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Steric effects in palladium-catalysed amination of aryl triflates and nonaflates with the primary amines PhCH(R)NH_2 (R=H, Me)

Rebecca E. Meadows, Simon Woodward*

School of Chemistry, The University of Nottingham, University Park, Nottingham, United Kingdom

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Abstract

A systematic study of the effects of aryl triflate and nonaflate structure on the yield of amination with the primary amines PhCH(R)NH_2 (R=H, Me) under palladium catalysis has been carried out. High throughput screening indicated that a catalyst composed of X–Phos/$Pd_2(dba)_3$/1,4-dioxane was optimal based on a model reaction of Ar(OR_f) [R_f=Tf (SO_2CF_3), Nf ($SO_2(CF_2)_3CF_3$)] with $PhCH_2NH_2$. Comparisons of the reactivity of various ArOTf and ArONf [Ar=4-MePh, 2-naphthyl, 1-naphthyl, 2-PhC_6H_4] indicated that both *ortho* substitution in the aryl electrophile and at the α-position on the amine are detrimental to the coupling particularly when they occur in combination. Despite being formally a monodentate ligand use of X–Phos leads to only small degrees of racemisation when using (*R*)-PhCH(Me)NH_2 (typically resulting in a reduction from 97 to 86–94% ee for the amine stereocentre).

Keywords: Buchwald–Hartwig coupling; Phosphines; C–N coupling; Methodology

1. Introduction

In the last ten years palladium-catalysed amination of halides has become a versatile weapon in preparation of *N*-functionalised aryl and other species. However, such a superabundance of catalyst combinations now exists that even the highly extensive reviews[1] available sometimes struggle to make clear predictions as to the optimal system for a given C(sp^2)-X/amine combination. Three of the more versatile systems from the primary literature are summarised in Scheme 1 together with some popular 'tricks' for their further promotion.

We have an interest in the preparation of functional 1,1′-biphenol and 1,1′-binaphthol species for which amination via triflates or nonaflates potentially offer an attractive strategy for N-derivatisation. However, <5% of the present literature covers this particular coupling and particularly the effect of steric factors in such primary amine couplings has not been described to the best of our knowledge [related processes with aniline, amide, imine and *sec*-amine nucleophiles are delineated, see Ref. 1]. Steric factors are known to sometimes cause problems in Buchwald–Hartwig couplings and such factors are likely to be especially important in the use of 1,1′-binaphthol/biphenyl based substrates. Due to the lack of literature examples, we have conducted a small systematic study on the effect of steric factors in the coupling of various sulfonates **4** and **5** with $R^3R^4CHNH_2$ leading to secondary amines **6** (box in Scheme 1). Simple systems have been investigated to attempt to understand, which catalyst systems might be applicable in applications using 1,1′-biaryl based and other hindered substrates.

2. Results and discussion

As initial test substrates the *o*-phenyl triflate (**4a**, R^1=Ph, R^2=H, R_f=Tf) and nonaflate (**5a**, R^1=Ph, R^2=H, R_f=C_4F_9) were selected as representative moderately sterically hindered substrates. Both **4a** and **5a** are readily synthesised from the corresponding phenol **7**. Extensive catalyst screening of the coupling of **4a/5a** with benzylamine was carried out and

* Corresponding author. Fax: +44 115/9513564.
E-mail address: simon.woodward@nottingham.ac.uk (S. Woodward).

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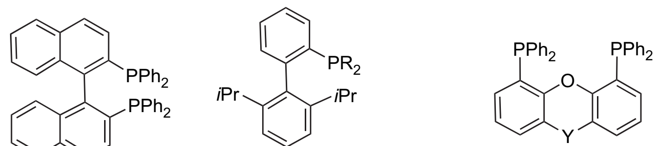
Aminating System	*Notes*	*Ref*
Pd/BINAP/Cs_2CO_3/toluene	* ArI activated in presence of ArCl	[2]
	* Slowed by steric factors in ArX and amine	[3]
Pd/X-Phos **1a**/Cs_2CO_3/toluene	* K_3PO_4 as alternative base	[1a]
	* Can couple ArOTf and ArOTs	[4]
Pd/DPE-Phos **2**/Cs_2CO_3/toluene	* Couples hindered ArX and ArOTf	[5]
	* Xant-Phos **3** as alternative	[1a]
	* Amides and Ph_2C=NH work best	[1a]



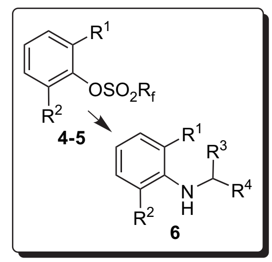
BINAP

1a X-Phos, R = cC_6H_{11}
1b *t*Bu-X-Phos, R = *t*Bu

2 DPE-Phos, Y = 2 x H
3 Xant-Phos, Y = CMe_2

Promotion 'tricks'

