC)Pd(R-allyl)Cl catalysts are isolated complexes, there is good control over the Pd:ligand ratio (optimally 1:1).[11,12] Additionally, these complexes can be made without a glovebox or even the need for dry solvents.[13,14] Work by Sigman has even shown that complexes of this type are stable enough to be purified *via* flash column chromatography on silica gel and that once prepared are indefinitely air- and moisture-stable.[13]

Nolan and co-workers have recently demonstrated that terminal substitution of the allyl scaffold in (NHC)Pd(allyl)Cl complexes results in more facile activation of the complex to afford the active species.[11] This substitution stabilises the complex by increasing the steric bulk about the Pd centre and by reducing the Pd–allyl electron back-bonding. It is postulated that this results in a lengthening of the Pd–C bond, hence making decomplexation of the allyl ligand more facile. Having shown improvements using crotyl and prenyl scaffolds, Nolan settled upon (NHC)Pd(cinnamyl)Cl complexes as those affording the highest activity in Buchwald–Hartwig and Suzuki couplings.[11]

Despite the remarkable developments associated with the (NHC)Pd(R-allyl)Cl class of catalyst, there are still opportunities for further developments. One of the key issues for any amine arylation protocol of this type is to develop a method which will be applicable to a wide range of the approximately 80 000 commercially available compounds containing an N–H moiety, and this has provided an impetus for further studies.[15] In this paper we present the results of our own study on the application of a new variant of (NHC)Pd(R-allyl)Cl catalysts and their application to aryl amination.

Results and discussion

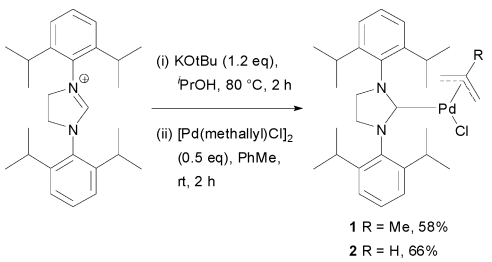
Catalyst preparation

Although (I*t*-Bu)Pd(methallyl)Cl had been prepared in an earlier study, subsequent research has shown that the preferred NHC ligand for amine arylation in most cases is SIPr (*N*,*N*′-bis(2,6-diisopropylphenyl)-4,5-dihydroimidazol-2-ylidene).[4,6] Therefore, (SIPr)Pd(methallyl)Cl **1** was selected for examination, as prior

[a]*Department of Chemistry, University College London, London, WC1H 0AJ, UK. E-mail: s.caddick@ucl.ac.uk*
[b]*Department of Chemistry and Biochemistry, University of Sussex, Brighton, BN1 9QJ, UK*
[c]*AstraZeneca, Alderley Park, Mereside, Cheshire, SK10 4TG, UK*
† Electronic supplementary information (ESI) available: Additional experimental information. See DOI: 10.1039/b801479e

studies had not specifically evaluated the effect of non-terminal allyl substitution. (SIPr)Pd(allyl)Cl **2** was also prepared for the purposes of comparison.[9,14]

These procedures consisted of *in situ* formation of the NHC through deprotonation of SIPr·HCl using KO*t*-Bu at 80 °C. This was followed by addition of the relevant $[Pd(R\text{-allyl})Cl]_2$ complex and stirring at room temperature to afford the catalyst (Scheme 2). In the case of **2** it was possible to follow the literature procedure closely, as this gave a pure sample of the complex (as confirmed by elemental and spectroscopic analysis) in a yield of 66% (*cf.* literature yield of 82%).[14] However, in the case of catalyst **1** it was only possible to obtain a pure sample of the complex *via* column chromatography on silica gel (58% yield).[13] This illustrates the potential practicality of (NHC)Pd(R-allyl)Cl complexes, which are not only highly active (*vide infra*), but are also tolerant of routine manipulations generally carried out in organic chemistry laboratories.



Scheme 2 Preparation of (SIPr)Pd(R-allyl)Cl complexes.

