Homogeneous Catalysis

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Palladium-Catalyzed Amination of Aryl Mesylates**

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Palladium-catalyzed $C_{(sp_2)}$–N bond-forming reactions have evolved into a highly versatile and synthetically attractive transformation in targeting pharmaceutically useful intermediates.[1] Since the discovery of the first catalytic amination method,[2] efforts have been made toward increasing the reaction efficacy.[3] Notable ligands, such as tBu$_3$P,[4] Beller and co-workers' PAP,[5] Buchwald and co-workers' biaryl phosphines,[6] Hartwig and co-workers' Q-Phos,[7] and Verkade and co-workers' amino phosphine[8] (Figure 1) provide excellent catalytic activity in the cross-coupling of aryl halides (especially aryl chlorides).[9,10] X-Phos, in particular, is effective in the handling of aryl tosylate/benzenesulfonate substrates in coupling reactions.[11]

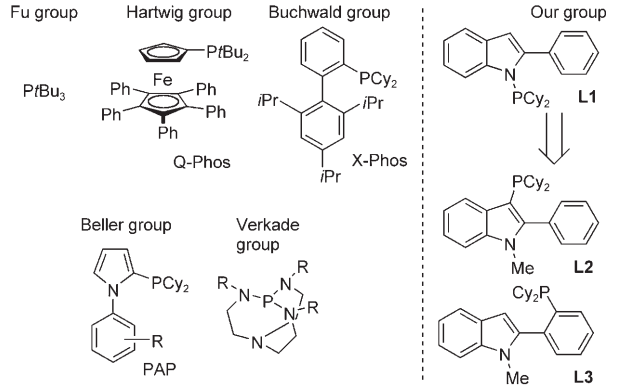


Figure 1. Recent developments on effective phosphine ligands. Present study depicted on the right.

Aside from the use of aryl tosylates (ArOTs) and benzenesulfonates as electrophiles in palladium-catalyzed C–C and C–X bond-forming reactions,[12] aryl mesylates (ArOMs) have also seen some use in cross-coupling processes.[13] To our knowledge, they have never been applied to amination reactions. Aryl mesylates can be easily accessed from phenols and, owing to their lower molecular mass, cross-coupling reactions utilizing these reagents have the advantage of higher atom economy than those employing the corresponding aryl tosylates.[14] However, their relatively inert leaving-group activity, with respect to tosylates, has limited their application in coupling reactions (Figure 2).[15]

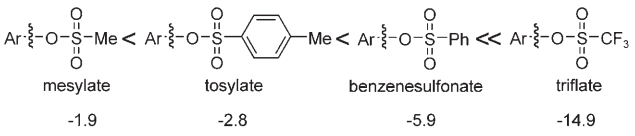
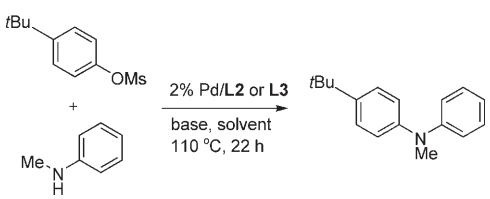


Figure 2. A comparison on the leaving-group activity of commonly used sulfonate groups, based on the pK_a value of their conjugate acids (given below names).

We recently reported the synthesis and application of an amino phosphine ligand **L1** (with phosphorus bound at N; Figure 1), which showed excellent catalytic activity as a ligand for palladium-catalyzed C–C bond-forming reactions.[16] The versatile 2-arylindole scaffold can be simply synthesized and diversified by Fischer indolization of acetophenones and arylhydrazines. However, ligand **L1** may undergo hydrolysis under harsh reaction conditions. We therefore proceeded to convert the amino phosphine ligand **L1** into a class of phosphine derivatives **L2**–**L3** (in which phosphorus is bound at C), without significant change to the ligand skeleton (Figure 1).

