DOI: 10.1002/chem.201002354

Palladium-Catalyzed Direct Arylation of Heteroarenes with Aryl Mesylates

Chau Ming So, Chak Po Lau, and Fuk Yee Kwong*[a]

Dedicated to Professor Albert S. C. Chan on the occasion of his 60th birthday

The palladium-catalyzed cross-coupling repertoire has been successful in modular organic synthesis for connecting two different fragments together through the formation of carbon–carbon and/or carbon–heteroatom bonds.[1] To construct useful biaryl motifs,[2] coupling methods such as Kumada coupling, Negishi coupling, Stille coupling, and Suzuki–Miyaura coupling have been found to be versatile in recent decades.[1] Although these reactions are effective, possible drawbacks still exist in that corresponding organometallic nucleophiles need to be prepared in situ (e.g., Ar–MgCl, Ar–ZnCl) or require isolation prior to the catalysis (e.g., Ar–$B(OH)_2$). Indeed, the assembly and subsequent disposal of stoichiometric organometallic agents are undesirable. Recently, C–H activation and direct arylation of heteroarenes have received considerable attention. These new methodologies serve as attractive alternatives to conventional coupling protocols in terms of better atom economy, environmental friendliness and streamlined chemical synthesis.[3,4]

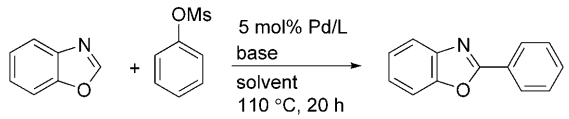
Reports by Fagnou et al., Itami et al., Lautens et al., Miura et al., Sames et al., Sanford et al. and others on the arylation of heteroarenes were achieved by using aryl iodides and bromides.[5] In fact, direct arylation by using non-activated aryl chlorides remains less explored.[5r,6] Stoichiometric amounts of copper salt additives are necessary to facilitate some heterocycle arylations.[7] Recently, Daugulis et al. reported a general protocol for the direct arylation of heteroarenes with ArCl by using a Pd/*n*BuP$(Ad)_2$ catalytic system at 125 °C.[8] Apart from aryl halides, it is worth developing methods for phenolic compounds (pseudo-halides) to serve as electrophiles. In fact, these compounds usually offer different or unique substituted groups in the aromatic ring, in which the corresponding aryl halides are not commonly available or require additional synthetic steps to manipulate the pattern of complementary substitution. Although it possesses unique scope, the direct arylation of heteroaromatics with aryl sulfonates has attracted less attention. In most cases, only expensive aryl triflates were used as electrophiles.[9,10] Indeed, aryl tosylates or mesylates are excellent substitution for the corresponding aryl triflates as electrophiles in cross-coupling reactions. Although they have several beneficial features, their superior stability reflects their inferior reactivity in palladium-catalysed coupling processes.[11,12] Consequently, the general palladium-catalysed cross-coupling reactions of aryl tosylates[13] and mesylates[14] with organometallic nucleophiles were only developed very recently. In 2009, Ackermann et al. reported the first palladium-catalyzed direct arylation of heteroarenes with aryl tosylates and two examples of activated aryl mesylates that employed Buchwald's biaryl-type X-Phos/Pd system[15] in the present of sub-stoichiometric amounts of *t*BuCO_2H additive.[16] In fact, the use of aryl mesylates in the coupling reactions is more atom economical than the corresponding aryl tosylates due to their significantly lower molecular weight. Nevertheless, there has been a long-standing problem for applying aryl mesylates in C–H bond functionalisation because they are even more inactive than aryl tosylates in palladium catalysis. This is because the inherent C_{Ar}–OSO_2Me bond strength in aryl mesylate is stronger than that of the corresponding aryl tosylate.[17] Excluding the difficulties of activating the aryl mesylates, we believe that direct arylation by using aryl mesylates is highly favourable, especially given that the reaction conditions do not require extra additives. Herein, we uncover our efforts to establish a general and additive-free palladium-catalyzed direct arylation of benzoxazole and their derivatives with aryl mesylates.

