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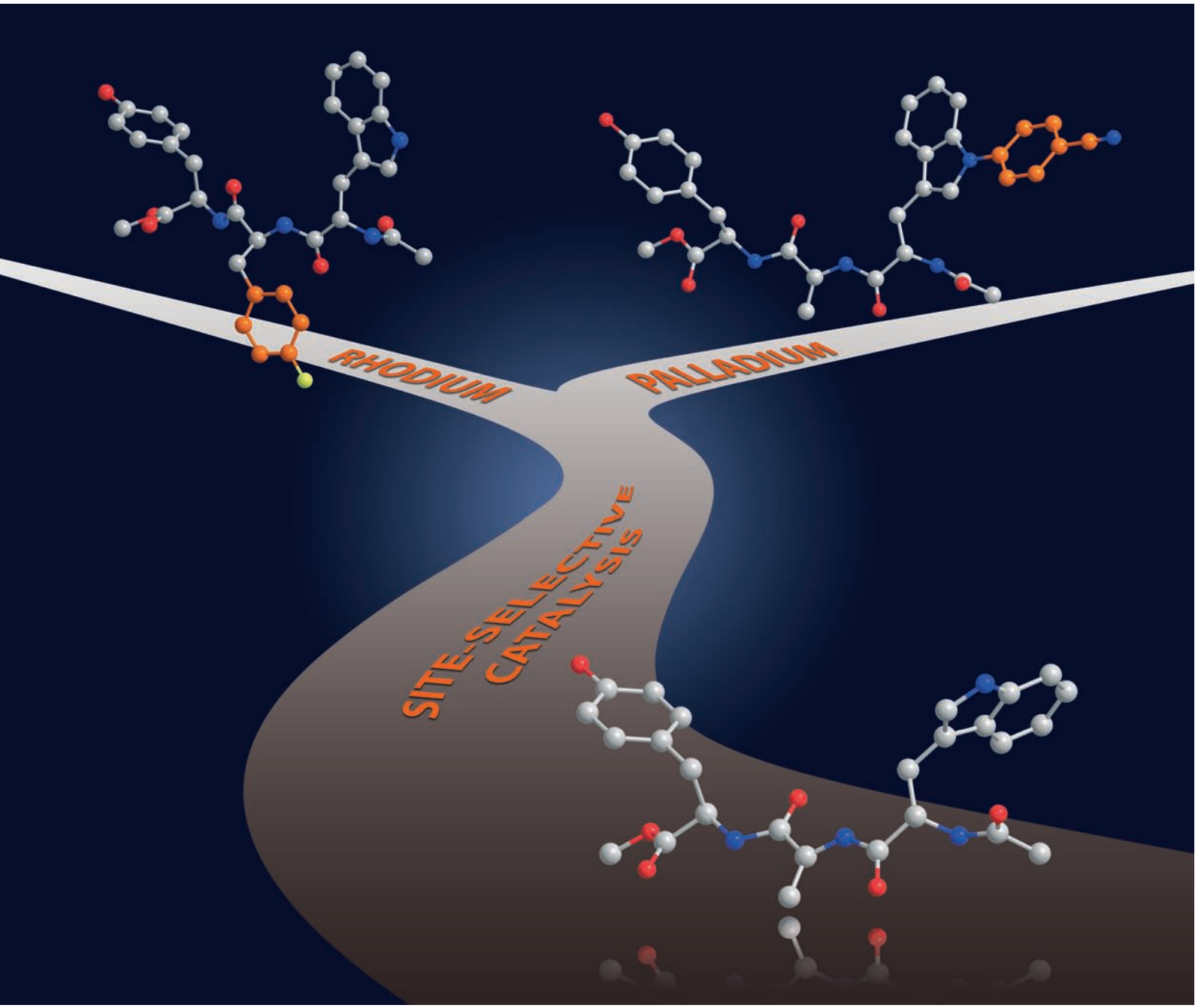

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Site-selective modification of peptides using rhodium and palladium catalysis: complementary electrophilic and nucleophilic arylation†