Precedent for palladium-catalyzed cross-coupling of aryl mesylates is limited, with only one publication to date.[17] This area remains highly challenging as mesylates are regarded as the least active sulfonate leaving group. Therefore, there is still a need to develop a general palladium catalyst for coupling unactivated aryl mesylate substrates. We disclose herein a highly active palladium indolyl phosphine catalyst system, which allows the successful amination of aryl mesylates for the first time. Notably, this reaction can be performed in aqueous medium without diminishing the product yields.

We initially examined the feasibility of the amination of unactivated aryl mesylate compounds [Eq. (1)].[18] The amination reaction incorporating indolyl ligand **L3** provided excellent conversion while **L2** was apparently ineffective.



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These results indicated the great diversity of potential reactions to which this ligand scaffold could be applied. We next investigated the other reaction parameters, such as base and solvent effects.[19] K_2CO_3, K_3PO_4, and CsF gave good yields of the desired product whereas Cs_2CO_3 and Na_2CO_3 afforded the product in low yields. When NaO*t*Bu was employed as a base in the amination reaction, a significant amount of phenolic side product was detected (as indicated by GC-MS analysis). As a solvent, *t*BuOH was found to give the best results. DMF and toluene afforded the product only in moderate yield.

The scope of the amination reaction with regard to aryl mesylates and amines was next investigated (Table 1). The coupling of an unactivated aryl mesylate with *N*-methylaniline was performed in good yield with 0.5 mol% of Pd (Table 1; entry 2). Sterically hindered aniline and diphenylamine were transformed to their corresponding product, also in good yields (Table 1; entries 3,4). Secondary cyclic and acyclic amines were effective coupling partners (Table 1; entries 5–7). *p*-Cyanophenyl mesylate was found to be a feasible substrate (Table 1; entry 10), as was the deactivated *p*-anisyl mesylate (Table 1; entry 11). Conversely, on application of the *p*-chlorophenyl mesylate substrate a highly selective aryl chloride coupling took place (Table 1; entry 12).

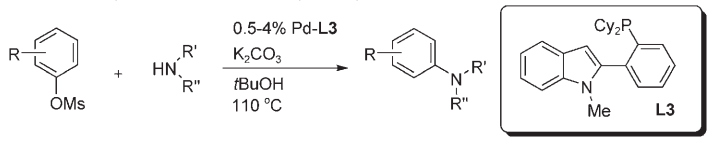
To further explore the wide-ranging effectiveness of the {Pd/**L3**} catalytic system, the cross-coupling of aryl mesylates with a range of nitrogen heterocycles was investigated (Table 2). Indole and substituted indoles were N-arylated smoothly in good yields (Table 2; entries 1–4). Pyrrole and carbazole were also effective substrates (Table 2; entries 5,6). Furthermore, keto and methyl ester groups were shown to be stable under these reaction conditions (Table 2; entries 7,8).

The amination of aryl mesylates has been shown to proceed under solvent-free reaction conditions with no detrimental effects (Table 3). Moreover, kinetic studies showed that the rate of reaction is slightly higher than when performed in organic solvents, presumably owing to the higher concentration of reactants. Anilines, indole, and pyrrole were all successfully coupled with aryl mesylates to generate the corresponding products in good to excellent yields (Table 3).

Recently, much attention has been given to aqueous transition-metal-catalyzed reactions.[20] Aryl halides are reported to be applicable substrates for cross-coupling in aqueous media. However, sulfonate couplings under aqueous conditions are more challenging, as they are known to be easily decomposed through alkaline hydrolysis, to form the phenolic side products. Pleasingly, the {Pd/**L3**} catalyst system can effect the amination of aryl mesylate even in water (Table 4). Under unoptimized reaction conditions for this aqueous catalysis, various anilines and indole were successfully coupled with aryl mesylates to afford the corresponding products in good yields.