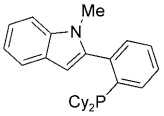
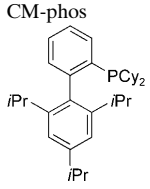
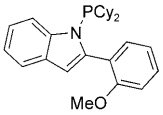
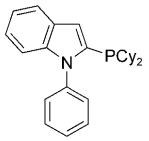
To probe the feasibility of direct arylation of heteroarenes with aryl mesylates, a series of initial screenings were carried out (Table 1). Benzoxazole and electronically neutral phenyl mesylate were used as model substrates, and 5 mol% of $Pd(OAc)_2$ with CM-phos ligand was used as the initial

[a] Dr. C. M. So, Prof. Dr. C. P. Lau, Prof. Dr. F. Y. Kwong
State Key Laboratory of Chirosciences and
Department of Applied Biology and Chemical Technology
The Hong Kong Polytechnic University
Hung Hom, Kowloon, Hong Kong (Hong Kong)
Fax: (+852)-2364-9932
E-mail: bcfyk@inet.polyu.edu.hk

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201002354.

Table 1. Initial screening of direct arylation with non-activated ArOMs.[a]



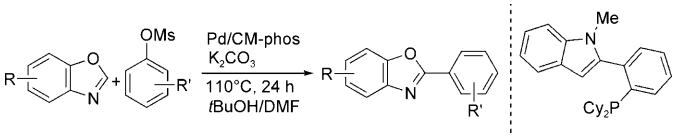
Entry	Solvent	Ligand	Base	Yield[b] [%]
1	*t*BuOH	 CM-phos	K_2CO_3	53
2	DMF	CM-phos	K_2CO_3	45
3	THF	CM-phos	K_2CO_3	3
4	toluene	CM-phos	K_2CO_3	2
5	*t*BuOH/dioxane (1:2)	CM-phos	K_2CO_3	11
6	*t*BuOH/DMF (1:2)	CM-phos	K_2CO_3	86
7	*t*BuOH/DMF (1:2)	CM-phos	KOAc	13
8	*t*BuOH/DMF (1:2)	CM-phos	Na_2CO_3	24
9	*t*BuOH/DMF (1:2)	CM-phos	K_3PO_4	3
10	*t*BuOH/DMF (1:2)	 XPhos	K_2CO_3	25
11	*t*BuOH/DMF (1:2)	 L1		0
12	*t*BuOH/DMF (1:2)	 CataCXium A	K_2CO_3	2
13	*t*BuOH/DMF (1:2)	 CataCXium PInCy	K_2CO_3	2
14[c]	*t*BuOH/DMF (1:2)	CM-phos	K_2CO_3	0
15	*t*BuOH/DMF (1:2)	–	K_2CO_3	0

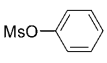
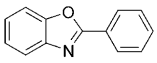
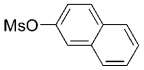
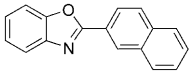
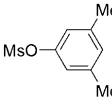
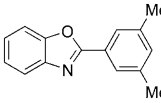
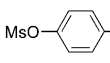
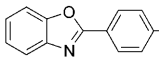
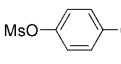
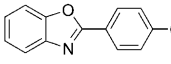
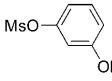
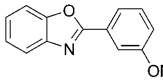
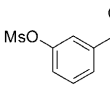
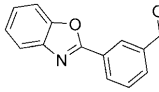
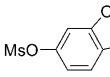
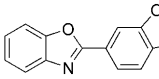
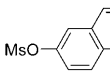
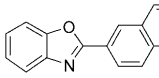
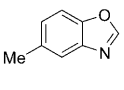
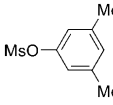
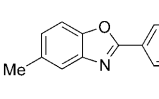
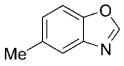
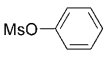
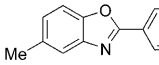
[a] Reaction conditions: benzoxazole (0.5 mmol), ArOMs (1.0 mmol), base (2.0 mmol), $Pd(OAc)_2$ (5 mol%), Pd/L = 1:4, solvent (total volume = 3.0 mL), at 110 °C under N_2 for 20 h. [b] Isolated yields. [c] Performed in the absence of $Pd(OAc)_2$ salt.