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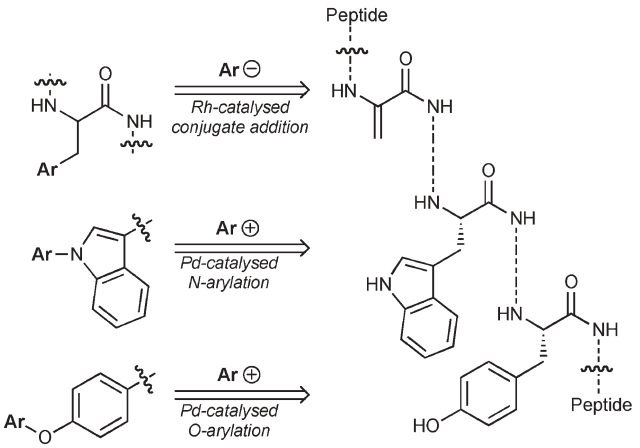
The site-selective modification of peptides containing dehydroalanine, tyrosine and tryptophan residues has been achieved using rhodium catalysed conjugate additions or palladium catalysed aryl-amination and -etherification reactions.

The ability to modify individual residues of peptides or proteins selectively and reliably opens a number of exciting possibilities in chemical biology. For example, modification of individual amino acids has been shown to be responsible for changes in peptide conformation, allows for bioconjugation to construct diagnostic arrays and chemical probes, and for the elucidation of an individual residue's biological function.[1] The majority of methods used to achieve these modifications are based on biochemical techniques, however the number of examples of modifications achieved using small molecule (chemical) reactivity is increasing.[2,3]

The rhodium catalysed conjugate addition of boronic acids provides an attractive method to effect a nucleophilic arylation of alkene acceptors.[4] Dehydroalanine residues can be revealed by the activation and β-elimination of cysteine or serine derivatives;[5] conjugate addition to these unsaturated residues represents a convenient strategy for incorporating unnatural phenylalanine derivatives.[6] In order to develop suitable processes for the selective electrophilic functionalisation of tryptophan and tyrosine units we elected to use palladium catalysed hetero-arylation reactions (Scheme 1).[7]

Although the *N*-arylation of a variety of azoles has been reported,[8] we were attracted to the aryl-amidation conditions reported by Buchwald as the starting point of our investigation.[9] Thus, reaction of indole **1** with 4-bromobenzonitrile using $Pd(OAc)_2$, the ligand Xantphos, and the weak base Cs_2CO_3 in dioxane at 80 °C delivered the *N*-arylated product **2** in 87% yield (Table 1, entry1). The reaction temperature could be reduced to 55 °C with little effect on efficiency, however if the reactions were performed at 50 °C a low yield of the desired product was obtained (entries 2 and 3). The alternative bases K_2CO_3 and K_3PO_4 were less effective than Cs_2CO_3 (entries 4 and 5). Entry 6 demonstrates that toluene is also a suitable solvent for the transformation, with an 86% yield of the arylated compound being obtained. The final three entries employ alternative aryl bromide coupling partners

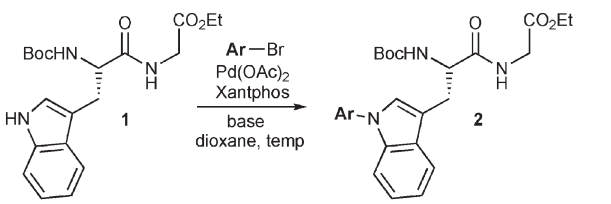


Scheme 1 Nucleophilic and electrophilic transition metal catalysed arylation of peptide chains.

and demonstrate that ester, sulfonamide and trifluoromethyl substituents can all be introduced successfully. The efficient arylation of peptide **1** shows that is possible to react selectively at the indole N–H in preference to the competitive amide and carbamate functional groups.

Our *O*-arylation study focused on tyrosine derivative **3** (Table 2). Our initial reaction conditions employed $Pd(OAc)_2$, ligand **4a** and K_3PO_4 in toluene at 100 °C,[10] and unfortunately provided only

Table 1 *N*-Arylation of tryptophan derivative **1**[a]