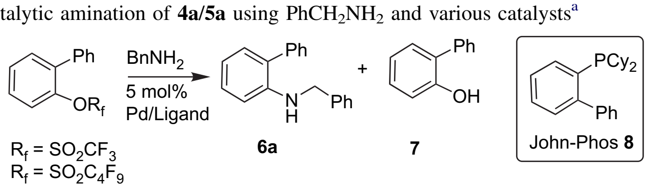
* Excess (3-5 equiv.) powdered Cs_2CO_3 for Pd/BINAP
* Excess (3-5 equiv.) powdered K_3PO_4 for Pd/X-Phos **1**
* Use of *t*-BuOH or amyl alcohol as solvent
* Use of 1,4-dioxane as solvent
* Can be faster with $Pd(OAc)_2$ than $Pd_2(dba)_3$



Scheme 1. Popular system for aryl amination and the challenge of hindered aryl fluorosulfonates (**4**, R_f=CF_3; **5**, R_f=C_4F_9) with primary amines.[1a,2−5]

some of the more successful combinations are reported in Table 1. To allow direct comparison all in situ screenings were carried out under identical conditions (100 °C for 16 h) using catalysts prepared from ligand addition to palladium acetate or $Pd_2(dba)_3$.

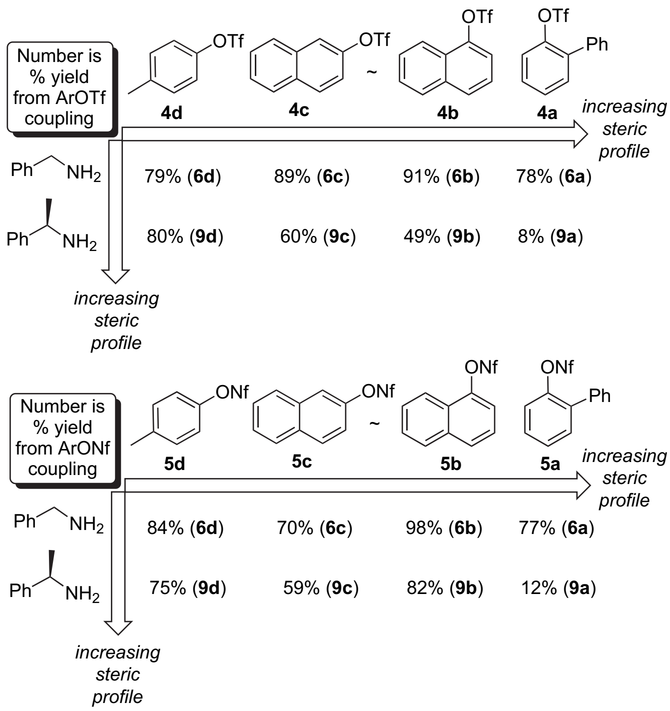
Table 1
Catalytic amination of **4a/5a** using $PhCH_2NH_2$ and various catalysts[a]



Run	Reagent (Pd source)[c]	Ligand	Base	Solvent	**6a**/%[b]	**7**/%[b]
1	**4a** (OAc)	BINAP	Cs_2CO_3	Toluene	3	33
2	**4a** (OAc)	X−Phos **1a**	Cs_2CO_3	Toluene	8	20
3	**4a** (dba)	DPE−Phos **2**	Cs_2CO_3	Toluene	<1	24
4	**4a** (OAc)	Xant−Phos **3**	Cs_2CO_3	Toluene	3	17
5	**4a** (OAc)	X−Phos **1a**	Cs_2CO_3	Dioxane	21	36
6	**5a** (OAc)	X−Phos **1a**	Cs_2CO_3	Dioxane	25	12
7	**4a** (dba)	X−Phos **1a**	K_3PO_4	Dioxane	66	0
8	**5a** (dba)	X−Phos **1a**	K_3PO_4	Dioxane	76	0
9	**4a** (dba)	*tert*-Bu−X−Phos **1b**	K_3PO_4	Dioxane	12	48
10	**5a** (dba)	*tert*-Bu−X−Phos **1b**	K_3PO_4	Dioxane	8	29
11	**4a** (dba)	John-Phos **8**	K_3PO_4	Dioxane	17	33
12	**5a** (dba)	John-Phos **8**	K_3PO_4	Dioxane	13	19

[a] Carried out on 0.5 mmol **4a/5a**, the ratio **4a** (or **5a**)/$PhCH_2NH_2$/base/$Pd_2(dba)_3$/ligand was 0.5:0.6:3.0:0.015:0.025; solvent volume 1 mL, 100 °C, 16 h.
[b] Determined by GC against a calibrated internal standard (phenyldecane) the mass balance of the reaction was starting **4a** and **4b**.
[c] 'OAc' indicates $Pd(OAc)_2$ was used; 'dba' that $Pd_2(dba)_3$ was employed.