catalytic system for our prototypical investigations. Of the commonly used organic solvents examined, *t*BuOH and DMF gave moderate yields whereas THF and toluene provided only poor conversions (Table 1, entries 1–4). Gratifyingly, *t*BuOH/DMF solvent mixtures afforded the best yield for the direct arylation (Table 1, entry 6). Of the commonly used inorganic bases, K_2CO_3 was found to be the most suitable base for the direct arylation reaction (Table 1, entry 6). Na_2CO_3 and KOAc were found to be inferior in the reaction (Table 1, entries 7, 8). If K_3PO_4 was used in this reaction, phenolic side products (from the hydrolysis of sulfonate) were observed and only poor product yield could be obtained (Table 1, entry 9). The Pd/XPhos system gave a poor yield in the direct arylation with aryl mesylate (Table 1, entry 10). Beller's ligands CataCXium® A[18] and CataCXium® PInCy[19] and our previously reported amino-phosphine L1[20] were inferior (Table 1, entries 11–13). Control experiment revealed that no reactions were observed either in the absence of palladium salt or without the supporting phosphine ligand (Table 1, entries 14, 15).

To test the effectiveness of the Pd/CM-phos catalytic system, the direct arylation of benzoxazole with a range of aryl mesylates was examined by using the preliminary optimized reaction conditions (Table 2). Electronically neutral aryl mesylates were effective substrates for the direct arylation of benzoxazole and gave the corresponding products in good to excellent yields (Table 2, entries 1–4). It is worth

Table 2. Direct arylation of benzoxazole with aryl mesylates.[a]

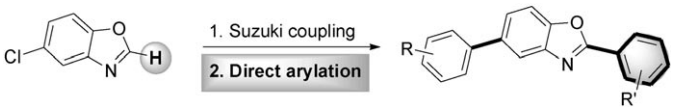


Entry	Heteroarene	ArOMs	Product	Yield[b] [%]
1				86
2				83
3				92
4				81
5				46
6				82
7[c]				51
8				41
9				69
10				82
11				82

[a] Reaction conditions: benzoxazole (0.5 mmol), ArOMs (1.0 mmol), K_2CO_3 (2.0 mmol), $Pd(OAc)_2$ (5 mol%), Pd/CM-phos = 1:4, *t*BuOH (1.0 mL)/DMF (2.0 mL), at 110 °C under N_2 for 24 h (reaction times were not optimized for each substrate). [b] Isolated yields. [c] 100 °C under N_2.

noting that the use of common additives for the C–H activation reaction, such as copper salts and organic acids, to improve the product yield are not necessary in our catalytic system. *m*-Methoxyphenyl mesylate was also an effective substrate for the direct arylation of benzoxazole, whereas the more electron-rich *p*-methoxyphenyl mesylate was converted to the desired product in moderate yield (Table 2, entries 5, 6). Thus, deactivated aryl mesylates are more demanding substrates for this direct arylation reaction.[21] Functionalized aryl mesylates and heteroaryl mesylates, such as quinolyl mesylate, were smoothly transformed into their desired products (Table 2, entries 7–9).[22] Furthermore, substituted benzoxazoles were converted to the products in good yields (Table 2, entries 10, 11).

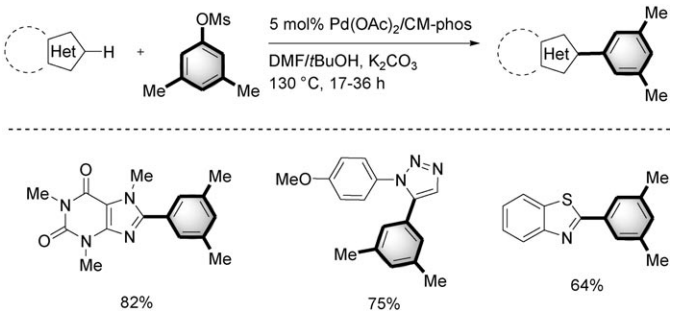
The selective stepwise arylation at the C2 and C5 positions of the benzoxazoles with different aryl rings can be applied to synthesize a series of important biological active compounds.[23] To demonstrate a possible pathway to synthesise these compounds, stepwise regioselective arylation of 5-chlorobenzoxazole has been attempted by using Pd/CM-phos-catalyzed Suzuki coupling at C5 of 5-chlorobenzoxazole with arylboronic acids followed by regioselective C2 direct arylation of the benzoxazole derivative with aryl mesylates (Scheme 1). 5-Chlorobenzoxazole was selectively coupled with arylboronic acids at the C5 chloro-position. The Suzuki-coupled products then underwent selective direct arylation with phenyl or 3,5-dimethylphenyl mesylates at the C2 position in good yields (Scheme 2).