Entry	Ar–Br	Base	Time (h)	Temp. (°C)	Yield (%)[b]
1	4-CN-Ph	Cs_2CO_3	18	80	87
2	4-CN-Ph	Cs_2CO_3	40	55	94
3	4-CN-Ph	Cs_2CO_3	40	50	31
4	4-CN-Ph	K_2CO_3	40	55	27
5	4-CN-Ph	K_3PO_4	40	55	65
6[c]	4-CN-Ph	Cs_2CO_3	40	55	86
7[d]	4-MeO_2C-Ph	Cs_2CO_3	40	60	54
8[d]	4-CF_3-Ph	Cs_2CO_3	16	80	70
9[d,e]	4-R_2NSO_2-Ph	Cs_2CO_3	40	60	86

[a] Conditions: Ar–Br (1.2 equiv.), $Pd(OAc)_2$ (5 mol%), Xantphos (7.5 mol%), base (1.4 equiv.), dioxane. [b] Isolated yields. [c] Toluene as solvent. [d] Ar–Br (2.4 equiv.). [e] R_2N = morpholino.

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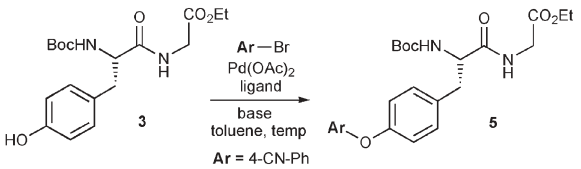
Table 2 *O*-Arylation of tyrosine derivative **3**[a]

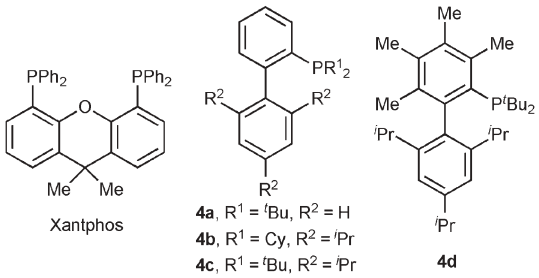


Entry	Pd-source	Ligand	Temp. (°C)	Time (h)	Yield (%)[b]
1	$Pd(OAc)_2$	**4a**	100	18	<5
2	$Pd(OAc)_2$	**4b**	100	18	6
3	$Pd(OAc)_2$	**4c**	100	18	64
4	$Pd(OAc)_2$	**4d**	100	18	22
5	$Pd_2(dba)_3$	**4c**	80	18	95
6	$Pd_2(dba)_3$	**4c**	60	40	94
7[c]	$Pd_2(dba)_3$	**4c**	80	40	91

[a] Conditions: Ar–Br (1.2 equiv.), Pd source (5 mol%), ligand (7.5 mol%), base (2.0 equiv.), toluene. [b] Isolated yields. [c] Dioxane as solvent.

