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Efficient palladium-catalysed carbonylative and Suzuki–Miyaura cross-coupling reactions with bis(di-*tert*-butylphosphino)-*o*-xylene

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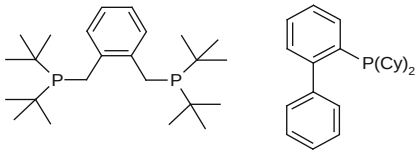
ABSTRACT

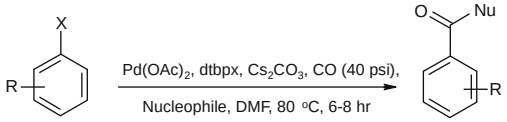
The use of the ligand bis(di-*tert*-butylphosphino)-*o*-xylene (dtbpx) in palladium-catalysed carbonylative and Suzuki–Miyaura cross-coupling reactions is described. Aryl and vinyl halides readily entered into the carbonylative catalytic cycle affording carboxylic acids, amides as well as primary, secondary and tertiary esters, respectively, in good yields. Aryl iodides, bromides and chlorides gave high yields of biphenyl products upon reaction with both activated and unactivated boronic acids.

We have been involved in the development of hindered phosphine ligands and active catalytic systems for palladium-catalysed cross-coupling reactions over the last few years.[1] In addition, the use of sustainable media such as phosphonium salt ionic liquids (PSILs) for these and other processes has been shown by us to be of synthetic and mechanistic significance employing these catalytic systems.[2] A large number of both mono- and bidentate phosphine ligands have been successfully used in the palladium-catalysed formation of C–N, C–O and C–C bonds.[3] In particular, hindered monodentate phosphines such as biaryl **2** and P(*t*Bu)$_3$ **3**, have been shown to be highly effective in the promotion of a wide range of C–C and C–heteroatom bond forming reactions.[3a–q]



dtbpx **1** **2**

As a continuation of our work, we were interested in bulky *ortho*-xylylphosphines such as the commercially available bis(di-*tert*-butylphosphino)-*o*-xylene (dtbpx) ligand **1**. Bulky, electron-donating phosphines generally favour the oxidative addition step in reaction with aryl or vinyl halides,[4] although it has also been shown that ligand exchange may be hindered using bidentate ligands such as dtbpx.[4e] The reductive elimination step is promoted by ligands that are either electron-poor, bulky, or that possess a wide bite angle.[5] Ligand **1** has been shown to be effective in the palladium-catalysed methoxycarbonylation of ethene, long chain alkenes (linear selectivity >95%), vinyl acetate (branched selectivity >77%) and unsaturated esters (to give α,ω-diesters).[6] Furthermore, it is active in the rhodium-catalysed carbonylation[7] of methanol giving acetic acid, a variant of the Monsanto process that involves oxidative addition to iodomethane or equivalent. The most important application developed so far with ligand **1** is in the palladium-catalysed methoxycarbonylation of ethene to form methyl propanoate, with high turnover and selectivity (99.98%).[8] This forms part of a two-stage route to methyl methacrylate, a process currently commercialised by Lucite.[9] Evidence has been provided that the highly unusual chemoselectivity favouring methoxycarbonylation using palladium complexes of **1** may actually involve a monodentate-doubly *ortho*-metalated palladium species.[8] It has also been shown that formation of methyl propanoate employing dtbpx **1** occurs via a catalytic mechanism involving a Pd(II) hydride species rather than the usual methoxycarbonyl cycle.[10] The use of dtbpx **1** in the carbonylation of chloroaromatic compounds has been shown to be of limited scope.[11] No other reports exist on the use of complexes of ligand **1** in the hydroxy-, alkoxy- or aminocarbonylation through oxidative addition to aryl and vinyl halides. All of the evidence would seem to indicate that palladium complexes of ligand **1** would be expected to be useful in



X = I, Br, Cl, OTf
Nu = OH, OR', NR'$_2$

Scheme 1. General reaction for carbonylative cross coupling using dtbpx.