Optimisation of Buchwald–Hartwig amine arylation

With the above complexes prepared, an investigation into the Buchwald–Hartwig reaction was undertaken. Optimisation was undertaken using the pre-catalyst **1** with the aim of achieving yields and reaction times comparable to or better than those afforded by other protocols.[11] Two simple substrates, 2-bromotoluene and morpholine, were chosen for this study. Firstly, it was found that when used as purchased, KO*t*-Bu was ineffective as a base in DME with both **1** and **2** (Table 1, entries 1–2), but that a low yield of the aniline could be obtained in THF with **1** (Table 1, entry 3). This result could not be improved upon through the use of a commercial 1 M solution of KO*t*-Bu in THF (Table 1, entry 4). As with our previous imidazolium salt protocol, LHMDS was shown to be fundamental to the success of amine arylation, with 1 mol% of **1** leading to complete conversion within thirty minutes (Table 1, entry 5). Further investigation revealed that the bulk of the amination occurred in the first ten minutes, and that when using 3 mol% of (SIPr)Pd(methallyl)Cl, the reaction was complete within one minute in excellent yield (Table 1, entry 8).[11]

Table 1 Buchwald–Hartwig reaction of 2-bromotoluene and morpholine using (SIPr)Pd(R-allyl)Cl catalysis[a]

Entry	Catalyst	Base	Solvent	Time	Yield (%)
1	1 mol% **1**	KO*t*-Bu	DME	24 h	—
2	1 mol% **2**	KO*t*-Bu	DME	24 h	—
3	1 mol% **1**	KO*t*-Bu	THF	6 h	<5
4[b]	1 mol% **1**	KO*t*-Bu	THF	6 h	<5
5	1 mol% **1**	LHMDS	THF	30 min	95
6	1 mol% **1**	LHMDS	THF	10 min	82
7	2 mol% **1**	LHMDS	THF	2 min	93
8	3 mol% **1**	LHMDS	THF	1 min	99
9	3 mol% **2**	LHMDS	THF	2 min	89

[a] *Reagents and conditions*: 4-bromotoluene (1.0 mmol), amine (1.2 mmol), base (1.1 mmol), and rt. [b] KO*t*-Bu administered as 1 M solution in THF.

It was clear that (SIPr)Pd(methallyl)Cl had more potential use as the catalyst in a general protocol than our previously described *in situ* imidazolium salt method.[5] It should also be noted that although reactions were not possible using (SIPr)Pd(allyl)Cl and the alkoxide base, this catalyst was shown to be more active with LHMDS as base (Table 1, entry 9).

Despite the high yield obtained using **1** and LHMDS, the role of the solvent was investigated further. As one of the key mechanistic steps in the catalytic cycle is thought to be deprotonation of the transmetalation complex,[12] investigation was undertaken into how solvents might affect this step and hence the reaction overall.

Accordingly, arylation of morpholine was performed in several different aprotic solvents of varying dielectric constant (Table 2). Only 1 mol% of **1** was employed to ensure that differences in reactivity would be more noticeable. 1,4-Dioxane was found to afford faster coupling than THF, albeit in a slightly reduced yield. The use of toluene gave an increase in reaction time and a reduction in yield compared to THF and 1,4-dioxane, but a moderate yield was obtained nonetheless. DME has been reported to be the preferred solvent for this reaction when used in conjunction with KO*t*-Bu.[11] However, it was found to not be suitable for this protocol, affording only a low yield which was also observed with diethyl ether. The reaction in DMF only afforded 17% of the aniline product; no coupling product was obtained in DMA. This appeared to show that highly polar solvents are not suitable in this reaction, which was in agreement with a previous study by Kiil.[16] The availability of commercial THF solutions of LHMDS also made this a convenient and practical choice for further studies.

Arylation of morpholine

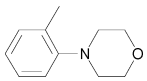
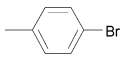
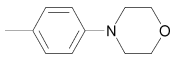
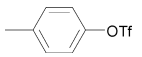
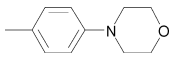
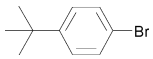
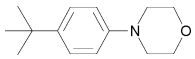
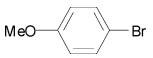
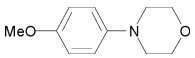
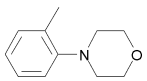
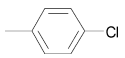
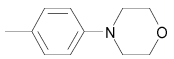
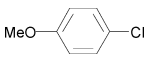
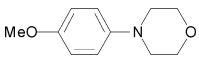
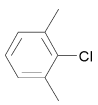
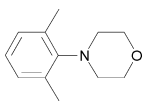
Morpholine is a highly reactive substrate in amine arylation due to its cyclic structure.[17] Thus, with optimisation complete, the arylation of morpholine was studied first. As with the previous study, the reaction of 4-bromotoluene and morpholine was shown to be a particularly facile reaction, with the reaction complete in near quantitative yield within a minute at room temperature (Table 3, entry 2). *p*-Tolyl triflate was found to react as quickly as 4-bromotoluene.[18] However, the yield with the aryl triflate was slightly lower at only 70% (Table 3, entry 3), meaning that further investigation and optimisation may be required.[19]