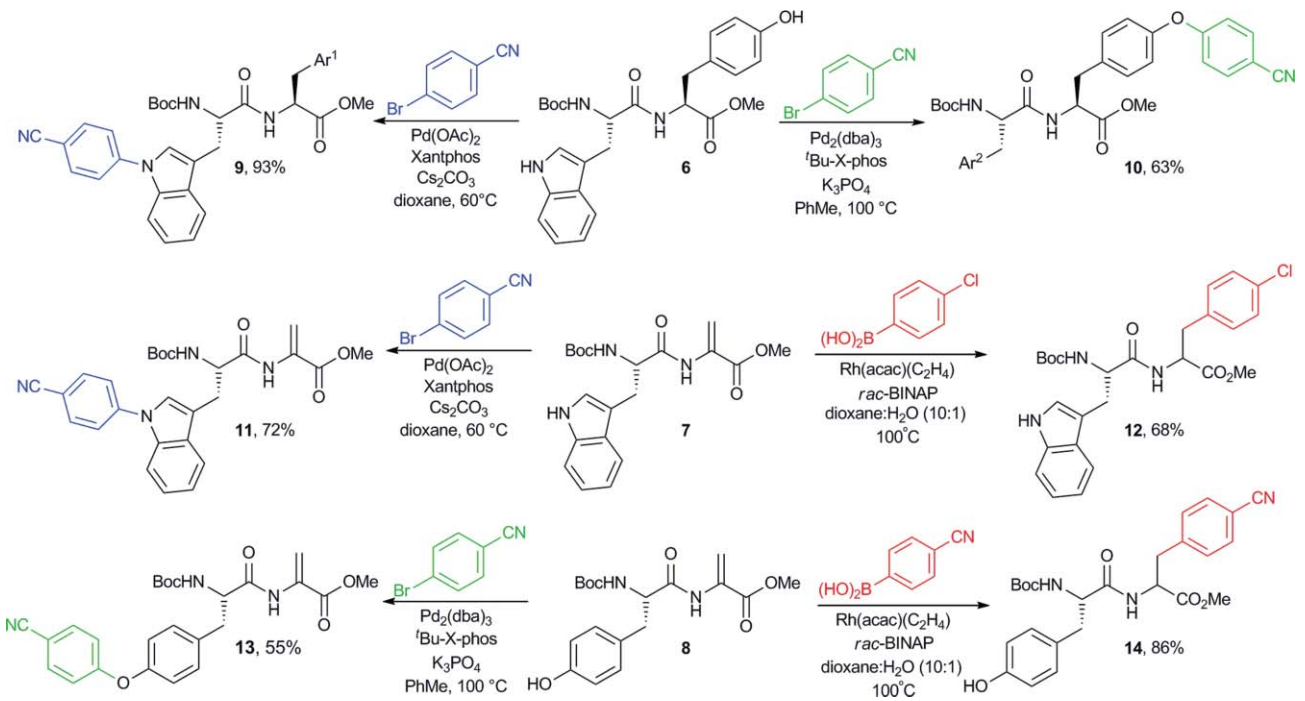
trace amounts of the desired product (entry 1). Evaluation of alternative electron-rich biphenyl-based ligands showed that ^{t}Bu-phosphine derivative **4c** was the most successful,[11] although this system still provided only a 64% yield of the *O*-arylated product **5** (entries 2–4). An improvement in yield to 95% was achieved when $Pd_2(dba)_3$ was used as the Pd source (entry 5). Provided a longer reaction time was used then the temperature could be reduced to 60 °C and still achieve efficient conversion (entry 6). Finally, dioxane could also be used successfully in place of toluene (entry 7).

The next stage of our study was to investigate the chemoselectivity of the individual reactions; peptides **6**, **7** and **8**, each containing two of the reactive functional groups, were prepared and reacted under our optimized conditions (Scheme 2). Dipeptide **6** contains both tyrosine and tryptophan residues and we considered the Pd-catalysed chemoselective functionalisation of

