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Palladium-Catalyzed Direct Arylations, Alkenylations, and Benzylations through C−H Bond Cleavages with Sulfamates or Phosphates as Electrophiles

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ABSTRACT

A catalytic system comprised of Pd(OAc)$_2$ and bidentate ligand dppe enabled first direct arylations with moisture-stable aryl sulfamates as electrophiles, and proved applicable to unprecedented C−H bond functionalizations with easily accessible alkenyl phosphates as well as benzyl phosphates.

Transition metal-catalyzed direct $C(sp^2)-C(sp^2)$ bond formations through C−H bond cleavages are environmentally and economically sound alternatives to traditional cross-coupling reactions between organic electrophiles and stoichiometric amounts of organometallic nucleophiles.[1] Particularly, methods that enable the use of simple (hetero)arenes as surrogates for preactivated organometallic reagents enable a reduction of byproduct formation as well as an overall streamlining of organic synthesis. Until recently, rather expensive and/or moisture-sensitive aryl iodides, bromides, and triflates or iodonium salts were largely employed as arylating reagents for these C−H bond functionalizations. However, significant recent progress was achieved through the development of catalytic systems that proved generally applicable to more convenient electrophiles, such as aryl chlorides,[2] tosylates,[3,4] or mesylates,[4] as well as to phenols[5] as proelectrophiles. Unfortunately, transformations with these (pseudo)halides continue to be challenging because of the inherent high strength of their C−Cl or C−OR bonds.

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(1) Select recent reviews: (a) Ackermann, L.; Vicente, R.; Kapdi, A. *Angew. Chem., Int. Ed* **2009**, *48*, 9792–9826. (b) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094–5115. (c) Thansandote, P.; Lautens, M. *Chem.—Eur. J.* **2009**, *15*, 5874–5883. (d) Daugulis, O.; Do, H.-Q.; Shabashov, D. *Acc. Chem. Res.* **2009**, *42*, 1074–1086. (e) Kakiuchi, F.; Kochi, T. *Synthesis* **2008**, 3013–3039. (f) Li, B.-J.; Yang, S.-D.; Shi, Z.-J. *Synlett* **2008**, 949–957. (g) Lewis, J. C.; Bergman, R. G.; Ellman, J. A. *Acc. Chem. Res.* **2008**, *41*, 1013–1025. (h) Satoh, T.; Miura, M. *Chem. Lett.* **2007**, *36*, 200–205. (i) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174–238. (j) Seregin, I. V.; Gevorgyan, V. *Chem. Soc. Rev.* **2007**, *36*, 1173–1193. (k) Pascual, S.; de Mendoza, P.; Echavarren, A. M. *Org. Biomol. Chem.* **2007**, *5*, 2727–2734. (l) Campeau, L.-C.; Stuart, D. R.; Fagnou, K. *Aldrichim. Acta* **2007**, *40*, 35–41. (m) Ackermann, L. *Synlett* **2007**, 507–526.

(2) For representative examples of intermolecular direct arylations with aryl chlorides, see: (a) Ackermann, L. *Org. Lett.* **2005**, *7*, 3123–3125. (b) Campeau, L.-C.; Parisien, M.; Jean, A.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 581–590. (c) Lafrance, M.; Rowley, C. N.; Woo, T. K.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 8754–8756. (d) Ackermann, L.; Born, R.; Spatz, J. H.; Althammer, A.; Gschrei, C. J. *Pure Appl. Chem.* **2006**, *78*, 209–214. (e) Chiong, H. A.; Daugulis, O. *Org. Lett.* **2007**, *9*, 1449–1451. (f) Ackermann, L.; Born, R.; Álvarez-Bercedo, P. *Angew. Chem., Int. Ed.* **2007**, *46*, 6364–6367. (g) Chiong, H. A.; Pham, Q.-N.; Daugulis, O. *J. Am. Chem. Soc.* **2007**, *129*, 9879–9884. (h) Ackermann, L.; Vicente, R.; Born, R. *Adv. Synth. Catal.* **2008**, *350*, 741–748. (i) Ackermann, L.; Born, R.; Vicente, R. *ChemSusChem* **2009**, 546–549.