Scheme 1. Stepwise arylation of 5-chlorobenzoxazole.

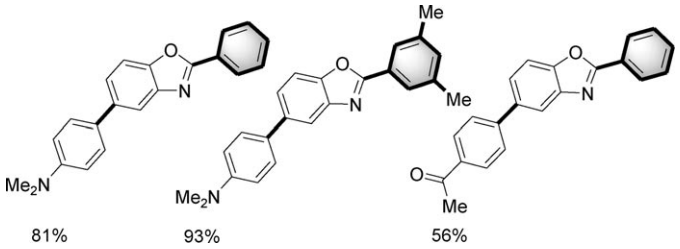
Apart from benzoxazoles, benzothiazoles, 1,2,3-triazoles and xanthines (e.g., caffeine, theophyline and theobromine) are all possess a series of biological properties.[24] For example, heteroaryl-substituted xanthines are highly potent and selective antagonists for human A_{2B} adenosine receptors[25] and highly effective luminescence/fluorescent frameworks for cancer imaging.[26] Additionally, benzothiazoles are widely used as Ca^{2+} channel antagonists and antitumor agents,[27] and 1,2,3-triazole moieties are emerging as highly useful and powerful pharmacophores.[28]

With an effective catalytic system in hand, we attempted to explore the scope of the direct arylation reaction for these important heteroarenes with neutral aryl mesylates. Caffeine, 1-(4-methoxyphenyl)-1,2,3-triazole and benzothiazole were used as model substrates to represent each set of heteroarenes for direct arylation with 3,5-dimethylphenyl mesylate (Scheme 3). Caffeine, 1-(4-methoxyphenyl)-1,2,3-triazole, and benzothiazole were effectively functionalized to give moderate to good yields. In particular, the direct arylation of 1-(4-methoxyphenyl)-1,2,3-triazole with 3,5-dimethylphenyl mesylate occured in a highly regioselective manner and thus only the 5-substituted product was obtained.



Scheme 3. Direct arylation of various heteroarenes with electronically neutral aryl mesylates.

In summary, we have uncovered an effective system that enables the first general palladium-catalyzed direct arylation of heteroarenes with aryl mesylates. Particularly worth noting is that the palladium catalyst with CM-phos can smoothly catalyse the direct arylation reaction without the addition of supplementary acid or copper salt additives. Because the substitution patterns between the phenolic compounds and aryl halides are usually different, this protocol potentially offers facile access to a variety of arylated heteroarenes that are not easily accessible from aryl halides. The viability of using challenging aryl mesylates in this direct arylation could potentially open up a versatile foundation for future frontier C–H functionalization/arylation explorations with relevant difficult sulfonate electrophiles.



Scheme 2. Suzuki coupling and direct arylation of benzoxazole (yields in scheme represent the direct arylation step).

Acknowledgements

We thank the Research Grants Council of Hong Kong (project no. CERG: PolyU5008/07P) for financial support, and are grateful to PolyU funding (SEG 01 PolyU) for NMR instrumental support.

Keywords: aryl mesylates · C–H activation · direct arylation · heterocycles · palladium

[1] a) *Metal-Catalyzed Cross-Coupling Reactions, Vols. 1–2*, 2nd ed. (Eds.: A. de Meijere, F. Diederich), Wiley-VCH, Weinheim **2004**; b) M. Beller, C. Bolm, *Transition Metals for Organic Synthesis Building Blocks and Fine Chemicals, Vols. 1–2*, 2nd ed., Wiley-VCH, Weinheim, **2004**; c) J. Hassan, M. Sévignon, C. Gozzi, E. Schulz, M. Lemaire, *Chem. Rev.* **2002**, *102*, 1359; d) J. Tsuji, *Palladium Reagents and Catalysts*, 2nd ed., Wiley, New York, **2004**; e) L. Yin, J. Liebscher, *Chem. Rev.* **2007**, *107*, 133; f) J.-P. Corbet, G. Mignani, *Chem. Rev.* **2006**, *106*, 2651; g) A. Roglans, A. Pla-Quintana, M. Moreno-Manas, *Chem. Rev.* **2006**, *106*, 4622; h) *Modern Arylation Methods* (Ed.: L. Ackermann), Wiley-VCH, Weinheim, **2009**.