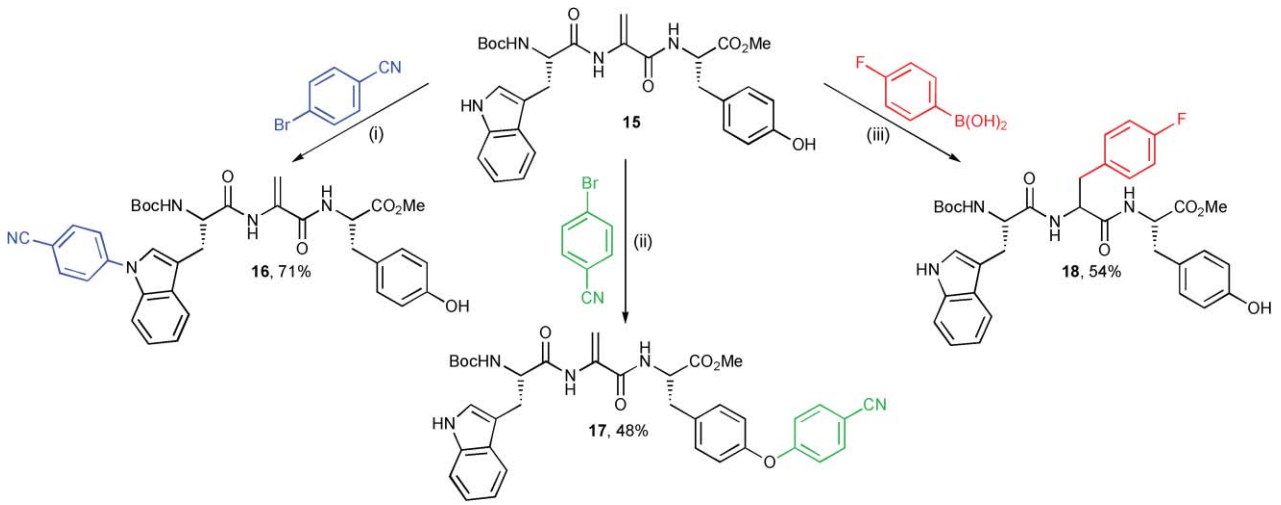


these two nucleophilic residues to present a significant challenge. In the event, both *N*- and *O*-arylation were achieved with good selectivity. *N*-Arylation proceeded under the standard conditions to deliver an excellent 93% yield of the expected product **9**. Under these conditions no *O*-arylation was observed. *O*-Arylation was less selective but still provided a 63% yield of the desired *O*-aryl material **10** along with 11% of an *N*,*O*-diarylated peptide. Dipeptide **7**, containing tryptophan and dehydroalanine residues, was combined with 4-bromobenzonitrile, exposed to the conditions developed in Table 1, and provided the desired *N*-arylated peptide **11** in a pleasing 72% yield. The rhodium catalysed conjugate addition of boronic acids to dehydroalanine derivatives proceeds in aqueous solvents in the presence of phosphine ligands.[12] These conditions allowed modification of the dehydroalanine residue with *p*-chlorophenyl boronic acid to reveal the arylated peptide **12** in good isolated yield (as a 1 : 1 mixture of diastereomers). The tyrosine and dehydroalanine containing dipeptide **8** was *O*-arylated using the standard conditions, but at 100 °C, to deliver 55% of the expected product **13**; reactions at lower temperatures were less effective. The conjugate addition to dipeptide **8** occurred in 86% overall yield to efficiently install a *p*-cyanophenylalanine residue **14**.

Scheme 3 illustrates our studies using tripeptide **15** that contains all three reactive functional groups. Chemoselective *N*-arylation of



Scheme 2 Chemoselective functionalisation of dipeptides **6**, **7** and **8**.



Scheme 3 Chemoselective functionalisation of tripeptide **15**. *Reagents and conditions*: (i) $Pd(OAc)_2$ (5 mol%), Xantphos (7.5 mol%), K_3PO_4 (1.4 equiv.), dioxane, 80 °C, 18 h; (ii) $Pd_2(dba)_3$ (5 mol%), **5c** (10 mol%), K_3PO_4 (2.0 equiv.), dioxane, 80 °C, 18 h; (iii) $Rh(acac)(C_2H_4)$ (6 mol%), *rac*-BINAP (6.6 mol%), dioxane : H_2O 10 : 1, 100 °C, 18 h.

the tryptophan residue was achieved in 71% yield using our standard conditions, with no *O*-arylated material being observed. Attempted *O*-arylation using the standard conditions was unsuccessful, however a switch from toluene to dioxane allowed *O*-arylation of the tyrosine unit in 48% yield. This was obtained along with 13% *N*-arylated material and 10% starting tripeptide. Pleasingly, the conjugate addition of *p*-fluorophenyl boronic acid to the embedded dehydroalanine proceeded under standard conditions to afford the novel peptide **18** in 54% yield (isolated as a single diastereomer).

In summary, we have demonstrated that highly selective arylation of short peptides is possible using complementary Rh-catalysed conjugate additions and Pd-catalysed *N*- and *O*-arylation reactions. All three processes show excellent chemoselectivity and good functional group tolerance. The substrates used in this study represent some of the most complex molecules to be functionalised using these processes. Success with these small peptide systems paves the way for application of this methodology to larger, more complex molecules.

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Notes and references

1 For a general discussion, see: J. Rademann, *Angew. Chem., Int. Ed.*, 2004, **43**, 4554; D. S. Y. Yeo, R. Srinivasan, G. Y. J. Chen and S. Q. Yao, *Chem.–Eur. J.*, 2004, **10**, 4664 and references therein.

2 D. Qi, C.-M. Tann and M. D. Distefano, *Chem. Rev.*, 2001, **101**, 3081; B. G. Davies, *Curr. Opin. Biotechnol.*, 2003, **14**, 379; J. M. Antos and M. B. Francis, *Curr. Opin. Chem. Biol.*, 2006, **10**, 253.