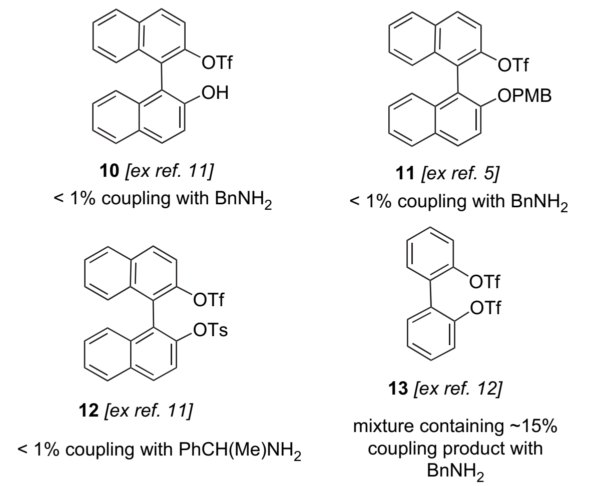
The superiority of X−Phos **1a** in the presence of K_3PO_4 and 1,4-dioxane (runs 7 and 8) was clearly evident; other ligands from the 'Buchwald ligand kit'[6] performing poorly. Attempted optimisation by both increasing (runs 9 and 10) or decreasing the ligand's steric profile (runs 11 and 12) had a detrimental effect on the yield of **5a**. The only high yield by-product in all these reactions was competing loss of the sulfonyl group; but this was eliminated by use of X−Phos **1a**/K_3PO_4. The mass balance of all reactions was accounted for by unreacted starting material **4a/5a**. As we were interested in a comparative study the reaction conversions were not followed after 16 h; all of the reactions were quenched at this point to allow direct comparison of the yield data under identical conditions. The use of alternative strong or aqueous bases or alcohol promoters (e.g., NaO*tert*-Bu, LiHDMS, KOH, *tert*-BuOH) was not tolerated with electrophiles **4/5**. Under these conditions, S−O ester hydrolysis became the major reaction. Hartwig's approach of adding the triflate slowly to avoid such behaviour was not investigated here because our reactions were carried out on small scale.[1b,7] However, we can note that a slightly smaller degree of hydrolysis was always encountered in the nonaflate series **5**. In our investigations $Pd_2(dba)_3$ proved a superior precatalyst than $Pd(OAc)_2$, which is in line with the work of both Fairlamb[8] and Fu.[9] The use of a dioxane solvent combined with effective stirring is vital in attaining high yields in the chemistry as shown in Table 1. In particular, in scaleup to >5.0 mmol amounts the yield of **6a** fell to unacceptable levels if the suspended K_3PO_3 was not efficiently agitated. Having identified a suitably active catalyst system we next compared a range of aryl triflates and nonaflates in couplings with both benzylamine and α-methylbenzyl amine using the optimal catalyst. The yields of coupled products (**6** from $BnNH_2$ and **9** from the chiral amine) attained in these studies are shown graphically in Scheme 2. Again, to allow direct comparison of the results the reactions were all carried out under identical conditions (dioxane, K_3PO_4 100 °C, 16 h) using the same X–Phos/$Pd_2(dba)_3$ catalyst.



Scheme 2. Isolated chemical yields of C–N coupling products resulting from Pd/X–Phos **1a**/K_3PO_4 catalysis of aryl triflates and nonaflates (identical conditions to Table 1; product shown in parentheses).

It can be clearly seen from Scheme 2 that the X–Phos/Pd C–N coupling reaction is less tolerant of steric requirements in the amine than it is of those in the aryl triflate or nonaflate. In the cases where both partners have large steric requirements the reaction essentially shuts down. The nonaflates do not offer any exceptional synthetic benefits for these problematic combinations. In accord with the findings of Scheme 2 attempted couplings of triflates **10–13** (Scheme 3) were found to be highly challenging—at best only traces of the desired coupling products could be detected in the reaction mixtures of the precursor triflates and benzyl amine or (*R*)-PhCH(Me)NH_2.[10]

In early work Buchwald had stated that monophosphane–Pd catalysts had a tendency to racemise α-methylbenzylamine when it was used in intermolecular couplings employing P(*o*-Tol)$_3$.[13] We are aware of only two other chiral C–N coupling studies. Ohta demonstrated partial kinetic resolutions of (±)-α-methylbenzylamine when reacted with aryl halides under Pd^0–Tol–BINAP catalysis.[14a] Similarly, Ma could show that L-valine could be coupled to PhBr without racemisation using $PdCl_2$[P(*o*-Tol)$_3$]$_2$ in the presence CuI. In the absence of CuI the reaction did not precede and the methodology failed for L-glutamic acid and L-serine.[14b] It is therefore pertinent to chek to see if extensive racemisation is encountered in the use of the Pd/X–phos **1a**/K_3PO_4 catalysis described here.



Scheme 3. Attempted amine couplings of 1,1′-binaphthyl and 1,1′-biphenyl substrates.[5,11,12]

The isolated amines **9a–d** (all from 100 °C, 16 h runs under identical conditions) were subjected to chiral HPLC analysis. Within experimental error (±2% on repeated runs) only modest degradation of the parent amines' enantiopurities was observed (Scheme 4). The behaviour of the system is independent of the electrophile—in those cases where the equivalent nonaflate was used an equivalent level of racemisation was observed. It is apparent from these studies that X–Phos does not act as a simple monodentate phosphine in these couplings [as was proposed for P(*o*-Tol)$_3$]. One likely explanation is that the X–Phos adopts a *P*,*C*═*C* chelate binding mode akin to that in the crystallographically characterised **14**.[15] Occasional disruption of the semi-labile chelate would fashion the free site required for β-hydride elimination—the prerequisite for amine racemisation. Alternatively, minor amounts of ligand-free palladium species may be responsible.