Table 2 Effect of solvent in the Buchwald–Hartwig reaction of 4-bromotoluene and morpholine using catalyst **1**[a]

Entry	Solvent	ε_r	Time/min	Yield (%)
1	1,4-Dioxane	2.21	10	89
2	Toluene	2.38	60	65
3	Et_2O	4.34	30	50
4	DME	7.20	45	38
5	THF	7.52	20	97
6	DMF	36.7	30	17
7	DMA	37.8	30	—

[a] *Reagents and conditions*: halide (1.0 mmol), morpholine (1.2 mmol), **1** (1 mol%), LHMDS (1.1 mmol), solvent (1.1 mL), rt.

Table 3 Buchwald–Hartwig reactions of aryl halides and morpholine using catalyst **1**[a]

Entry	Halide	Product	Time[b]/min	Yield[a] (%)
1			1	99
2			1	98
3			1	70
4			5	91
5			5	90
6			25	94
7			5	95
8			10	49
9			60 (10)	24 (52)

[a] *Reagents and conditions*: halide (1.0 mmol), amine (1.2 mmol), **1** (3 mol%), LHMDS (1.1 mmol, 1 M in THF), rt. [b] Values in parentheses refer to reactions performed at 70 °C.‡

The presence of *para*-electron-donating groups did not significantly hinder coupling with morpholine (Table 3, entries 4–5).[20] In fact, the exotherm that could be felt on the reaction vessel at the start of the reaction[11] was most obvious in the case of 4-*tert*-butylbromobenzene. The reaction of 2-chlorotoluene was also high yielding and rapid (Table 3, entry 6). This was an interesting result, as our previous imidazolium salt method required several days to successfully mediate the room temperature coupling of aryl chlorides and then only in moderate yields.[5] The reaction was even faster with the less hindered 4-chlorotoluene (Table 2, entry 7). However, the more electron-donating 4-chloroanisole afforded only 49% of the desired aniline (Table 2, entry 8).[20] The highly hindered 2,6-dimethylchlorobenzene yielded only 24% of the desired aniline. However, the yield was raised to 52% by performing the reaction at 70 °C rather than room temperature (Table 3, entry 9).‡

Scope of secondary alkyl amine

With investigations into the aryl halide component complete, further studies to examine the scope of amines were initiated (Table 4). Having tested a range of halides, the decision was then taken to keep the aryl halide component constant in several reactions and to evaluate the effect of amine variation. 4-Bromotoluene was selected for this role due to it being unhindered and relatively electronically neutral.