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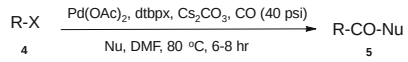
Table 1
Carbonylation using dtbpx as ligand[14]



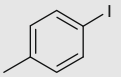
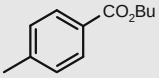
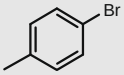
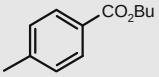
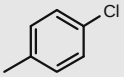
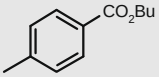
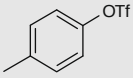
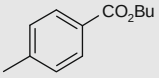
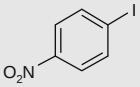
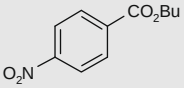
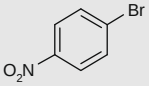
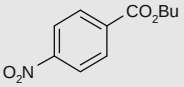
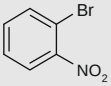
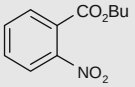
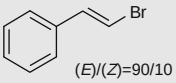
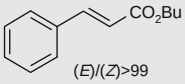
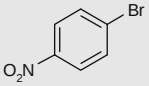
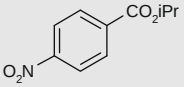
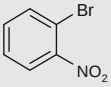
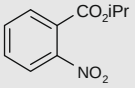
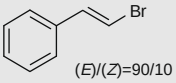
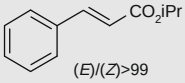
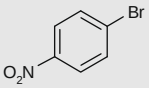
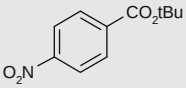
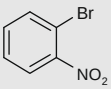
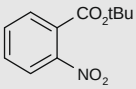
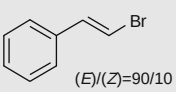
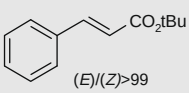
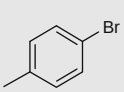
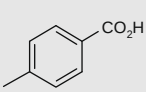
Entry	R-X	Nu	Product 5	Isolated yield of 2 (%)
1		BuOH		95
2		BuOH		84
3		BuOH		27
4		BuOH		20
5		BuOH		97
6		BuOH		95
7		BuOH		80
8		BuOH		81
9		*i*-PrOH		72
10		*i*-PrOH		65
11		*i*-PrOH		64
12		*t*-BuOH		42
13		*t*-BuOH		39
14		*t*-BuOH		36
15		H_2O		77

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Table 1 (*continued*)

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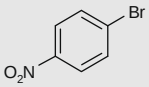
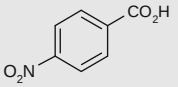
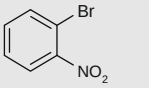
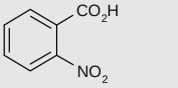
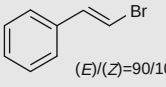
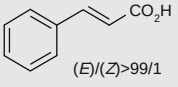
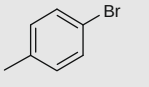
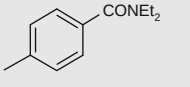
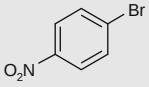
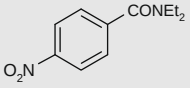
16		H_2O		84
17		H_2O		78
18	 (*E*)/(*Z*)=90/10	H_2O	 (*E*)/(*Z*)>99/1	76
19		$NHEt_2$		83
20		$NHEt_2$		86

general cross-coupling reactions proceeding via oxidative addition. Nonetheless, a recent publication reported palladium complexes of ligand **1** to be poor to moderately successful in C–N bond formation (up to 40% conversion) and Suzuki–Miyaura cross coupling (up to 60% conversion).[12] These results appeared to be unusual. The high reactivity of monodentate phosphines such as **2** in many cross-coupling reactions[3] coupled with the involvement of monodentate Pd-complexes being formed of **1**,[8] the high reactivity of **1** in carbonylation-type reactions, the demonstrated potential of ligand **1** in oxidative addition reactions[11] and the bulky electron-rich nature of the ligand all indicate that a highly active catalytic species should be accessible under the right conditions. Herein we report on our findings that palladium complexes of **1** are indeed useful general catalysts in both carbonylation and Suzuki–Miyaura palladium cross-coupling reactions.