Finally, we can note that the (+) antipode of **9d** resulting from Ohta's kinetic resolution studies with (*R*)-Tol–BINAP corresponds to (*R*)-**9d**.[14a]

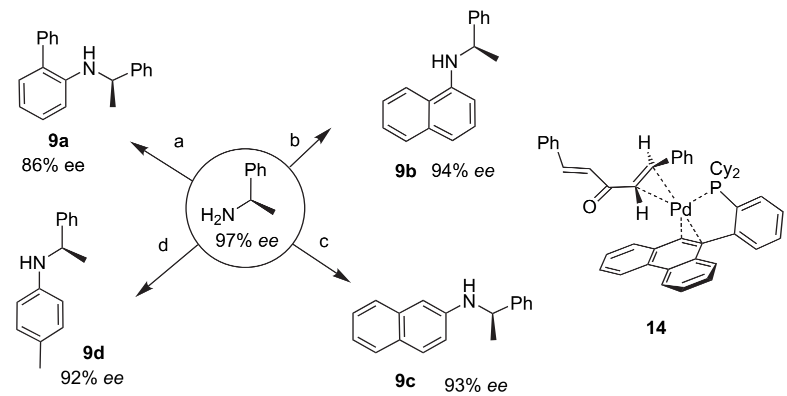
3. Conclusion

We have described an investigation of steric factors in the couplings of primary amines with aryl triflates (nonaflates) that makes it clear that the coupling of 1,1-binaphthol or 1,1′-biphenyl systems will be extremely challenging when the amine is α-branched. For less demanding electrophiles the combination of X–Phos/$Pd_2(dba)_3$/K_3PO_4 is a potent catalyst that is somewhat protected from racemising chiral secondary amines by its potential ability to form a *P*,*C*═*C* chelate.

4. Experimental

4.1. General methods

Procedures involving air or moisture sensitive reagents/intermediates were performed under atmospheres of argon using standard Schlenk techniques. Chromatography was performed



Scheme 4. Racemisation in C–N couplings promoted by $Pd_2(dba)_3$/X–Phos/K_3PO_4 (100 °C, 16 h). Reagents: (a) 1,2-C_6H_4Ph(OTf); (b) 2-$C_{10}H_7$OTf; (c) 1-$C_{10}H_7$OTf; (d) 4-MePhOTf or 4-MePhONf.

using forced flow (flash chromatography) with the solvent systems indicated in the relevant experimental procedures. The stationary phase used was silica gel 60 (220–240 mesh) supplied by Fluka. Thin layer chromatography (TLC) was performed on pre-coated plates (0.25 mm) silica. The plates were visualised by the use of a combination of ultraviolet light (254 and 366 nm) and aqueous potassium permanganate or phosphomolybdic acid (PMA) solution. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker (AV400) spectrometer. All chemical shifts (δ) were referenced to chloroform and are reported in parts per million (ppm). Coupling constants (J) are given in hertz. The following abbreviations apply: (br) broad, (s) singlet, (d) doublet, (t) triplet, (m) multiplet, (dd) double doublet, etc. Mass spectra (MS) were recorded at high resolution (HRMS) on a micromass LCT or VG micromass 70E mass spectrometers using electrospray ionisation (ESI) or electron impact (EI). Optical rotations were measured using a JASCO DIP370 Digital polarimeter at ambient temperature (nominally 22 °C) and are quoted as 10^{-1} deg cm^2 g^{-1}. Concentration (c) is given in units of g/100 cm^3. GC analysis was performed on a Varian 3380 gas chromatograph using suitable cyclodextrin based stationary phases, with phenyldecane as internal standard. Chiral HPLC analysis was performed on a Hewlett Packard 1100LC chromatograph using Daicel Chiracel AD-H (250 mm) stationary phase column. Light petroleum refers to that fraction boiling at 40–60 °C. Dioxane was dried over 4 Å molecular sieves before use. Liquid starting materials were dried by distillation of suitable drying agents and stored over 4 Å molecular sieves under argon. The following triflates were prepared by literature methods: **4a**,[16] **4b**,[17] **4c** and **4d**.[18]

4.2. Biphenyl perfluorobutanesulfonate (nonaflate) *5a*

Solid 2-phenylphenol (5.0 g, 29.4 mmol) was dissolved in dry dichloromethane (90 mL) and triethylamine (12.4 mL, 88.1 mmol) added. Perfluoro-1-butane sulfonylfluoride (*Toxic*! 6.86 mL, 38.2 mmol) in dichloromethane (90 mL) was then added dropwise at −78 °C and the reaction mixture was allowed to come to room temperature overnight. After this time, the reaction was quenched with HCl 2 M, washed with HCl 2 M (2×100 mL) and water (100 mL), and the aqueous layer was extracted with dichloromethane. The organic layer was then dried over magnesium sulfate, filtered and the solvent removed in vacuo. Purification by column chromatography (2:1 light petrol/dichloromethane) gave **5a** as a colourless oil (12.51 g, 27.7 mmol, 94% yield). R_f 0.91 (25% dichloromethane in light petrol). ^{1}H NMR (400.1 MHz, $CDCl_3$) δ_H=7.50–7.38 (m, 8H, 8×Ar–H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C=147.1 (C–O), 135.8 (C), 135.7 (C), 132.0 (CH), 129.4 (2×CH, Ph-o), 129.0 (CH), 128.5 (CH), 128.5 (2×CH, Ph-m), 128.3 (CH), 122.0 (CH) ppm. HRMS found (ESI) (M+H)$^+$ 453.0201; $C_{16}H_{10}O_3F_9S$ requires M 453.0207. Compound **5a** has appeared in the literature[4a] but no spectroscopic data was presented.