[2] For reviews concerning the applications of cross-coupling in preparing pharmaceutically useful intermediates, see: a) K. C. Nicolaou, P. G. Bulger, D. Sarlah, *Angew. Chem.* **2005**, *117*, 4516; *Angew. Chem. Int. Ed.* **2005**, *44*, 4442; b) K. C. Nicolaou, E. J. Sorensen, *Classic in Total Synthesis II, More Targets, Strategies and Methods*, Wiley-VCH, Weinheim, **2003**.

[3] For recent reviews, see: a) B. J. Li, S. D. Yang, Z. J. Shi, *Synlett* **2008**, 949–957; b) J. C. Lewis, R. G. Bergman, J. A. Ellman, *Acc. Chem. Res.* **2008**, *41*, 1013; c) T. Satoh, M. Miura, *Top. Organomet. Chem.* **2007**, *24*, 61; d) L. Ackermann, *Top. Organomet. Chem.* **2007**, *24*, 35; e) D. Kalyani, M. S. Sanford, *Top. Organomet. Chem.* **2007**, *24*, 85; f) S. Pascual, P. de Mendoza, A. M. Echavarren, *Org. Biomol. Chem.* **2007**, *5*, 2727; g) L. Ackermann, *Synlett* **2007**, 0507; h) D. Alberico, M. E. Scott, M. Lautens, *Chem. Rev.* **2007**, *107*, 174; i) O. Daugulis, H.-Q. Do, D. Shabashov, *Acc. Chem. Res.* **2009**, *42*, 1074; j) X. Chen, K. M. Engle, D.-H. Wang, J.-Q. Yu, *Angew. Chem.* **2009**, *121*, 5196; *Angew. Chem. Int. Ed.* **2009**, *48*, 5094; k) L. Ackermann, R. Vicente, A. R. Kapdi, *Angew. Chem.* **2009**, *121*, 9976; *Angew. Chem. Int. Ed.* **2009**, *48*, 9792; l) F. Bellina, R. Rossi, *Tetrahedron* **2009**, *65*, 10269; m) L. Joucla, L. Djakovitch, *Adv. Synth. Catal.* **2009**, *351*, 673; n) T. W. Lyons, M. S. Sanford, *Chem. Rev.* **2010**, *110*, 1147; o) G. Dyker, *Handbook of C–H Transformations*, Wiley-VCH, Weinheim, **2005**.

[4] For recent superb advancements in C–H functionalization, see: a) D. R. Stuart, K. Fagnou, *Science* **2007**, *316*, 1172; b) R. J. Phipps, M. J. Gaunt, *Science* **2009**, *323*, 1593; c) D.-H. Wang, K. M. Engle, B.-F. Shi, J.-Q. Yu, *Science* **2010**, *327*, 315.

[5] For selected recent references on the Pd-catalyzed direct functionalization of heteroarenes by using ArI and ArBr, see: a) T. Okazawa, T. Satoh, M. Miura, M. Nomura, *J. Am. Chem. Soc.* **2002**, *124*, 5286; b) B. S. Lane, M. A. Brown, D. Sames, *J. Am. Chem. Soc.* **2005**, *127*, 8050; c) G. L. Turner, J. A. Morris, M. F. Greaney, *Angew. Chem.* **2007**, *119*, 8142; *Angew. Chem. Int. Ed.* **2007**, *46*, 7996; d) X. Wang, D. V. Gribkov, D. Sames, *J. Org. Chem.* **2007**, *72*, 1476; e) N. Lebrasseur, I. Larrosa, *J. Am. Chem. Soc.* **2008**, *130*, 2926; f) L.-C. Campeau, M. Bertrand-Laperle, J.-P. Leclerc, E. Villemure, S. Gorelsky, K. Fagnou, *J. Am. Chem. Soc.* **2008**, *130*, 3276; g) S. I. Gorelsky, D. Lapointe, K. Fagnou, *J. Am. Chem. Soc.* **2008**, *130*, 10848; h) S. Yanagisawa, K. Ueda, H. Sekizawa, K. Itami, *J. Am. Chem. Soc.* **2009**, *131*, 14622; i) J.-P. Leclerc, K. Fagnou, *Angew. Chem.* **2006**, *118*, 7945; *Angew. Chem. Int. Ed.* **2006**, *45*, 7781; j) N. R. Deprez, D. Kalyani, A. Krause, M. S. Sanford, *J. Am. Chem. Soc.* **2006**, *128*, 4972; k) A. Battace, M. Lemhadri, T. Zair, H. Doucet, M. Santelli, *Organometallics* **2007**, *26*, 472; l) A. L. Gottumukkala, H. Doucet, *Eur. J. Inorg. Chem.* **2007**, *3629*; m) D. G. Hulcoop, M. Lautens, *Org. Lett.* **2007**, *9*, 1761; n) L. Ackermann, S. Barfüer, *Synlett* **2009**, *808*; o) F. Shibahara, E. Yamaguchi, T. Murai, *Chem. Commun.* **2010**, *46*, 2471; for the Pd-catalyzed direct functionalization of arenes by using ArI and ArBr, see: p) M. Lafrance, K. Fagnou, *J. Am. Chem. Soc.* **2006**, *128*, 16496; q) D. Kalyani, N. R. Deprez, L. V. Desai, M. S. Sanford, *J. Am. Chem. Soc.* **2005**, *127*, 7330; for selected recent Ni catalyses, see: r) J. Canivet, J. Yamaguchi, I. Ban, K. Itami, *Org. Lett.* **2009**, *11*, 1733; s) H. Hachiya, K. Hirano, T. Satoh, M. Miura, *Org. Lett.* **2009**, *11*, 1737.