To afford a better structural insight into the new palladium catalyst system, we attempted to prepare the complex from the indolyl phosphine ligand **L3**. Palladium complex **4** was synthesized from $Pd(OAc)_2$ with **L3** under basic conditions at room temperature [Eq. (2)]. Single crystals of **4** were grown from a CH_2Cl_2 solution lay-

Table 1: Palladium-catalyzed amination of aryl mesylates.[a]



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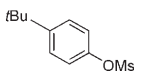
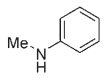
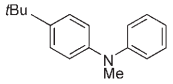
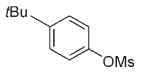
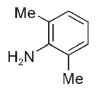
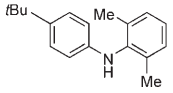
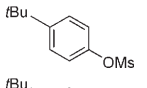
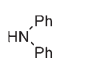
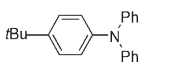
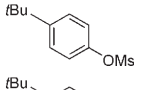
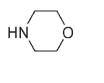
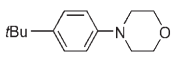
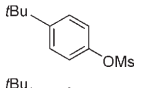
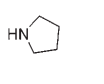
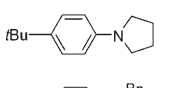
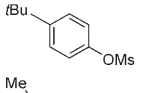
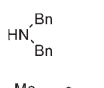
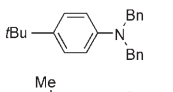
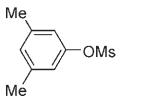
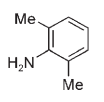
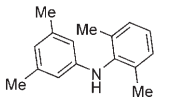
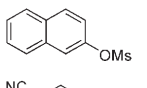
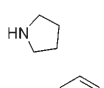
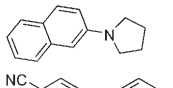
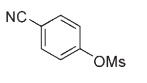
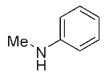
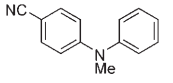
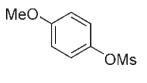
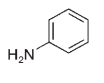
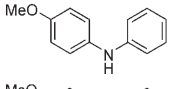
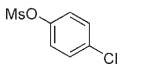
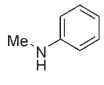
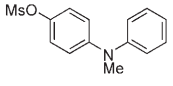
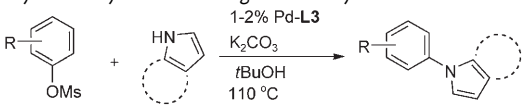
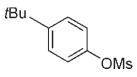
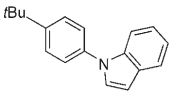
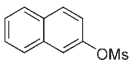
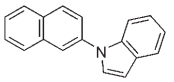
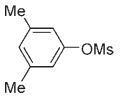
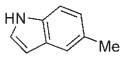
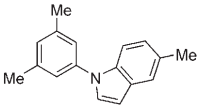
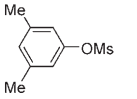
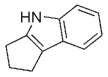
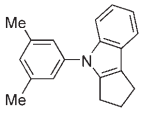
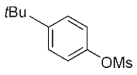
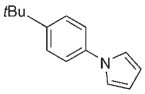
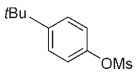
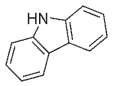
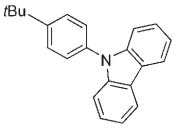
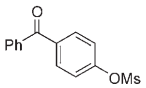
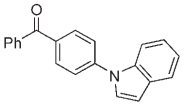
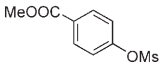
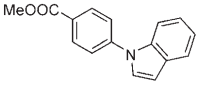
1				2	4	93
2				0.5	24	96
3				1	24	90
4				4	24	80
5				1	18	90
6[c]				2	24	93
7[c]				4	24	81
8				1	24	87
9				2	24	85
10				1	24	82
11				2	24	78
12[d]				1	24	89

[a] Reaction conditions: ArOMs (1.0 mmol), amine (1.5 mmol), K_2CO_3 (2.5 mmol), $Pd(OAc)_2$/**L3** (mol% as indicated), $PhB(OH)_2$ (0.04 mmol) *t*BuOH (4.0 mL), at 110°C under N_2 for the indicated time (see Supporting Information for experimental details). [b] Yield of isolated product. [c] K_3PO_4 was used in place of K_2CO_3. [d] ArOMs (1.5 mmol), amine (1.0 mmol).