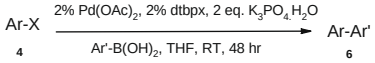
The general reaction for carbonylation with $Pd(OAc)_2$/dtbpx is outlined in Scheme 1. The initial carbonylation screen proved immediately successful. A catalyst system was developed (2.5% $Pd(OAc)_2$, 5% dtbpx, 1.5 equiv Cs_2CO_3, 2 equiv butanol, CO at 40 psi, DMF at 80 °C) and screened using 4-iodotoluene as substrate. This gave butyl 4-methylbenzoate in 95% isolated yield after only 6–8 h. The scope of the reaction was then expanded to include aryl bromides (Table 1, entries 2 and 6). Under these conditions aryl chlorides and triflates suffered from poor conversion to butyl esters (Table 1, entries 3 and 4). This is in accordance with the previous report[11] which demonstrated that, amongst a range of aryl chlorides, only the more electrophilically activated substrates (such as 4-chloroacetophenone) could be successfully carbonylated, and then only with alcohols of low nucleophilicity, such as 2,2,2-trifluoroethanol. Although a few reports[13] exist on the use of palladium complexes of 1,4-bis(diphenylphosphino)butane (dppb), 1,4-bis(diphenylphosphino)ferrocene (dppf) and 1,4-bis(dicyclohexylphosphino)ferrocene for the methoxycarbonylation of aryl and heteroaryl chlorides, these substrates remain a challenge due largely to the presence of the good π-acceptor CO which reduces the tendency towards oxidative addition at the metal centre and also promotes formation of palladium clusters. Returning to the aryl and vinyl bromides, *ortho*-steric effects were observed to be minimal (Table 1, entry 7), and vinyl halides (e.g., β-bromostyrene) gave the corresponding α,β-unsaturated butyl ester (Table 1, entry 8) with complete (*E*)-geometry in 81% isolated yield. Steric effects were seen to be significant on the part of the alcohol with yields decreasing as the bulk of the alcohol increases. For example, yields on the alkoxycarbonylation of 2-nitrobromobenzene decreased from *n*-BuOH (80%), *i*-PrOH (65%) to *t*-BuOH (39%), (Table 1 entries 7, 10 and 13). In general, *t*-butyl esters were obtained in the 36–42% yield range using this hindered nucleophile (Table 1, entries 12–14).

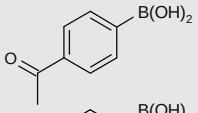
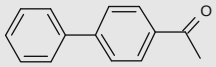
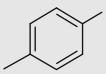
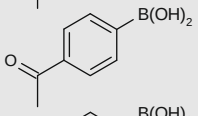
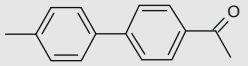
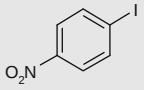
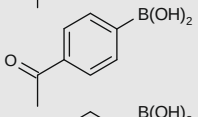
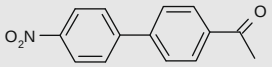
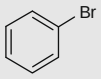
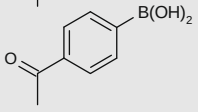
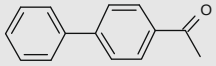
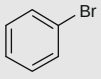
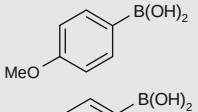
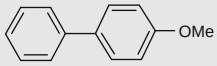
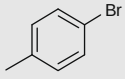
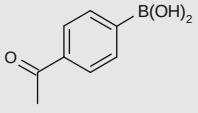
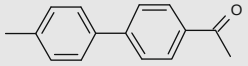
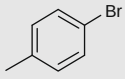
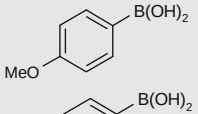
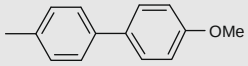
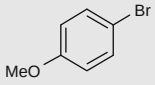
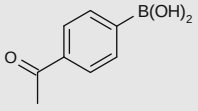
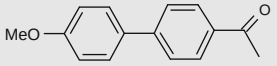
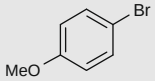
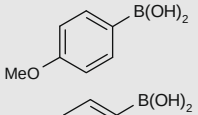
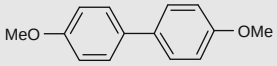
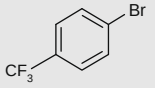
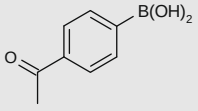
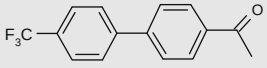
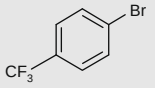
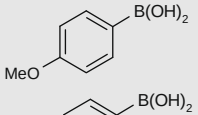
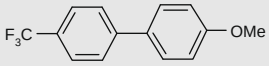
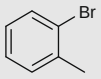
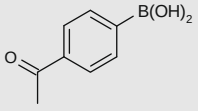
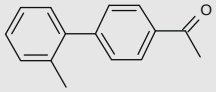
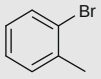
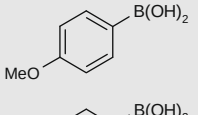
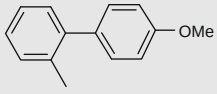
Both aryl and vinyl halides entered successfully into the hydroxycarbonylation cycle giving carboxylic acids in 76–84% isolated yield, with electronic and steric effects apparently minimal (entries 15–18). The use of a secondary amine as incoming nucleophile was also demonstrated in the conversion of aryl bromide substrates to the corresponding diethylamides (Table 1, entries 19 and 20).