[6] For activated ArCl, see: Y. Aoyagi, A. Inoue, I. Koizumi, R. Hashimoto, K. Tokunaga, K. Gohma, J. Komatsu, K. Sekine, A. Miyafuji, J. Kunoh, R. Honma, Y. Akita, A. Ohta, *Heterocycles* **1992**, *33*, 257.

[7] a) S. Pivasa-Art, T. Satoh, Y. Kawamura, M. Miura, M. Nomura, *Bull. Chem. Soc. Jpn.* **1988**, *61*, 467; b) I. Čerňa, R. Pohl, B. Klepetářová, M. Hocek, *Org. Lett.* **2006**, *8*, 5389; c) F. Bellina, S. Cauteruccio, R. Rossi, *Eur. J. Org. Chem.* **2006**, *1379*; for Zn-salts-assisted pathways, see: d) R. D. Rieth, N. P. Mankad, E. Calimano, J. P. Sadighi, *Org. Lett.* **2004**, *6*, 3981.

[8] A. Chiong, O. Daugulis, *Org. Lett.* **2007**, *9*, 1449.

[9] For a review, see: Z. Gilson, R. Larock, *Chem. Rev.* **2006**, *106*, 4644.

[10] For examples of Pd-catalyzed direct arylations of aromatic derivatives through C–H activation by using aryl triflates, see: a) T. Hosoya, E. Takashiro, T. Matsumoto, K. Suzuki, *J. Am. Chem. Soc.* **1994**, *116*, 1004; b) G. Brigmann, A. Wuzik, J. Kraus, K. Peters, E.-M. Peters, *Tetrahedron Lett.* **1998**, *39*, 1545; c) L. Wang, P. B. Shevlin, *Tetrahedron Lett.* **2000**, *41*, 285; d) Y. Kametani, T. Satoh, M. Miura, M. Nomura, *Tetrahedron Lett.* **2000**, *41*, 2655; e) H. Nishioka, Y. Shoujiguchi, H. Abe, Y. Takeuchi, T. Harayama, *Heterocycles* **2004**, *64*, 463; f) O. Hara, T. Nakamura, F. Sato, K. Makino, Y. Hamada, *Heterocycles* **2006**, *68*, 1; g) M. Brenner, G. Mayer, A. Terpin, W. Steglich, *Chem. Eur. J.* **1997**, *3*, 70.

[11] For a mechanistic study on the oxidative addition of ArOTs by using Pd complexes, see:A. H. Roy, J. F. Hartwig, *Organometallics* **2004**, *23*, 194.

[12] Nickel-catalyzed cross coupling of aryl sulfonates were reported in a pioneering study, see: a) V. Percec, J.-Y. Bae, D. H. Hill, *J. Org. Chem.* **1995**, *60*, 1060; b) V. Percec, G. M. Golding, J. Smidrkal, O. Weichold, *J. Org. Chem.* **2004**, *69*, 3447; c) D. Zim, V. R. Lando, J. Dupont, A. L. Monteiro, *Org. Lett.* **2001**, *3*, 3049; d) Z. Y. Tang, Q. S. Hu, *J. Am. Chem. Soc.* **2004**, *126*, 3058.