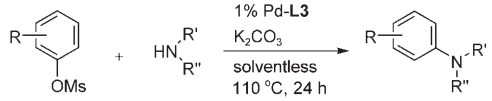
Table 2: Palladium-catalyzed N-arylation of nitrogen heterocycles.[a]

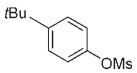
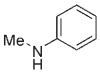
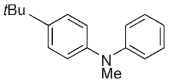
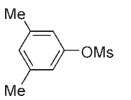
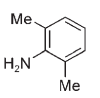
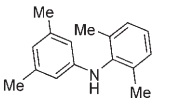
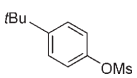
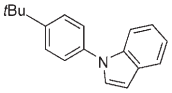
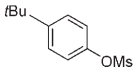
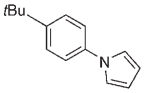


Entry	ArOMs	N-heterocycle	Product	Pd [mol%]	Time [h]	Yield [%][b]
1				1	24	93
2				1	20	89
3				1	24	96
4				2	24	84
5				1	24	80
6[c]				2	24	98
7				1	24	88
8				1	24	79

[a] Reaction conditions: ArOMs (1.0 mmol), *N*-heterocycle (1.5 mmol), K_2CO_3 (2.5 mmol), $Pd(OAc)_2$/**L3** (mol% as indicated), $PhB(OH)_2$ (0.04 mmol) *t*BuOH (4.0 mL), at 110°C under N_2 for indicated period of time. [b] Yield of isolated product. [c] ArOMs (1.5 mmol), carbazole (1.0 mmol) were used.

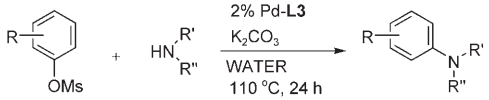
Table 3: Palladium-catalyzed solventless amination of aryl mesylates.[a]

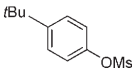


Entry	ArOMs	Amine	Product	Yield [%][b]
1				93
2				97
3				91
4				83

[a] Reaction conditions: ArOMs (1.0 mmol), amine (5.0 mmol), K_2CO_3 (2.5 mmol), $Pd(OAc)_2$/**L3** (1 mol%), $PhB(OH)_2$ (0.04 mmol) in solvent-free conditions at 110°C under N_2 (reaction times are unoptimized). [b] Yield of isolated product.

Table 4: Pd-catalyzed amination of aryl mesylates in aqueous medium.[a]

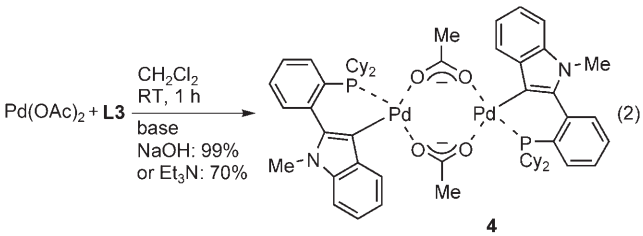


Entry	ArOMs	Amine	Product	Yield [%][b]
1				90
2				77
3				89
4				86
5				75

[a] Reaction conditions: ArOMs (1.0 mmol), amine (2.0 mmol), K_2CO_3 (2.5 mmol), $Pd(OAc)_2$/**L3** (2 mol%, unoptimized), $PhB(OH)_2$ (0.04 mmol), water (3.0 mL) at 110°C under N_2 (Note: reaction parameters are unoptimized). [b] Yield of isolated product.