A similar efficient catalytic system was also readily developed for Suzuki–Miyaura coupling, employing ligand **1**, $Pd(OAc)_2$ and the relatively mild conditions which are outlined in Table 2. All reactions reported in Table 2 were conducted under the conditions shown without further individual optimisation. Under these conditions aryl iodides reacted readily with 4-acetylphenylboronic acid affording the corresponding biphenyls in excellent yields (entries 1–3). Unactivated and electron-rich aryl bromides gave high yields of biphenyl products upon reaction with both electron-rich and electron-deficient boronic acids (Table 2, entries 4–9), while electron-deficient aryl bromides were efficiently converted to biphenyl adducts (Table 2, entries 10 and 11). The *ortho*-steric effects on the outcome of the reaction were again observed to be minimal (Table 2, entries 12 and 13). The coupling of 4-chloroacetophenone with 4-methoxyphenyl boronic acid (in toluene at 90 °C) gave the biphenyl product in 80% yield, whereas the less activated 4-chlorotoluene gave only 35% of biphenyl under these conditions. Entries 14 and 15 represent the first demonstration of dtbpx-mediated Suzuki–Miyaura coupling of aryl chlorides.

Taken together with the efficient conversion of aryl iodides and bromides, these results clearly demonstrate that the scope of the Suzuki–Miyaura cross-coupling reaction with dtbpx **1** is much wider than the single previously reported example using this ligand.[12] We note that in the report of Wills et al.,[12] bidentate 1,3- and 1,4-bis(di-*tert*-butylphosphino)-substituted propane and butane ligands, respectively, were shown to be more adept than dtbpx **1** at this transformation. In contrast, monodentate ligands as described by Fu et al.,[3d–f] utilising $Pd_2(dba)_3$ with $P(t\text{-}Bu)_3$ (1:2), and monophosphine-based biaryl ligands described by Buchwald[3o,q] are perhaps the benchmark systems for difficult Suzuki–Miyaura cross-couplings, including less-activated aryl chlorides.

Table 2
Suzuki-Miyaura cross coupling with dtbpx[15]



Entry	Ar-X	Ar′-B(OH)$_2$	Product 6	Isolated yield of 2 (%)
1				90
2				90
3				94
4				90
5				85
6				82
7				88
8				65
9				79
10				93
11				90
12				80
13				75
14				35
15				80

It is not clear whether the active catalytic species in the present system with ligand **1** is a bidentate-Pd^0 complex or a monodentate Pd(II) species of the type that has been reported,[8] nonetheless a highly active, general and useful Pd-complex of ligand **1** is generated. Gibson and co-workers have shown that mono *ortho*-diphenylphosphinotolyl-derived phosphapalladacyclic complexes are efficient in similar Suzuki cross-couplings with activated aryl bromides.[8b] Related species have been generated from both Pd^0