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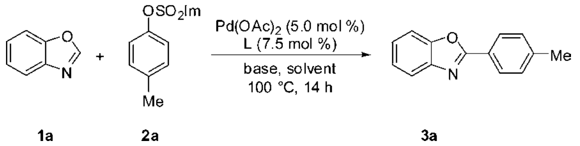
Recently, Albaneze-Walker and co-workers reported aryl sulfamates to be viable coupling partners for conventional Suzuki−Miyaura or Negishi cross-coupling reactions with stoichiometric amounts of preactivated boron- or zinc-based nucleophiles, respectively.[6] Considering the moisture-stable nature of the imidazolylsulfonates, along with the self-destructive, thus nongenotoxic, properties of the cross-coupling byproduct imidazolesulfonic acid, we probed C−H bond functionalizations with these user-friendly electrophiles. As a result of these efforts, we wish to report herein on first direct arylations of heteroarenes[1j,7,8] with convenient imidazolylsulfonates as arylating reagents. Additionally, we found that the optimized palladium(0) catalyst also allowed for direct C−H bond functionalizations with easily accessible benzyl and alkenyl phosphates[9] as electrophilic coupling partners.

At the outset of our studies, we tested representative ligands for the palladium-catalyzed direct arylation of benzoxazole (**1a**) with imidazolylsulfonate **2a** (Table 1).

Table 1. Optimization of Direct Arylation with Sulfamate **2a**[a]



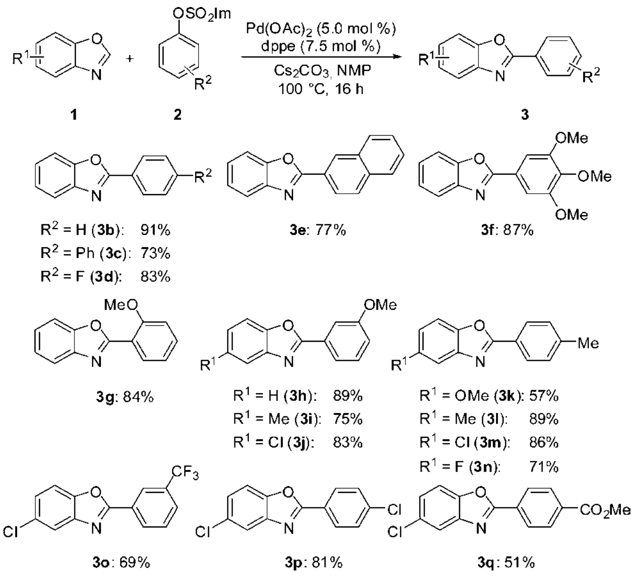
entry	L	base	solvent	yield, %
1	–	K$_3$PO$_4$	NMP	<5[c]
2	HIMesCl[b]	K$_3$PO$_4$	NMP	<5[c]
3	HIPrCl[b]	K$_3$PO$_4$	NMP	<5[c]
4	SHIPrCl[b]	K$_3$PO$_4$	NMP	<5[c]
5	PCy$_3$[b]	K$_3$PO$_4$	NMP	<5[c]
6	X-Phos[b]	K$_3$PO$_4$	NMP	<5[c]
7	PPh$_3$[b]	K$_3$PO$_4$	NMP	35
8	dppf	K$_3$PO$_4$	NMP	41
9	Xantphos	K$_3$PO$_4$	NMP	54
10	*rac*-BINAP	K$_3$PO$_4$	NMP	59
11	dppp	K$_3$PO$_4$	NMP	61
12	dppe	K$_3$PO$_4$	NMP	74
13	dppe	K$_2$CO$_3$	NMP	13[c]
14	dppe	Cs$_2$CO$_3$	PhMe	20[c]
15	dppe	Cs$_2$CO$_3$	DMSO	84
16	dppe	Cs$_2$CO$_3$	NMP	98
17	dppe	Cs$_2$CO$_3$	NMP	86[d]