[13] For Suzuki couplings with ArOTs substrates, see: a) H. N. Nguyen, X. Huang, S. L. Buchwald, *J. Am. Chem. Soc.* **2003**, *125*, 11818; b) L. Zhang, T. Meng, J. Wu, *J. Org. Chem.* **2007**, *72*, 9346; c) C. M. So, C. P. Lau, A. S. C. Chan, F. Y. Kwong, *J. Org. Chem.* **2008**, *73*, 7731; for Kumada coupling, see: d) A. H. Roy, J. F. Hartwig, *J. Am. Chem. Soc.* **2003**, *125*, 8704; e) M. E. Limmert, A. H. Roy, J. F. Hartwig, *J. Org. Chem.* **2005**, *70*, 9364; f) L. Ackermann, A. Althammer, *Org. Lett.* **2006**, *8*, 3457; for C–N bond coupling, see: g) X. Huang, K. W. Anderson, D. Zim, L. Jiang, A. Klapars, S. L. Buchwald, *J. Am. Chem. Soc.* **2003**, *125*, 6653; h) T. Ogata, J. F. Hartwig, *J. Am. Chem. Soc.* **2008**, *130*, 13848; for Sonogashira couplings by using activated ArOTs, see: i) D. Gelman, S. L. Buchwald, *Angew. Chem.* **2003**, *115*, 6175; *Angew. Chem. Int. Ed.* **2003**, *42*, 5993; j) O. R′kyek, N. Halland, A. Lindenschmidt, J. Alonso, P. Lindemann, M. Urmann, M. Nazaré, *Chem. Eur. J.* **2010**, *16*, 9986; for Hiyama couplings, see: k) L. Zhang, J. Wu, *J. Am. Chem. Soc.* **2008**, *130*, 12250; for carbonylation, see: l) R. H. Munday, J. R. Martinelli, S. L. Buchwald, *J. Am. Chem. Soc.* **2008**, *130*, 2754.

[14] For ArOMs in C–N bond formation, see: a) C. M. So, Z. Zhou, C. P. Lau, F. Y. Kwong, *Angew. Chem.* **2008**, *120*, 6502; *Angew. Chem. Int. Ed.* **2008**, *47*, 6402; b) B. P. Fors, D. A. Watson, M. R. Biscoe, S. L. Buchwald, *J. Am. Chem. Soc.* **2008**, *130*, 13552; for ArOMs in Suzuki coupling, see: c) C. M. So, C. P. Lau, F. Y. Kwong, *Angew. Chem.* **2008**, *120*, 8179; *Angew. Chem. Int. Ed.* **2008**, *47*, 8059; d) B. Bhayana, B. P. Fors, S. L. Buchwald, *Org. Lett.* **2009**, *11*, 3954; e) W. K. Chow, C. M. So, C. P. Lau, F. Y. Kwong, *J. Org. Chem.* **2010**, *75*, 5109; for Hiyama coupling, see: f) L. Zhang, J. Qing, P. Yang, J. Wu, *Org. Lett.* **2008**, *10*, 4971; g) C. M. So, H. W. Lee, C. P. Lau, F. Y. Kwong, *Org. Lett.* **2009**, *11*, 317; for Sonogashira coupling, see: h) P. Y. Choy, W. K. Chow, C. M. So, C. P. Lau, F. Y. Kwong, *Chem. Eur. J.* **2010**, *16*, 9982; for cyanation, see: i) P. Y. Yeung, C. M. So, C. P. Lau, F. Y. Kwong, *Angew. Chem.* **2010**, *122*, 9102; *Angew. Chem. Int. Ed.* **2010**, *49*, 8918.

[15] For Buchwald's initial development of X-Phos in C–C coupling reactions, see reference [13a].

[16] L. Ackermann, A. Althammer, S. Fenner, *Angew. Chem.* **2009**, *121*, 207; *Angew. Chem. Int. Ed.* **2009**, *48*, 201.

[17] Typically, the lower the pK_a of the conjugate acid, the better the leaving group. (c.f., methanesulfonic acid, $pK_a = -1.9$; *p*-toluenesulfonic acid, $pK_a = -2.8$; benzenesulfonic acid, $pK_a = -6.5$; triflic acid, $pK_a = -14.9$), see: *Ionization Constants of Organic Acids in Solution,*

IUPAC Chemical Data Series No. 23 (Eds.: E. P. Serjeant, B. Dempsey), Pergamon Press, Oxford, **1979**.