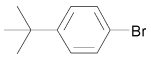
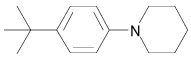
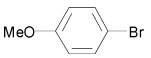
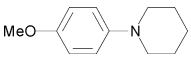
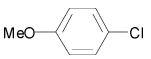
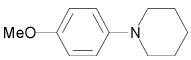
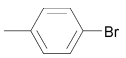
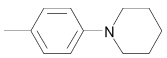
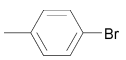
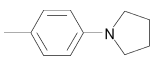
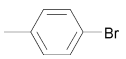
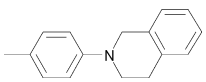
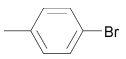
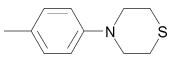
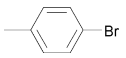
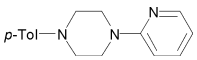
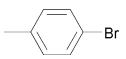
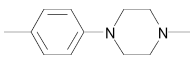
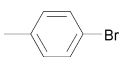
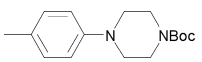
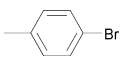
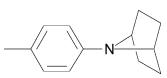
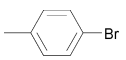
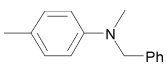
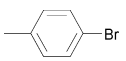
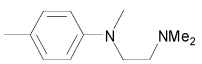
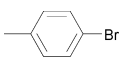
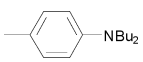
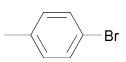
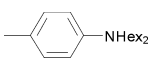
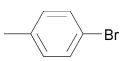
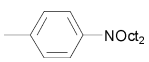
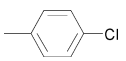
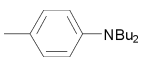
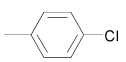
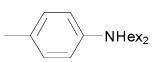
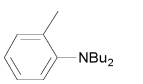
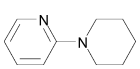
High yields were obtained with several secondary cyclic amines. Interestingly, thiamorpholine was shown to couple with a reduced yield of 60% (Table 4, entry 7; *cf.* morpholine (Table 3, entry 2)). This was nonetheless an important result, as it showed that the (SIPr)Pd(methallyl)Cl precatalyst would enable the reactions of sulfur-containing reagents, which have been reported to poison palladium catalysts.[20] Performing the coupling at 70 °C was found to enhance the reactions of less reactive substrates, particularly with secondary acyclic amines. It was also successfully demonstrated that heteroaryl halides would react under this protocol: 2-bromopyridine was coupled with piperidine in a high yield within 1 minute at room temperature, indicating that the lone pair of the nitrogen on the pyridyl ring was not detrimental to the reactivity of the Pd-NHC complex (Table 4, entry 20).§ Further investigations are now underway with additional heteroaryl halides.

Not all reactions of secondary alkyl amines were successful. The hindered *N*-methyl-*tert*-butylamine, *N*-(tetrahydropyran-4-yl)methylamine and *cis*-2,6-dimethylpiperidine all failed to react,

‡ In reactions quoted as being carried out at 70 °C, the hot plate for the oil bath was set at 70 °C with only the bottom of the Schlenk tube placed in the oil. In these reactions, no bubbling of the solvent was observed, suggesting either that its boiling point was slightly elevated by the solutes or rather that the actual temperature in the tube was no higher than 65 °C.

§ This reaction failed when repeated at room temperature without (SIPr)Pd(methallyl)Cl with stirring for 6 hours.

Table 4 Buchwald–Hartwig reactions of aryl halides with other secondary amines using **1**[a]

Entry	Halide	Product	Time[b]	Yield[b] (%)
1			20 min	82
2			20 min	93
3			15 min	43
4			5 min	85
5			5 min (2 min)	40[c] (84)
6			30 min	65
7			10 min	60
8			5 min	96
9			5 min	80
10			5 min	96
11			16 h (3 h)	—[c] (9)[c]
12			5 min	83
13			18 h (5 h)	38[c] (85)
14			18 h (60 min)	42[c] (86)
15			24 h (60 min)	— (98)
16			24 h (60 min)	— (82)
17			(30 min)	(10)
18			(30 min)	(25)
19			24 h (90 min)	— (21)
20			1 min	91

[a] *Reagents and conditions*: halide (1.0 mmol), amine (1.2 mmol), **1** (3 mol%), LHMDS (1.1 mmol, 1 M in THF), rt. [b] Values in parentheses refer to reactions performed at 70 °C.‡ [c] Reaction did not reach completion.

either at room temperature or at 70 °C. It may be that they were too sterically hindered for the N–H moiety to be able to access the palladium centre in the transmetalation step.[12]

Arylation of primary amines

With a range of secondary amines studied, evaluation of the reactivity of primary amines was undertaken. In the reaction of 4-bromotoluene with four equivalents of *n*-hexylamine, the halide was consumed within one hour in THF at 70 °C, affording 64% yield of the desired product. As in the previous study, heating was deemed to be necessary with primary amines. However, bisarylation was still observed, albeit in only 12% yield (Table 5, entry 1).