sources ($Pd_2(dba)_3$)[8b] through oxidative addition as well as from Pd(II) sources ($Pd(TFA)_2$).[8c] However, in the work of Gibson et al.,[8b] 4-chloroacetophenone did not react with phenylboronic acid compared with 80% conversion (Table 2, entry 15) with the present dtbpx system. These workers also showed that the di-*tert*-butylphosphinotolyl palladacycle was effective in the coupling of 4-chlorobenzaldehyde to phenylboronic acid. The available evidence on the presently reported reactivity of Pd-complexes of dtbpx **1** in the carbonylative and Suzuki-Miyaura cross-coupling reactions is consistent with the involvement of a doubly *ortho*-metalated bimetallic Pd(II) complex of **1** formed in situ from $Pd(OAc)_2$.[8a] Nonetheless, Suzuki–Miyaura cross-coupling reactions normally proceed via Pd^0-mediated catalytic cycles raising questions as to the nature of the catalytic cycle. Similar questions were raised on the Heck reaction using related Pd(II) complexes.[8c] Work is currently in progress to identify the formation and involvement of such a species[8a] in the present system.

In summary, we have demonstrated the efficacy of dtbpx **1** in palladium-catalysed carbonylative and Suzuki–Miyaura cross-coupling. A range of electron-rich and electron-deficient aryl as well as vinyl substrates are tolerated in hydroxy-, alkoxy- and aminocarbonylation reactions, while aryl chlorides and triflates are more problematic. The scope of the Suzuki–Miyaura reaction with dtbpx is shown to be quite broad with, in addition to aryl iodides and bromides, activated aryl chlorides readily entering the catalytic cycle; and deactivated aryl chlorides to a lesser extent. Further study into the scope of cross-coupling and the nature of the active catalyst system in the present case is in progress.