4.3. 1-Naphthyl perfluorobutanesulfonate (nonaflate) *5b*

As **5a** using 1-naphthol (0.721 g, 5.0 mmol), triethylamine (2.09 mL, 15.0 mmol) and perfluoro-1-butane sulfonylfluoride (1.08 mL, 6.0 mmol) in dichloromethane (15 mL). Purification by column chromatography (2:1 light petrol/dichloromethane) gave the product as a colourless crystalline solid (2.06 g, 4.84 mmol, 97% yield). R_f 0.86 (25% dichloromethane in light petrol). ^{1}H NMR (400.1 MHz, $CDCl_3$) δ_H=8.12 (d, J=8.4 Hz, 1H, 8-H), 7.92 (d, J=8.0 Hz, 1H, 5-H), 7.87 (dd, J_1=6.0, J_2=3.4 Hz, 1H, 3-H), 7.66 (ddd, J_1=8.2, J_2=6.9, J_3=1.3 Hz, 1H, 6 or 7-H), 7.60 (ddd, J_1=8.2, J_2=7.0, J_3=1.3 Hz, 1H, 6 or 7-H), 7.49 (d, J=3.4 Hz, 1H, 2-H) overlapped with 7.49 (d, J=6.0 Hz, 1H, 4-H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C=145.8 (C–O), 134.9 (C), 128.5 (CH), 128.0 (CH), 127.9 (CH), 127.4 (CH), 126.5 (C), 125.1 (CH), 120.9 (CH), 117.8 (CH) ppm. HRMS found (EI) M$^+$ 425.9976; $C_{14}H_7O_3F_9S$ requires M 425.9972, found (EI) 143.0497. $C_{10}H_7O$ requires 143.0497]. These data were in accord with an alternative preparation.[19]

4.4. 2-Naphthyl perfluorobutanesulfonate (nonaflate) *5c*

As **5a** using 2-naphthol (0.721 g, 5.0 mmol), triethylamine (2.09 mL, 15.0 mmol) and perfluoro-1-butane sulfonylfluoride (1.08 mL, 6.0 mmol) in dichloromethane (15 mL). Purification by column chromatography (2:1 light petrol/dichloromethane) gave the product as a colourless oil (1.91 g, 4.47 mmol, 89% yield). R_f 0.82 (25% dichloromethane in light petrol). ^1H NMR (400.1 MHz, $CDCl_3$) δ_H=7.93 (d, J=9.0 Hz, 1H, 5-H), 7.90 (d, J=6.5 Hz, 1H, 4-H), 7.88 (d, J=6.4 Hz, 1H, 3-H), 7.77 (d, J=2.4 Hz, 1H, 1-H), 7.58 (ddd, J_1=12.8, J_2=6.9, J_3=2.0 Hz, 1H, 6 or 7-H) overlapped with 7.58 (ddd, J_1=12.7, J_2=6.9, J_3=1.9 Hz, 1H, 6 or 7-H), 7.39 (dd, J_1=9.0, J_2=2.5, 1H, 8-H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C=147.3 (C–O), 133.3 (C), 132.3 (C), 130.6 (CH), 128.1 (CH), 127.9 (CH), 127.6 (CH), 127.2 (CH), 119.6 (CH), 119.2 (CH) ppm. HRMS found (EI) M^+ 425.9986; $C_{14}H_7O_3F_9S$ requires M 425.9972. These data were in accord with an alternative preparation.[19]

4.5. 4-Tolyl perfluorobutanesulfonate (nonaflate) **5d**

As **5a** using *p*-cresol (0.541 g, 5.0 mmol), triethylamine (2.09 mL, 15.0 mmol) and perfluoro-1-butane sulfonylfluoride (1.08 mL, 6.0 mmol) in dichloromethane (15 mL). Purification by column chromatography (2:1 light petrol/dichloromethane) gave the product as a colourless oil (1.85 g, 4.75 mmol, 95% yield). R_f 0.9 (25% dichloromethane in light petrol). ^1H NMR (400.1 MHz, $CDCl_3$) δ_H=7.49 (app. d, J=8.8 Hz, 2H, Ts-*o*), 7.19 (app. d, J=8.7 Hz, 2H, Ts-*m*), 2.40 (s, 3H, Ts-CH_3) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C=147.8 (C), 138.5 (C), 130.6 (2×CH, Ts-*o*), 121.0 (2×CH, Ts-*m*), 20.9 (CH_3) ppm. HRMS found (EI) M^+ 389.9973; $C_{11}H_7O_3F_9S$ requires M 389.9972. Only limited data have appeared for this compound.[20]

4.6. Parallel catalyst screening procedure for amination trials

In a flame-dried carousel tube in a Radleys reactor,[21] Pd catalyst (3 mol %), ligand (5 mol %) and base (300 mol %) were dissolved in dry solvent (1 mL) and **4a/5a** (100 mol %) and benzylamine (120 mol %) were added. The carousel tubes were heated to reflux (100 °C) and left overnight. After this time, the reactions were quenched with water or HCl (2 M), and internal standard (phenyldecane, 25 μL) was added. The reaction mixture was then extracted with diethyl ether, filtered through a plug of silica and GC analysis of the crude reaction mixture was carried out (50 min, 220 °C isotherm) for yield and conversion results, calibrated against the internal standard.