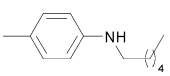
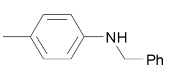
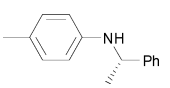
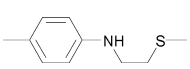
Under the same conditions, the reactions of 4-bromotoluene with benzylamine and (*R*)-(+)-1-phenylethylamine proceeded selectively, with no bisarylation being observed (Table 5, entries 2–3). The selectivity here might be attributable to the greater steric bulk of these amines.[11,21] However, greater steric bulk also proved problematic, since *tert*-butylamine and adamantylamine failed to react. In the case of *tert*-butylamine (bp 46 °C), arylation also failed to occur at 40 °C or at higher temperatures.

The sulfur-containing amine 2-(methylthio)ethylamine was found to undergo arylation, but only afforded 14% yield of the desired product (Table 5, entry 4). Nonetheless, this is promising, showing that it might be possible to develop an amine arylation protocol with these types of sulfur-containing substrates.

Catalyst loading

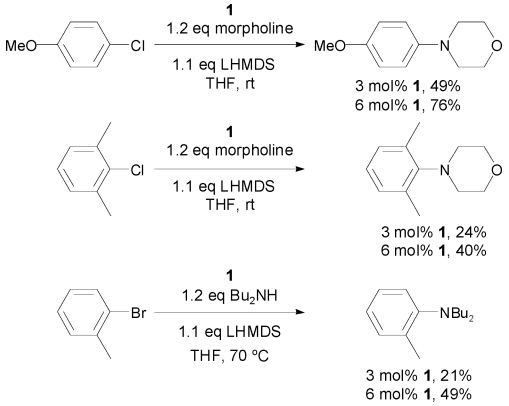
In the optimisation process, the benefits of higher catalytic loading were illustrated through higher yields and decreasing reaction times. Although 3 mol% (SIPr)Pd(methallyl)Cl has been shown to afford high yields with the more reactive substrates such as morpholine and *para*-substituted aryl bromides, when dealing with highly bulky substrates or deactivated aryl chlorides it was not sufficient to mediate very efficient coupling. It appears here that hydrodehalogenation may be the preferred reaction instead. In such cases, a remedy may be to use higher catalyst loading.[11,20,22]

Table 5 Buchwald–Hartwig reactions of 4-bromotoluene and primary amines using catalyst **1**[a]

Entry	Product	Time/min	Yield (%) Mono	Bis
1		60	64	12
2		30	45	—
3		30	70	—
4		60	14	—

[a] *Reagents and conditions*: 4-bromotoluene (1.0 mmol), amine (4.0 mmol), **1** (3 mol%), LHMDS (1.1 mmol, 1 M in THF), 70 °C.‡

Higher catalyst loading was shown to promote the room temperature couplings of the deactivated 4-chloroanisole and the highly bulky 2,6-dimethylchlorobenzene with morpholine (Scheme 3). This also enhanced the yield when mediating the reaction of 2-bromotoluene and di-*n*-butylamine.



Scheme 3 Yield enhancement of through increased catalyst loading.

Conclusions

Although a general protocol has not yet been developed, the present study has provided significant advances in the Buchwald–Hartwig reaction. With suitable catalyst loading and/or heating, (SIPr)Pd(methallyl)Cl and LHMDS effects the coupling of a wide range of aryl halides with primary and secondary alkyl amines; however, difficulties may be encountered when using bulky substrates.

Studies will now concentrate on attempts at extending the scope of amines that will undergo arylation in the presence of (SIPr)Pd(methallyl)Cl.