3 H. Dibowski and F. P. Schmidtchen, *Angew. Chem., Int. Ed.*, 1998, **37**, 476; D. T. Bong and M. R. Ghadiri, *Org. Lett.*, 2001, **3**, 2509; N. S. Joshi, L. R. Whitaker and M. B. Francis, *J. Am. Chem. Soc.*, 2004, **126**, 15942; J. M. Antos and M. B. Francis, *J. Am. Chem. Soc.*, 2004, **126**, 10256; J. M. McFarland and M. B. Francis, *J. Am. Chem. Soc.*, 2005, **127**, 13490; A. Ojida, H. Tsutsumi, N. Kasagi and I. Hamachi, *Tetrahedron Lett.*, 2005, **46**, 3301; S. D. Tilley and M. B. Francis, *J. Am. Chem. Soc.*, 2006, **128**, 1080.

4 For reviews see: T. Hayashi, *Synlett*, 2001, 879; T. Hayashi and K. Yamasaki, *Chem. Rev.*, 2003, **103**, 2829; K. Fagnou and M. Lautens, *Chem. Rev.*, 2003, **103**, 169.

5 S. A. Burrage, T. Raynham and M. Bradley, *Tetrahedron Lett.*, 1998, **39**, 2831; P. M. T. Ferreira, H. L. S. Maia and L. S. Monteiro, *Tetrahedron Lett.*, 1998, **39**, 9575; Z. Miao and P. J. Tam, *Org. Lett.*, 2000, **2**, 3711.

6 L. Wang and P. G. Schultz, *Angew. Chem., Int. Ed.*, 2004, **44**, 34.

7 For reviews of Pd-catalysed C–N and C–O cross-coupling of aryl halides, see: (*a*) J. F. Hartwig, in *Handbook of Organopalladium Chemistry for Organic Synthesis*, ed. E. I. Negishi, Wiley-Interscience, New York, 2002, vol. 1, p. 1051; (*b*) J. F. Hartwig, in *Handbook of Organopalladium Chemistry for Organic Synthesis*, ed. E. I. Negishi, Wiley-Interscience, New York, 2002, vol. 1, p. 1097; (*c*) A. R. Muci and S. L. Buchwald, *Top. Curr. Chem.*, 2002, **219**, 131; (*d*) D. Prim, J.-M. Campagne, D. Joseph and B. Andrioletti, *Tetrahedron*, 2002, **58**, 2041.

8 G. Mann, J. F. Hartwig, M. S. Driver and C. Fernández-Rivas, *J. Am. Chem. Soc.*, 1998, **120**, 827; J. F. Hartwig, M. Kawatsura, S. I. Hauck, K. H. Shaughnessy and L. M. Alcazar-Roman, *J. Org. Chem.*, 1999, **64**, 5575; D. W. Old, M. C. Harris and S. L. Buchwald, *Org. Lett.*, 2000, **2**, 1403; M. Watanabe, M. Nishiyama, T. Yamamoto and Y. Koie, *Tetrahedron Lett.*, 2000, **41**, 481; G. A. Grasa, M. S. Viciu, J. Huang and S. P. Nolan, *J. Org. Chem.*, 2001, **66**, 7729; K. W. Anderson, R. E. Tundel, T. Ikawa, R. A. Altman and S. L. Buchwald, *Angew. Chem., Int. Ed.*, 2006, **45**, 6523.

9 J. Yin and S. L. Buchwald, *Org. Lett.*, 2000, **2**, 1101; J. Yin and S. L. Buchwald, *J. Am. Chem. Soc.*, 2002, **124**, 6043.

10 A. Aranyos, D. W. Old, A. Kiyomori, J. P. Wolfe, J. P. Sadighi and S. L. Buchwald, *J. Am. Chem. Soc.*, 1999, **121**, 4369.

11 A. V. Vorogushin, X. Huang and S. L. Buchwald, *J. Am. Chem. Soc.*, 2005, **127**, 8146; C. H. Burgos, T. E. Barder, X. Huang and S. L. Buchwald, *Angew. Chem., Int. Ed.*, 2006, **45**, 4321.

12 M. T. Reetz, D. Moulin and A. Gosberg, *Org. Lett.*, 2001, **3**, 4083; C. J. Chapman and C. G. Frost, *Adv. Synth. Catal.*, 2003, **345**, 353; C. J. Chapman, K. J. Wadsworth and C. G. Frost, *J. Organomet. Chem.*, 2003, **680**, 206.