ered with hexane at room temperature. The X-ray crystallographic data revealed that **4** is a dimeric complex with two acetate bridging groups (Figure 3). The six-membered cyclometallated ring is puckered and the bite angle of C10-Pd1-P1 is 82.01(10)°. The bond length on the palladacyclic Pd–C_σ bond Pd1-C10 is 1.986(3) Å, (Figure 3) similar to other palladacycles [21] but is significantly shorter than Pd–C_{ipso} coordination (c.f. 2.191(3) Å).[22]

In summary, we have succeeded in showing the first amination of aryl mesylates. The new ligand **L3** in combination with the precatalyst $Pd(OAc)_2$ can is applicable to a range of aryl mesylate substrates as well as amine nucleophiles including anilines, aliphatic amines, indole, pyrrole, and carbazole. Notably, we also showed the first examples of aryl mesylate coupling that can be performed under aqueous basic medium with no detrimental effects. Further expanding the scope and detail of the reaction, kinetic



4

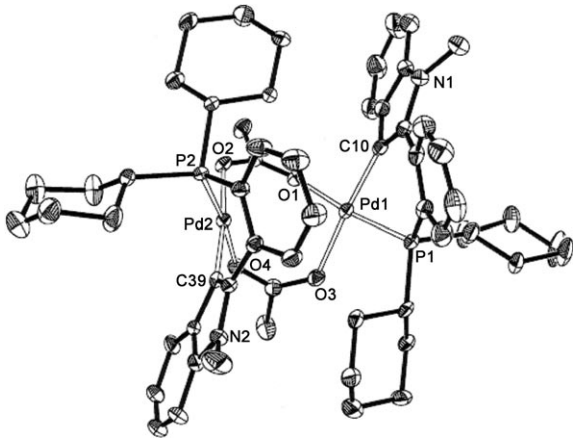


Figure 3. ORTEP representation of dimeric complex **4** (30% probability ellipsoids). Hydrogen atoms have been omitted for clarity. Selected bond distances [Å] and angles [°]: Pd1–C10 1.986(3), Pd1–O3 2.123(3), Pd1–O1 2.138(2), Pd1–P1 2.2108(10), Pd2–C39 2.005(3), Pd2–O4 2.117(2), Pd2–O2 2.124(2), Pd2–P2 2.2036(7), C10–Pd1–O3 173.07(11), C10–Pd1–O1 92.92(12), O3–Pd1–O1 86.43(10), C10–Pd1–P1 82.01(10).

studies on the ligand skeleton (with a view to its catalytic activity) are underway.

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[1] a) A. O. King, N. Yasuda in *Organometallics in Process Chemistry* (Ed.: R. D. Larsen), Springer, Berlin, **2004**, pp. 205 – 246, and references therein; b) S. A. Lawrence, *Amines, Synthesis Properties, and Application*; Cambridge University Press, Cambridge, **2004**.

[2] For early report on catalytic amination, see: a) M. Kosugi, M. Kameyama, T. Migita, *Chem. Lett.* **1983**, 927. For early reports on Buchwald-Hartwig amination, see: b) A. S. Guram, R. A. Rennels, S. L. Buchwald, *Angew. Chem.* **1995**, *107*, 1456; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1348; c) J. Louie, J. F. Hartwig, *Tetrahedron Lett.* **1995**, *36*, 3609.

[3] For selected reviews: see: a) A. R. Muci, S. L. Buchwald, *Top. Curr. Chem.* **2002**, *219*, 131; b) J. F. Hartwig in *Handbook of Organopalladium Chemistry for Organic Synthesis* (Ed.: E. Negishi), Wiley-Interscience, New York, **2002**; c) L. Jiang, S. L. Buchwald in *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed. (Eds.: A. de Meijere, F. Diederich), Wiley, Weinheim, **2004**.