Experimental

(SIPr)Pd(methallyl)Cl 1

A two-necked flask with a magnetic stirrer was charged with SIPr·HCl (1.9 g, 4.2 mmol) and potassium *tert*-butoxide (0.4 g, 3.6 mmol). A septum was placed on one neck and the remaining neck was attached to a nitrogen line, after which the flask was cycled with nitrogen and vacuum three times. Under a positive flow of nitrogen, technical grade isopropanol (35 mL) was added *via* syringe through the septum and the mixture was stirred for 2 h at 80 °C. After cooling to room temperature over 45 min, the septum was removed, $[Pd(methallyl)Cl]_2$ (0.55 g, 1.5 mmol) was added quickly and the septum was replaced. The mixture was stirred for 2 h at room temperature, over which time its colour gradually turned grey. It was opened to the air and stirred for 15 min. Water (100 mL) was added and a solid precipitated. The water was removed by filtration and the solid was taken up in chloroform (100 mL). This solution was filtered through phase-separating filter paper to remove the water and was concentrated *in vacuo* to give a yellow oil. This crude residue was purified *via* flash column chromatography (silica gel) using an eluent of diethyl ether–petroleum spirit (3 : 2) to afford the title compound as an off-white crystalline solid (1.02 g, 2.17 mmol, 72%, decomposes at 155 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.12 (s, 3H, CH_2CMeCH_2), 1.22 (d, $J = 6.9$ Hz, 6H, $CHMe_2$), 1.29 (d, $J = 6.9$ Hz, 6H, $CHMe_2$), 1.34 (d, $J = 6.9$ Hz, 6H, $CHMe_2$), 1.50 (d, $J = 6.7$ Hz, 6H, $CHMe_2$), 1.56 (s, 1H, CH_2CMeCH_2), 1.75 (s, 1H, CH_2CMeCH_2), 2.68 (d, $J =$ 3.6 Hz, 1H, CH_2CMeCH_2), 3.33–3.57 (m, 4H, $CHMe_2$), 3.69 (d, $J = 3.1$ Hz, 1H, CH_2CMeCH_2), 3.97–4.08 (m, 4H, NCH_2), 7.25–7.19 (m, 4H, Ar), 7.34 (t, $J = 7.7$ Hz, 2H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.4, 23.7, 23.8, 26.6, 26.7, 28.4, 28.6, 49.5, 53.8, 72.2, 124.3, 124.4, 129.0, 129.7, 136.6, 147.1, 147.3. C.I. MS (relative intensity): 550 (10), 496 (50), 389 (10), 347 (10), 188 (15), 146 (13), 91 (31). HRMS C.I. [M$^+$], Calcd.: 587.23841. Actual: 587.23643. Anal. Calcd.: C 63.37, H 7.72, N 4.77. Actual: C 63.41, H 7.80, N 4.65. IR (KBr, cm^{-1}) 2962, 2925, 2868, 1448, 1425, 1382, 1363, 1326, 1267, 1240, 1055, 837, 802, 758, 731, 700, 621.

General procedure for amine arylation

An oven-dried Schlenk tube was charged with an aryl halide (1.0 mmol), an amine (1.2 mmol, 1.2 eq.), (SIPr)Pd(methallyl)Cl (18 mg, 0.03 mmol, 3.0 mol%) and a magnetic stirrer bar, and sealed with a septum. The flask was evacuated and backfilled with inert gas three times, after which LHMDS (1.1 mL of 1M solution in THF, 1.1 mmol, 1.1 eq.) was added *via* syringe. The mixture was stirred until the aryl halide had been consumed, as judged by TLC. It was diluted with ethyl acetate and filtered through a short plug of silica. The solvent was removed *in vacuo* and the crude material was purified *via* flash column chromatography on silica gel using an eluent of ethyl acetate–*n*-hexane.

***N*-(4-Methylphenyl)thiamorpholine (Table 4, entry 7).** The coupling of thiamorpholine and 4-bromotoluene was performed using the general procedure to afford 116 mg (60%) of the title compound within 10 min as a white solid (mp 40 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.29 (s, 3H, $ArCH_3$), 2.75–2.79 (m, 4H, SCH_2), 3.46–3.49 (m, 4H, NCH_2), 6.85 (d, $J = 8.8$ Hz, 2H, Ar), 7.08 (d, $J = 8.8$ Hz, 2H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.5, 27.2, 52.8, 117.7, 129.6, 129.8, 149.6. E.I. MS (relative intensity): 193 (M$^+$, 54), 119 (100). HRMS E.I. [M$^+$], Calcd.: 193.09197. Actual: 193.09170. IR (KBr, cm^{-1}): 2954, 2908, 2873, 2827, 2754, 1616, 1573, 1514, 1450, 1415, 1336, 1290, 1224, 1193, 1168, 1136, 1029, 970, 893, 819, 530.

Acknowledgements

We wish to gratefully acknowledge the financial support of AstraZeneca and EPSRC in this programme of research. Sincere gratitude is also extended to James Mok for his assistance in this study. We also gratefully acknowledge BBSRC, Wellcome Trust, CEM UK and GSK for support of our programme. We acknowledge the provision of mass spectra from the EPSRC Mass Spectrometry Service at Swansea.