[18] A. Zapf, A. Ehrentraut, M. Beller, *Angew. Chem.* **2000**, *112*, 4315; *Angew. Chem. Int. Ed.* **2000**, *39*, 4153.

[19] A. Zapf, M. Beller, *Chem. Commun.* **2005**, 431.

[20] a) C. M. So, C. P. Lau, F. Y. Kwong, *Org. Lett.* **2007**, *9*, 2795; for other related types of indolyl phosphines, see: b) H. W. Lee, F. L. Lam, C. M. So, C. P. Lau, A. S. C. Chan, F. Y. Kwong, *Angew. Chem.* **2009**, *121*, 7572; *Angew. Chem. Int. Ed.* **2009**, *48*, 7436; c) C. M. So, W. K. Chow, P. Y. Choy, C. P. Lau, F. Y. Kwong, *Chem. Eur. J.* **2010**, *16*, 7996.

[21] In our preliminary study, the kinetic isotopic effect of 2-deuteriated-benzoxazole with respect to benzoxazole in Ph-OMs coupling were $k_D/k_H \approx 1$, which suggests that C–H bond cleavage is not the rate-determining step. For the rate of direct arylation of benzoxazole with *p*-OMe-C_6H_4-OMs and *p*-H-C_6H_4-OMs, the *p*-OMe-C_6H_4-OMs substrate exhibited a slower rate of reaction. These preliminary results suggest that the oxidative addition of ArOMs is presumably the rate-determining step. (A detailed kinetic study is currently underway).

[22] We found that electron-deficient ArOMs underwent hydrolysis to form the corresponding phenols. Therefore, an anhydrous solvent is essential if electron-deficient ArOMs are used as an arylating agent.

[23] a) M. Jalali-Heravi, M. Asadollahi-Baboli, P. Shahbazikhah, *Eur. J. Med. Chem.* **2008**, *43*, 548; b) S. M. Courtney, P. A. Hay, R. T. Buck, C. S. Colville, D. W. Porter, D. I. C. Scopes, F. C. Pollard, M. J. Page, J. M. Bennett, M. L. Hircock, E. A. McKenzie, C. R. Stubberfield, P. R. Turner, *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3269.

[24] a) M. R. Deluca, S. M. Kerwin, *Tetrahedron Lett.* **1997**, *38*, 199; b) S. Sato, T. Kajiiura, M. Noguchi, K. Takehana, T. Kobayash, *T. Tsuji, J. Antibiot.* **2001**, *54*, 102.

[25] a) R. V. Kalla, E. Elzein, T. Perry, X. Li, V. Palle, V. Varkhedkar, A. Gimbel, T. Maa, D. Zeng, J. Zablocki, *J. Med. Chem.* **2006**, *49*, 3682; b) L. Yan, C. E. Müller, *J. Med. Chem.* **2004**, *47*, 1031; c) A. M. Hayallah, J. S. Ramrez, U. Reith, U. Schobert, B. Preiss, B. Schumacher, J. W. Daly, C. E. Müller, *J. Med. Chem.* **2002**, *45*, 1500; d) D. Zhao, W. Wang, S. Lian, F. Yang, J. Lan, J. You, *Chem. Eur. J.* **2009**, *15*, 1337.

[26] D. Zhao, W. Wang, F. Yang, J. Lan, Li Yan, G. Gao, J. You, *Angew. Chem.* **2009**, *121*, 3346; *Angew. Chem. Int. Ed.* **2009**, *48*, 3296.

[27] a) E. Kashiyama, I. Huchinson, M. S. Chau, S. F. Stinson, L. R. Phillips, G. Kaur, E. A. Sausville, T. D. Bradshaw, A. D. Westwell, M. F. G. Stevens, *J. Med. Chem.* **1999**, *42*, 4172; b) T. D. Bradshaw, M. F. G. Stevens, A. D. Westwell, *Curr. Med. Chem.* **2001**, *8*, 203.

[28] a) Y. Bourne, H. C. Kolb, Z. Radic', K. B. Sharpless, P. Taylor, P. Marchot, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 1449.

Received: August 16, 2010
Published online: December 16, 2010