[4] a) M. Nishiyama, T. Yamamoto, Y. Koie, *Tetrahedron Lett.* **1998**, *39*, 617; b) M. R. Netherton, G. C. Fu, *Org. Lett.* **2001**, *3*, 4295.

[5] F. Rataboul, A. Zapf, R. Jackstell, S. Harkal, T. Riermeier, A. Monsees, U. Dingerdissen, M. Beller, *Chem. Eur. J.* **2004**, *10*, 2983.

[6] J. P. Wolfe, H. Tomori, J. P. Sadighi, J. Yin, S. L. Buchwald, *J. Org. Chem.* **2000**, *65*, 1158.

[7] N. Kataoka, Q. Shelby, J. P. Stambuli, J. F. Hartwig, *J. Org. Chem.* **2002**, *67*, 5553.

[8] a) S. Urgaonkar, J.-H. Xu, J. G. Verkade, *J. Org. Chem.* **2003**, *68*, 8416; b) C. V. Reddy, J. V. Kingston, J. G. Verkade, *J. Org. Chem.* **2008**, *73*, ASAP.

[9] For a review on aryl chloride couplings, see: A. F. Littke, G. C. Fu, *Angew. Chem.* **2002**, *114*, 4350; *Angew. Chem. Int. Ed.* **2002**, *41*, 4176.

[10] For recent review on the development and application of bulky electron-rich phosphines for palladium-catalyzed cross-coupling reaction of aryl halides and sulfonates, see: A. Zapf, M. Beller, *Chem. Commun.* **2005**, 431 and references therein.

[11] For Suzuki coupling, see: a) H. N. Nguyen, X. Huang, S. L. Buchwald, *J. Am. Chem. Soc.* **2003**, *125*, 11818; for Buchwald–Hartwig C–N bond coupling, see: b) X. Huang, K. W. Anderson, D. Zim, L. Jiang, A. Klapars, S. L. Buchwald, *J. Am. Chem. Soc.* **2003**, *125*, 6653; for Sonogashira coupling using activated ArOTs, see: c) D. Gelman, S. L. Buchwald, *Angew. Chem.* **2003**, *115*, 6175; *Angew. Chem. Int. Ed.* **2003**, *42*, 5993;.

[12] For ArOTs substrates, for Kumada couplings, see: a) A. H. Roy, J. F. Hartwig, *J. Am. Chem. Soc.* **2003**, *125*, 8704; b) M. E. Limmert, A. H. Roy, J. F. Hartwig, *J. Org. Chem.* **2005**, *70*, 9364; c) L. Ackermann, A. Althammer, *Org. Lett.* **2006**, *8*, 3457; for amination, see d) B. C. Hamann, J. F. Hartwig, *J. Am. Chem. Soc.* **1998**, *120*, 7369; for C–S bond formation (one substrate example), see: e) M. A. Fernández-Rodríguez, Q. Shen, J. F. Hartwig, *J. Am. Chem. Soc.* **2006**, *128*, 2180; for Suzuki coupling, see: f) L. Zhang, T. Meng, J. Wu, *J. Org. Chem.* **2007**, *72*, 9346. For alkenyl OTs substrates, Suzuki coupling, see: g) D. Steinhuebel, J. M. Baxter, M. Palucki, I. W. Davies, *J. Org. Chem.* **2005**, *70*, 10124; for Buchwald-Hartwig amidation, see: h) A. Klapars, K. R. Campos, C.-y. Chen, R. P. Volante, *Org. Lett.* **2005**, *7*, 1185; for Heck coupling, see: i) A. L. Hansen, T. Skrydstrup, *Org. Lett.* **2005**, *7*, 5585; j) A. L. Hansen, J.-P. Ebran, M. Ahlquist, P.-O. Norrby, T. Skrydstrup, *Angew. Chem.* **2006**, *118*, 3427; *Angew. Chem. Int. Ed.* **2006**, *45*, 3349.