[a] Reaction conditions: **1a** (0.50 mmol), **2a** (0.60 mmol), Pd(OAc)$_2$ (5.0 mol %), L (7.5 mol %), base (1.00 mmol), solvent (2.0 mL), 100 °C, 14 h. [b] L (15 mol %). [c] GC-conversion; HIMes = *N*,*N*′-bis(2,4,6-trimethylphenyl)imidazolium, (S)HIPr = *N*,*N*′-bis(2,6-diisopropylphenyl)imidazol(in)ium. [d] With PdCl$_2$ (5.0 mol %).

Unfortunately, electron-rich σ-donor ligands, such as N-heterocyclic carbenes (entries 2−4) or tertiary alkyl-substituted phosphines (entries 5 and 6), provided only unsatisfactory results. Contrarily, a palladium catalyst derived from an aryl-substituted phosphine displayed a superior catalytic efficacy (entry 7), which could be further improved when employing bidentate ligands (entries 8−12). Among a variety of bidentate phosphine ligands, dppe gave rise to optimal results, particularly when using Cs$_2$CO$_3$ as base and NMP as solvent (entry 16).[10] It is noteworthy that satisfactory isolated yields were also obtained with PdCl$_2$ as a less expensive metal precursor (entry 17).

Subsequently, we explored the scope of the optimized catalytic system in direct arylations of benzoxazoles **1** with differently substituted imidazolylsulfonates **2** (Scheme 1).

Scheme 1. Direct Arylation with Imidazolylsulfonates **2**



Remarkably, the catalyst turned out to be broadly applicable, and hence enabled the efficient conversion of electron-

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(6) (a) Albaneze-Walker, J.; Raju, R.; Vance, J. A.; Goodman, A. J.; Reeder, M. R.; Liao, J.; Maust, M. T.; Irish, P. A.; Espino, P.; Andrews, D. R. *Org. Lett.* **2009**, *11*, 1463–1466. For related recent studies, see: (b) Luo, Y.; Wu, J. *Organometallics* **2009**, *28*, 6823–6826. (c) Goegsig, T. M.; Lindhardt, A. T.; Skrydstrup, T. *Org. Lett.* **2009**, *11*, 4886–4888. (d) Quasdorf, K. W.; Riener, M.; Petrova, K. V.; Garg, N. K. *J. Am. Chem. Soc.* **2009**, *131*, 17748–17749.

(7) Recent reviews on direct arylations of heteroarenes: (a) Bellina, F.; Rossi, R. *Tetrahedron* **2009**, *65*, 10269–10310. (b) Joucla, L.; Djakovitch, L. *Adv. Synth. Catal.* **2009**, *351*, 673–714.

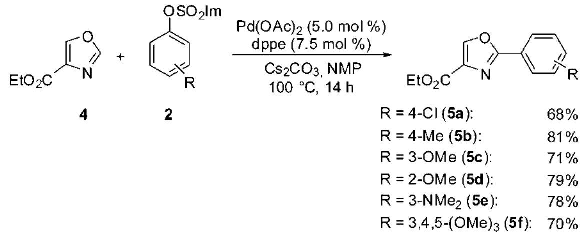
(8) For select recent examples of direct arylations employing oxazoles, see: (a) Canivet, J.; Yamaguchi, J.; Ban, I.; Itami, K. *Org. Lett.* **2009**, *11*, 1733–1736. (b) Hachiya, H.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2009**, *11*, 1737–1740. (c) Flegeau, E. F.; Popkin, M. E.; Greaney, M. F. *Org. Lett.* **2008**, *10*, 2717–2720. (d) Sanchez, R. S.; Zhuravlev, F. A. *J. Am. Chem. Soc.* **2007**, *129*, 5824–5825. (e) Do, H.-Q.; Daugulis, O. *J. Am. Chem. Soc.* **2007**, *129*, 12404–12405, and references cited therein.