4.7. Optimised amination conditions

In a flame-dried Schlenk tube, $Pd_2(dba)_3$ (0.014 g, 0.015 mmol), X–Phos **1a** (0.012 g, 0.025 mmol) and K_3PO_4 (0.318 g, 1.5 mmol) were dissolved in dry 1,4-dioxane (1 mL) and substrate (0.5 mmol) and amine (0.6 mmol) were added. The reaction mixture was then heated to 100 °C and left overnight. Efficient stirring was attained by use of a medium cross shape PTFE magnetic stirring bar.[22] After 16 h the reaction mixture was cooled to room temperature, water added, and the product extracted with diethyl ether, dried over magnesium sulfate, filtered and the solvent removed in vacuo. Column chromatography with the relevant solvent system gave the aminated product.

4.8. Benzyl(biphenyl-2-yl)amine **6a**

Column chromatography (2:1 light petrol/dichloromethane) gave **6a** as a colourless crystalline solid (0.101 g, 0.40 mmol, 78% yield). Mp 84–87 °C. R_f 0.53 (25% dichloromethane in light petrol). ^1H NMR (400.1 MHz, $CDCl_3$) δ_H=7.49–7.42 (m, 4H, 4×Ar–*H*), 7.37–7.30 (m, 5H, 5×Ar–*H*), 7.20 (ddd, J_1=9.0, J_2=7.4, J_3=1.6 Hz, 1H, Ar–*H*), 7.12 (dd, J_1=7.4, J_2=1.6 Hz, 1H, Ar–*H*), 6.79 (ddd, J_1=J_2=7.4, J_3=1.1 Hz, 1H, Ar–*H*), 6.68 (app. d, J=8.2 Hz, 1H, Ar–*H*), 4.53 (br s, 1H, N*H*), 4.34 (s, 2H, CH_2) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C=144.8 (C), 139.4 (CH), 130.2 (CH), 129.3 (2×CH, Ph-*o*), 128.9 (2×CH, Ph-*o*), 128.6 (CH), 128.5 (2×CH, Ph-*m*), 127.6 (C), 127.2 (CH), 126.9 (2×C, 2×CH, Ph-*m*), 117.1 (CH), 110.7 (CH), 48.0 (CH_2) ppm. HRMS found (ESI) $(M+H)^+$ 260.1439; $C_{19}H_{18}N$ requires 260.1439. These data were in accord with **6a** produced by an alternative route.[23]

4.9. Benzyl(1-naphthyl)amine **6b**

Column chromatography (2:1 light petrol/dichloromethane) gave the product as a colourless crystalline solid (0.114 g, 0.489 mmol, 98% yield). Mp 66–68 °C. R_f 0.47 (25% dichloromethane in light petrol). ^1H NMR (400.1 MHz, $CDCl_3$) δ_H=7.85–7.82 (m, 2H, 8-H, 5-H), 7.50–7.33 (m, 8H, Ph-*o*, Ph-*m*, Ph-*p*, 3-H, 6-H, 7-H), 7.28 (d, J=8.2 Hz, 1H, 4-H), 6.66 (d, J=7.4 Hz, 1H, 2-H), 4.73 (br s, 1H, N*H*), 4.52 (s, 2H, CH_2) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C=143.2 (C–N), 139.0 (C), 134.3 (C), 128.7 (2×CH, Ph-*o*), 128.7 (CH), 127.7 (2×CH, Ph-*m*), 127.4 (CH), 126.6 (CH), 125.7 (CH), 124.7 (CH), 123.3 (C), 119.9 (CH), 117.6 (CH), 104.7 (CH) 48.6 (CH_2) ppm. HRMS found (ESI) $(M+H)^+$ 234.1277; $C_{17}H_{16}N$ requires $M+H$ 124.1283. These data were in accord with **6b** produced by an alternative route.[24]

4.10. Benzyl(2-naphthyl)amine **6c**

Column chromatography (2:1 light petrol/dichloromethane) gave the product as a pale yellow crystalline solid (0.104 g, 0.446 mmol, 89% yield. Mp 60–62 °C. R_f 0.26 (25% dichloromethane in light petrol). ^1H NMR (400.1 MHz, $CDCl_3$) δ_H=7.68 (d, J=8.1 Hz, 1H, 4-H), 7.65 (d, J=8.8 Hz, 1H, 5-H), 7.60 (d, J=8.3 Hz, 1H, 3-H), 7.43 (app. d, J=7.2 Hz, 2H, Ph-*o*), 7.39–7.29 (m, 4H, Ph-*m*, Ph-*p*, 7-H), 7.20 (ddd, J_1=8.0, J_2=7.0, J_3=1.2 Hz, 1H, 6-H), 6.93 (dd, J_1=8.8, J_2=2.4 Hz, 1H, 8-H), 6.86 (d, J=2.1 Hz, 1H, 1-H), 4.45 (s, 2H, CH_2), 4.32 (br s, 1H, N*H*) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C=145.7 (C–N), 139.1 (C), 135.1 (C), 128.9 (CH), 128.7 (2×CH, Ts-*o*), 127.6 (2×CH, Ts-*m*), 127.3 (CH), 126.3 (CH), 126.0 CH), 122.0 (CH), 117.8 (CH), 104.7 (CH) 43.4 (CH_2) ppm. HRMS found (ESI) $(M+H)^+$