Acknowledgements

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References and notes

1. (a) Adjabeng, G.; Brenstrum, T.; Wilson, J.; Frampton, C. S.; Robertson, A. J.; Hillhouse, J.; McNulty, J.; Capretta, A. *Org. Lett.* **2003**, *5*, 953; (b) Ohnmacht, S. A.; Brenstrum, T.; Bleicher, K. H.; McNulty, J.; Capretta, A. *Tetrahedron Lett.* **2004**, *45*, 5661; (c) Adjabeng, G.; Brenstrum, T.; Frampton, C. S.; Robertson, A. J.; Hillhouse, J.; McNulty, J.; Capretta, A. *J. Org. Chem.* **2004**, *69*, 5082; (d) Brenstrum, T.; Gerritsma, D. A.; Adjabeng, G.; Frampton, C. S.; Robertson, A. J.; Hillhouse, J.; McNulty, J.; Capretta, A. *J. Org. Chem.* **2004**, *69*, 5082; (e) Brenstrum, T.; Clattenburg, J.; Britten, J.; Zavorines, S.; Dyck, J.; Robertson, A. J.; McNulty, J.; Capretta, A. *Org. Lett.* **2006**, *8*, 103.
2. (a) McNulty, J.; Capretta, A.; Wilson, J.; Dyck, J.; Adjabeng, G.; Robertson, A. J. *Chem. Commun.* **2002**, 1986; (b) Gerritsma, D. A.; Robertson, A. J.; McNulty, J.; Capretta, A. *Tetrahedron Lett.* **2004**, *45*, 7629–7631; (c) McNulty, J.; Cheekoori, S.; Nair, J. J.; Larichev, V.; Capretta, A.; Robertson, A. J. *Tetrahedron Lett.* **2005**, *46*, 3641; (d) McNulty, J.; Nair, J. J.; Cheekoori, S.; Larichev, V.; Capretta, A.; Robertson, A. J. *Chem. Eur. J.* **2006**, *12*, 9314; (e) McNulty, J.; Cheekoori, S.; Bender, T. P.; Coggan, J. A. *Eur. J. Org. Chem.* **2007**, *9*, 1423; (f) McNulty, J.; Nair, J. J.; Robertson, A. J. *Org. Lett.* **2007**, *9*, 4575.
3. (a) Wolfe, J. P.; Singer, R. A.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9550; (b) Wolfe, J. P.; Tomori, H.; Sadighi, J. P.; Yin, J. J.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1158; (c) Streiter, E. R.; Blackmond, D. G.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 13978; (d) Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020; (e) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **1998**, *37*, 3387; (f) Littke, A. F.; Fu, G. C. *J. Org. Chem.* **1999**, *64*, 10; (g) Hartwig, J. F.; Kawatsura, M.; Hauck, S. I.; Shaughnessy, K. H.; Alcazar-Roman, L. M. *J. Org. Chem.* **1999**, *64*, 5575; (h) Nishiyama, M.; Yamamoto, T.; Koie, Y. *Tetrahedron. Lett.* **1998**, *39*, 617; (i) Leadbeater, N. E. *Chem. Commun.* **2005**, 2881; (j) Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **1996**, *61*, 9550; (k) Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1144; (l) Old, D. W.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 9722; (m) Huang, X.; Anderson, K. W.; Zim, D.; Jiang, L.; Klupers, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 6653; (n) Aranyos, A.; Old, D. W.; Kiyomori, A.; Wolfe, J. P.; Sadighi, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 4369; (o) Martin, R.; Buchwald, S. L. *Acc. Chem. Res.* **2008**, *41*, 1461; (p) Fu, G. C. *Acc. Chem. Res.* **2008**, *41*, 1555; (q) Billingsley, K.; Buchwald, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 3358.
4. (a) Portnoy, M.; Milstein, D. *Organometallics* **1993**, *12*, 1665; (b) Hills, I. D.; Netherton, M. R.; Fu, G. C. *Angew. Chem., Int. Ed.* **2003**, *42*, 5749; (c) Galardon, E.; Ramdeehul, S.; Brown, J. M.; Cowley, A.; Hii, K.; Jutand, A. *Angew. Chem., Int. Ed.* **2002**, *41*, 1760; (d) Tschoerner, M.; Pregosin, P. S.; Albinati, A. *Organometallics* **1999**, *18*, 670; Alcazar-Roman, L. M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 12905; (e) Clarke, M. L.; Heydt, M. *Organometallics* **2005**, *24*, 6475.
5. (a) Meerwin, R. K.; Schnabel, R. C.; Koola, J. D.; Roddick, D. M. *Organometallics* **1992**, *11*, 2972; (b) Brown, J. M.; Guiry, P. J. *Inorg. Chim. Acta* **1994**, *220*, 249; (c) Mann, G.; Shelby, Q.; Roy, A. H.; Hartwig, J. F. *Organometallics* **2003**, *22*, 2775; (d) Culkin, D. A.; Hartwig, J. F. *Organometallics* **2004**, *23*, 3398.