References

1 For recent reviews, see: (*a*) W. A. Herrmann, *Angew. Chem., Int. Ed.*, 2002, **41**, 1291–1309; D. Bourissou, O. Guerret, P. Gabbai and G. Bertrand, *Chem. Rev.*, 2000, **100**, 39; (*b*) A. J. Arduengo, *Acc. Chem. Res.*, 1999, **32**, 913; (*c*) R. Regitz, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 725 and references therein.
2 For a review of Pd-NHC catalysis, see: E. Assen, B. Kantchev, C. J. O'Brien and M. G. Organ, *Angew. Chem., Int. Ed.*, 2007, **46**, 2768–2813.
3 For a recent review, see: B. Schlummer and U. Scholz, *Adv. Synth. Catal.*, 2004, **346**, 1599–1626 and references therein.
4 A. J. McCarroll, D. A. Sandham, L. R. Titcomb, A. K. de K. Lewis, F. G. N. Cloke, B. P. Davies, A. P. de Santana, W. Hiller and S. Caddick, *Mol. Diversity*, 2003, **7**, 115–123.
5 I. Conesa-Lerma, M. J. Cawley, F. G. N. Cloke, K. Arentsen, J. S. Scott, S. E. Pearson, J. Hayler and S. Caddick, *J. Organomet. Chem.*, 2005, **690**, 5841–5848.
6 S. Caddick, F. G. N. Cloke, G. K. B. Clentsmith, P. B. Hitchcock, D. McKerrecher, L. R. Titcomb and M. R. V. Williams, *J. Organomet. Chem.*, 2001, **617**, 635–639.
7 M. S. Viciu, R. F. Germaneau, O. Navarro, E. D. Stevens and S. P. Nolan, *Organometallics*, 2002, **21**, 5470–5472.
8 M. S. Viciu, O. Navarro, R. F. Germaneau, R. A. Kelly III, W. Sommer, N. Marion, E. D. Stevens, L. Cavallo and S. P. Nolan, *Organometallics*, 2004, **23**, 1629–1635.
9 O. Navarro, H. Kaur, P. Mahjoor and S. P. Nolan, *J. Org. Chem.*, 2004, **69**, 3173–3180.
10 M. S. Viciu, R. F. Germaneau and S. P. Nolan, *Org. Lett.*, 2002, **4**, 4053–4056.
11 N. Marion, O. Navarro, J. Mei, E. D. Stevens, N. M. Scott and S. P. Nolan, *J. Am. Chem. Soc.*, 2006, **128**, 4101–4111.
12 A. C. Hillier, G. A. Grasa, M. S. Viciu, H. M. Lee, C. Yang and S. P. Nolan, *J. Organomet. Chem.*, 2002, **653**, 69–82.
13 D. R. Jensen and M. S. Sigman, *Org. Lett.*, 2003, **5**, 63–65.
14 O. Navarro and S. P. Nolan, *Synthesis*, 2006, 366–367.
15 According to Scifinder search.
16 H. Christensen, S. Kiil, K. Dam-Johansen, O. Nielsen and M. B. Sommer, *Org. Process Res. Dev.*, 2006, **10**, 762–769.
17 R. W. Bladock and A. R. Katritzky, *Tetrahedron Lett.*, 1968, **10**, 1159–62; J. J. Sloan and R. Kewley, *Can. J. Chem.*, 1969, **47**, 3453–62.
18 J. Louie, M. S. Driver, B. C. Hamann and J. F. Hartwig, *J. Org. Chem.*, 1997, **62**, 1268–1273.
19 J. F. Hartwig, *Angew. Chem., Int. Ed.*, 1998, **37**, 2046–2067.
20 R. W. Joyner and J. B. Pendry, *Catal. Lett.*, 1988, 1–6.
21 S. Urgaonkar, M. Nagarajan and J. G. Verkade, *J. Org. Chem.*, 2003, **68**, 452–459.
22 J.-F. Marcoux, S. Wagaw and S. L. Buchwald, *J. Org. Chem.*, 1997, **62**, 1568–1569.