234.1277; $C_{17}H_{16}N$ requires $M+H$ 234.1283. These data were in accord with **6b** produced by an alternative route.[25]

4.11. Benzyl(4-tolyl)amine **6d**

Column chromatography (2:1 light petrol/dichloromethane) gave the product as a low melting point solid (0.082 g, 0.418 mmol, 82% yield). R_f 0.33 (25% dichloromethane in light petrol). ^{1}H NMR (400.1 MHz, $CDCl_3$) δ_H=7.34–7.33 (m, 4H, Ph-*o*, Ph-*m*), 7.28 (tt, J_1=6.9, J_2=1.7 Hz, 1H, Ph-*p*), 7.00 (app. d, *J*=8.0 Hz, 2H, Ts-*o*), 6.58 (dt, J_1=8.4, J_2=2.0 Hz, 2H, Ts-*m*), 4.32 (s, 2H, CH_2), 3.92 (br s, 1H, N*H*), 2.25 (s, 3H, Ts–CH_3) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C=145.9 (C), 139.6 (C), 129.7 (2×CH, Ts-*o*), 128.6 (2×CH, Ph-*o*), 127.6 (2×CH, Ts-*m*), 127.1 (Ph-*p*), 126.7 (C), 113.0 (2×CH, Ph-*m*), 48.6 (CH_2), 20.4 (CH_3) ppm. HRMS found (ESI) $(M+H)^+$ 198.1277; $C_{14}H_{16}N$ requires *M* 198.1283. These data were in accord with **6b** produced by an alternative route.[26]

4.12. (R)-(+)-Biphenyl-2-yl-(1-phenyl-ethyl)amine **9a**

Column chromatography (2:1 light petrol/dichloromethane) gave the product as a colourless solid (0.016 g, 0.059 mmol, 12% yield). Mp 49–51 °C. R_f 0.47 (25% dichloromethane in light petrol). $[\alpha]_D$ 0.56 (*c* 1.07, $CHCl_3$) for 86% ee material. ^{1}H NMR (400.1 MHz, $CDCl_3$) δ_H=7.53–7.48 (m, 4H, 4×Ar–*H*), 7.41–7.22 (m, 6H, 6×Ar–*H*), 7.10–7.05 (m, 2H, 2×Ar–*H*), 6.72 (t, *J*=7.3 Hz, 1H, Ph-*p*), 6.46 (d, *J*=8.0 Hz, 1H, Ar–*H*), 4.49 (q, *J*=6.7 Hz, 1H, C*H*), 4.32 (br s, 1H, N*H*), 1.41 (d, *J*=6.7 Hz, 3H, CH_3) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C=145.2 (C), 144.0 (C), 139.6 (C), 130.1 (CH), 129.3 (2×CH, Ph-*o*), 129.3 (2×CH, Ph-*o*), 128.9 (2×CH, Ph-*m*), 128.5 (CH), 127.5 (C), 127.2 (CH), 126.8 (CH), 125.7 (2×CH, Ph-*m*), 116.9 (CH), 111.7 (CH), 53.5 (CH), 25.1 (CH_3) ppm. HRMS found (ESI) $(M+H)^+$ 274.1596; $C_{20}H_{19}N$ requires $M+H$ 274.1596. HPLC column: AD-H. Hexane/*i*-PrOH: 90:10, 0.5 mL/min; retention time of enantiomer 1: 15.2 min (*S*), retention time of enantiomer 2: 17.0 min (*R*).

4.13. (R)-(−)-1-Naphthyl-(1-phenyl-ethyl)amine **9b**

Column chromatography (2:1 light petrol/dichloromethane) gave the product as a colourless crystalline solid (0.114 g, 0.462 mmol, 92% yield). Mp 68–71 °C. R_f 0.59 (25% dichloromethane in light petrol). $[\alpha]_D$ −239 (*c* 0.9, $CHCl_3$) for 94% ee material. ^{1}H NMR (400.1 MHz, $CDCl_3$) δ_H=7.97–7.94 (m, 1H, Ar–*H*), 7.82–7.80 (m, 1H, Ar–*H*), 7.50 (m, 2H, 6-H, 7-H), 7.45 (d, *J*=7.16 Hz, 2H, Ph-*o*), 7.36–7.33 (m, 2H, 2×Ar–*H*), 7.28–7.24 (m, 1H, Ar–*H*), 7.21 (d, *J*=4.9 Hz, 2H, Ph-*m*) 6.43–6.40 (m, 1H, Ar–*H*), 4.76 (br s, 1H, N*H*), 4.70 (q, *J*=6.7 Hz, 1H, C*H*), 1.69 (d, *J*=6.7 Hz, 3H, CH_3) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C=144.9 (C), 142.1 (C), 128.7 (CH), 128.7 (2×CH, Ph-*o*), 126.9 (CH), 126.5 (CH), 125.8 (2×CH, Ph-*m*), 125.6 (CH), 124.6 (CH), 123.2 (C), 119.7 (CH), 117.2 (CH), 106.0 (C), 53.6 (CH), 25.2 (CH_3) ppm. HRMS found (ESI) $(M+H)^+$ 248.1434; $C_{18}H_{18}N$ requires $M+H$ 248.1439. HPLC Column AD-H. Hexane/*i*-PrOH: 90:10, 0.5 mL/min; retention time of enantiomer 1: 13.8 min (*R*), retention time of enantiomer 2: 16.8 min (*S*). Literature values give only a low optical rotation for this compound on a near racemate prepared by a different route.[27]