6. (a) Eastham, G. R.; Tooze, R. P.; Kilner, M.; Foster, D. F.; Cole-Hamilton, D. J. *J. Chem. Soc., Dalton Trans* **2002**, 1613; (b) Jimenez-Rodriguez, C.; Foster, D. F.; Eastham, G. R.; Cole-Hamilton, D. J. *Chem. Commun* **2004**, 1720; (c) Rucklidge, A. J.; Eastham, G. R.; Cole-Hamilton, D. J. Int. Pat, WO2004050599, 2004; (d) Rucklidge, A. J.; Morris, G. E.; Slawin, A. M. Z.; Cole-Hamilton, D. J. *Helv. Chim. Acta* **2006**, *89*, 1783; (e) Jimenez-Rodriguez, C.; Eastham, G. R.; Cole-Hamilton, D. J. *Inorg. Chem. Commun.* **2005**, *8*, 878; (f) Ooka, H.; Inoue, T.; Itsuno, S.; Tanaka, M. *Chem. Commun.* **2005**, 1173.
7. Jimenez-Rodriguez, C.; Pogorzelec, P. J.; Eastham, G. R.; Slawin, A. M. Z.; Cole-Hamilton, D. J. *J. Chem. Soc., Dalton Trans.* **2007**, 4160.
8. (a) Clegg, W.; Eastham, G. R.; Elsegood, M. R. J.; Tooze, R. P.; Wang, X. L.; Whiston, K. W. *Chem. Commun.* **1999**, 1877; (b) Gibson, S.; Foster, D. F.; Eastham, G. R.; Tooze, R. P.; Cole-Hamilton, D. J. *Chem. Commun.* **2001**, 779; (c) Ohff, M.; Ohff, A.; van der Boom, M. E.; Milstein, D. *J. Am. Chem. Soc.* **1997**, *119*, 11687.
9. (a) Tremblay, J. F. Chemical Engineering News, November 17th, 2008, Vol. 86, p. 8; (b) New MMA Technology, European Chemical News, October 30th–November 5th, 2000, p. 20.
10. Eastham, G. R.; Heaton, B. T.; Iggo, J. A.; Tooze, R. P.; Whyman, R.; Zacchini, S. *Chem. Commun.* **2000**, 609.
11. Jimenez-Rodriguez, C.; Eastham, G. R.; Cole-Hamilton, D. J. *J. Chem. Soc., Dalton Trans.* **2005**, 1826.
12. Morris, D. J.; Docherty, G.; Woodward, G.; Wills, M. *Tetrahedron Lett.* **2007**, *48*, 949.
13. (a) Beller, M.; Magerlein, W.; Indolese, A. F.; Fischer, C. *Synthesis* **2001**, 1098; (b) Magerlein, W.; Indolese, A. F.; Beller, M. *Angew. Chem., Int. Ed.* **2001**, *40*, 2856; (c) Magerlein, W.; Indolese, A. F.; Beller, M. *J. Organomet. Chem.* **2002**, *641*, 330.
14. *Sample procedure for carbonylative cross coupling*: Synthesis of butyl 4-methylbenzoate (Table 1, entry 1). 4-Iodotoluene (100.0 mg, 0.459 mmol), palladium (II) acetate (2.6 mg, 0.0114 mmol) and bis(di-*tert*-butylphosphino)-*o*-xylene (9.0 mg, 0.0229 mmol) were added consecutively to a steel reactor in a glove box under nitrogen, followed by 1 ml dry DMF (2 ml/mmol), butanol (84 μl, 0.917 mmol) and Cs_2CO_3 (22.4 mg, 0.688 mmol). The reactor was then sealed, removed from the glove box and connected via Swage line to a mini cylinder of CO. After three purges, the reactor was pressurised to 40 psi, submerged in an oil bath set at 80 °C and stirred via an internal magnet. After ~8 h, TLC (10% EtOAc/Hex) indicated the reaction to be complete. The mixture was diluted with 2 ml saturated NH_4Cl, extracted with ethyl acetate (3 × 5 ml), the combined organic fractions dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum into an amorphous residue which was chromatographed (10% EtOAc/Hex) on silica to give butyl 4-methylbenzoate in 95% yield. ^{1}H NMR ($CDCl_3$, 200 MHz); δ(ppm): 7.93 (2H, d, *J* = 8.0 Hz), 7.22 (2H, d, *J* = 8.0 Hz), 4.30 (2H, t, *J* = 6.0, 6.0 Hz), 2.40 (3H, s), 1.74 (2H, m), 1.47 (2H, m), 0.97 (3H, t, *J* = 7.3, 7.3 Hz). ^{13}C NMR ($CDCl_3$, 50 MHz); δ (ppm): 166.8 (s), 143.4 (s), 129.6 (2 × d), 129.0 (2 × d), 127.8 (s), 64.6 (t), 30.8 (t), 21.6 (q), 19.3 (t), 13.8 (q). CIMS 70 eV, *m/z* (rel. int.): 193 $[M+1]^+$ (20), 136 (46), 119 (100), 91 (30).
15. *General procedure for Suzuki–Miyaura cross-coupling reaction*: The aryl halide (1 mmol), boronic acid (1.2 mmol), palladium acetate (0.02 mmol), bis(di-*tert*-butylphosphino)-*o*-ylene (0.02 mmol) and K_3PO_4-monohydrate (2 mmol) were weighed into a reaction vial in a glove box under nitrogen. The vial was then capped, removed from the glove box and flushed with argon (3 cycles). Dry degassed THF (1.5 ml) was introduced and the mixture stirred under argon at rt for 48 h. After this time, the solution was diluted with 3 ml saturated NH_4Cl and extracted with 5 ml ethyl acetate (3 times), the combined organic layers were dried (Na_2SO_4), filtered and solvent removed under vacuum. The biaryl products were purified by flash chromatography (10% EtOAc/hexane) on silica gel.