[13] Aryl mesylate couplings have rarely been studied, only nickel-catalyzed C–C bond couplings have been reported, see: a) V. Percec, G. M. Golding, J. Smidrkal, O. Weichold, *J. Org. Chem.* **2004**, *69*, 3447; b) V. Percec, J.-Y. Bae, D. H. Hill, *J. Org. Chem.* **1995**, *60*, 1060; c) V. Percec, J.-Y. Bae, D. H. Hill, *J. Org. Chem.* **1995**, *60*, 1066; d) V. Percec, J.-Y. Bae, D. H. Hill, *J. Org. Chem.* **1995**, *60*, 6895; e) M. Ueda, A. Saitoh, S. Oh-tani, N. Miyaura, *Tetrahedron* **1998**, *54*, 13079; f) Y. Kobayashi, R. Mizojiri, *Tetrahedron Lett.* **1996**, *37*, 8531.

[14] For descriptions of atom economy, see: B. M. Trost, *Angew. Chem.* **1995**, *107*, 285; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 259.

[15] Usually the lower the pK_a value of the conjugate acid, the better the leaving group. (c.f. methanesulfonic acid, p$K_a = -1.9$; *p*-toluenesulfonic acid, p$K_a = -2.8$; benzenesulfonic acid, p$K_a = -5.9$; triflic acid, p$K_a = -14.9$). *Ionization Constants of Organic Acids in Solution* (Eds.: E. P. Serjeant, B. Dempsey), Pergamon, Oxford, UK, **1979** (IUPAC Chemical Data Series No. 23).

[16] C. M. So, C. P. Lau, F. Y. Kwong, *Org. Lett.* **2007**, *9*, 2795.

[17] R. H. Munday, J. R. Martinelli, S. L. Buchwald, *J. Am. Chem. Soc.* **2008**, *130*, 2754.

[18] For the purpose of comparison, in addition to ArOMs, we investigated the amination of ArOTs. Under the same reaction conditions as in Equation (1), using 4-*t*BuC_6H_4OTs instead of the corresponding mesylate, the reaction proceeded faster and

ran to completion within 3 h, giving the isolated product in > 95 % yield.
[19] See Supporting Information for initial screening details.
[20] a) C. J. Li, T. H. Chan, *Organic Reactions in Aqueous Media*, Wiley, New York, **1997**; b) *Aqueous-Phase Organometallic Catalysis* (Eds.: B. Cornils, W. A. Herrmann), Wiley-VCH, Weinheim, **1998**; c) U. M. Lindström, *Chem. Rev.* **2002**, *102*, 2751.
[21] For selected examples, see: A. A. Danopoulos, N. Tsoureas, S. A. Macgregor, C. Smith, *Organometallics* **2007**, *26*, 253.
[22] a) J. Cámpora, E. Gutierrez Puebla, J. A. Lopez, A. Monge, P. Palma, D. Del Rio, E. Carmona, *Angew. Chem.* **2001**, *113*, 3753; *Angew. Chem. Int. Ed.* **2001**, *40*, 3641; b) T. E. Barder, S. D. Walker, J. R. Martinelli, S. L. Buchwald, *J. Am. Chem. Soc.* **2005**, *127*, 4685. For a seminal work on MAP-type ligands, see: c) P. Koçovský, S. Vyskoèil, I. Cisaøová, J. Sejbal, I. Tislerova, M. Smrcina, G. C. Lloyd-Jones, S. C. Stephen, C. P. Butts, M. Murray, V. Langer, *J. Am. Chem. Soc.* **1999**, *121*, 7714. For Pd-$C_{\eta^3(arene)}$coordination, see: d) U. Christmann, D. A. Pantazis, J. Benet-Buchholz, J. E. McGrady, F. Maseras, R. Vilar, *J. Am. Chem. Soc.* **2006**, *128*, 6376.