4.14. (R)-(+)-2-Naphthyl-(1-phenyl-ethyl)amine **9c**

Column chromatography (1:1 light petrol/dichloromethane) gave the product as a colourless crystalline solid (0.074 g, 0.299 mmol, 60% yield). Mp 68–70 °C. R_f 0.41 (25% dichloromethane in light petrol). $[\alpha]_D$ +146 (*c* 0.9, $CHCl_3$) for 93% ee material. ^{1}H NMR (400.1 MHz, $CDCl_3$) δ_H=7.64 (d, *J*=8.0 Hz, 1H, 4-H), 7.60 (d, *J*=8.8 Hz, 1H, 5-H), 7.48 (d, *J*=8.2 Hz, 1H, 3-H), 7.42 (app. d, *J*=7.4 Hz, 2H, Ph-*o*), 7.34 (dd, J_1=J_2=7.3 Hz, 2H, Ph-*m*), 7.30 (ddd, J_1=8.2, J_2=6.9, J_3=1.2 Hz, 1H, 6 or 7-H), 7.24 (tt, J_1=7.3, J_2=1.2 Hz, 1H, Ph-*p*), 7.16 (ddd, J_1=8.0, J_2=6.9, J_3=1.1 Hz, 1H, 6 or 7-H), 6.90 (dd, J_1=8.8, J_2=2.4, 1H, 8-H), 6.64 (d, *J*=2.2 Hz, 1H, 1-H), 4.64 (q, *J*=6.7 Hz, 1H, C*H*), 4.24 (br s, 1H, N*H*), 1.59 (d, *J*=6.7 Hz, 3H, CH_3) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C=144.5 (C), 144.7 (C), 135.0 (C), 128.8 (CH), 128.7 (2×CH, Ph-*o*), 127.5 (CH), 127.3 (C), 126.9 (CH), 126.1 (CH), 125.9 (CH), 125.8 (2×CH, Ph-*m*), 121.9 (CH), 117.9 (CH), 53.4 (CH), 24.8 (CH_3) ppm. HRMS found (ESI) $(M+H)^+$ 248.1434; $C_{18}H_{18}N$ requires $M+H$ 248.1439. HPLC column: AD-H. Hexane/*i*-PrOH: 90:10, 0.5 mL/min; retention time of enantiomer 1: 14.0 min (*R*), retention time of enantiomer 2: 17.4 min (*S*). This compound has been prepared by a different route but no spectroscopic or related data were presented.[28]

4.15. (R)-(+)-4-Tolyl-(1-phenyl-ethyl)amine **9d**

Column chromatography (2:1 light petrol/dichloromethane) gave the product as a colourless crystalline solid (0.084 g, 0.398 mmol, 80% yield). Mp 51–53 °C. R_f 0.33 (25% dichloromethane in light petrol). $[\alpha]_D$ +5 (*c* 0.86, $CHCl_3$) for 92% ee material. ^{1}H NMR (400.1 MHz, $CDCl_3$) δ_H=7.38–7.30 (m, 4H, Ph-*o*, Ph-*m*), 7.24–7.20 (m, 1H, Ph-*p*), 6.90 (d, *J*=8.4 Hz, 2H, Ts-*o*), 6.44 (d, *J*=8.4 Hz, 2H, Ts-*m*), 4.46 (q, *J*=6.7 Hz, 1H, C*H*), 3.90 (br s, 1H, N*H*), 2.19 (s, 3H, Ts–CH_3), 1.51 (d, *J*=6.7 Hz, 3H, CHCH_3) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C=145.4 (C), 145.0 (C), 129.6 (2×CH, Ph-*o*), 128.6 (2×CH, Ph-*m*), 126.8 (Ph-*p*), 126.3 (C), 125.8 (2×CH, Ts-*o*), 113.4 (2×CH, Ts-*m*), 53.6 (CH), 25.0 (CH_3), 20.3 (Ts–CH_3) ppm. HRMS found (ESI) $(M+H)^+$ 212.1434, $C_{15}H_{18}N$ requires *M* 212.1439. HPLC column AD. Hexane/*i*-PrOH: 95:5, 1.0 mL/min; retention time of enantiomer 1: 5.5 min (*S*), retention time of enantiomer 2: 6.1 min (*R*). Prepared by a different method **9d** had $[\alpha]_D$ +27 (*c* 0.7, EtOAc) for 91% ee material.[29]

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