(9) For representative recent examples of *conventional* cross-coupling reactions with phosphates as electrophiles, see: (a) Gauthier, D.; Beckendorf, S.; Gøgsig, T. M.; Lindhardt, A. T.; Skrydstrup, T. *J. Org. Chem.* **2009**, *74*, 3536–3539. (b) Yoshikai, N.; Matsuda, H.; Nakamura, E. *J. Am. Chem. Soc.* **2009**, *131*, 9590–9599. (c) Bedford, R. B.; Huwe, M.; Wilkinson, M. C. *Chem. Commun.* **2009**, 600–602. (d) Hansen, A.; Ebran, J.-P.; Gøgsig, T. M.; Skrydstrup, T. *J. Org. Chem.* **2007**, *72*, 6464–6472. (e) Ebran, J.-P.; Hansen, A. L.; Gøgsig, T. M.; Skrydstrup, T. *J. Am. Chem. Soc.* **2007**, *129*, 6931–6942. (f) Hansen, A. L.; Ebran, J.-P.; Ahlquist, M.; Norrby, P.-O.; Skrydstrup, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 3349–3353. (g) McLaughlin, M. *Org. Lett.* **2005**, *7*, 4875–4878. A review: (h) Lindhardt, A. T.; Skrydstrup, T. *Chem.−Eur. J.* **2008**, *14*, 8756–8766, and references cited therein.

deficient as well as electron-rich sulfamates **2**, even when bearing ortho-substituents. Moreover, substituted benzoxazoles **1** could be employed, thus allowing for the synthesis of products **3i**−**q**, displaying valuable functional groups for further synthetic elaboration.

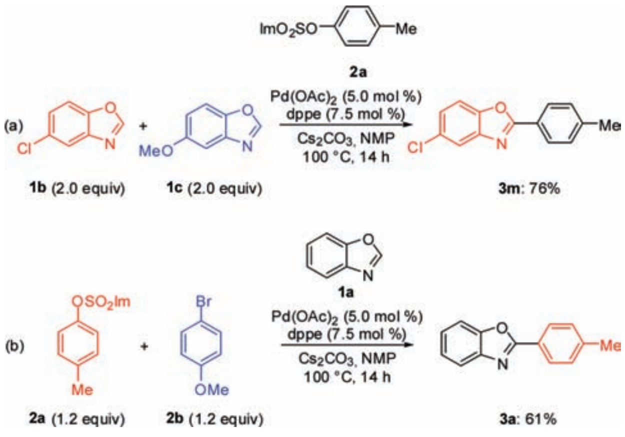
Importantly, the protocol was found not to be restricted to benzoxazoles **1**, but could be applied to C−H bond functionalizations on oxazole **4** as well (Scheme 2).

Scheme 2. Direct Arylation of Heteroarene **4**



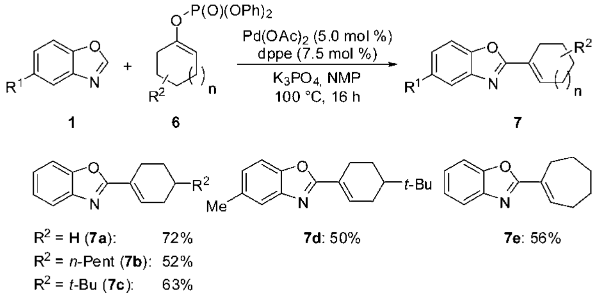
It is worth noting that a competition experiment between differently substituted benzoxazoles **1** revealed that more electron-deficient heteroarene **1b** reacted preferentially (Scheme 3a). As to the organic electrophiles, intra- (Scheme 1) and intermolecular (Scheme 3b) competition experiments indicated the following series in order of decreasing reactivity: $ArOSO_2Im > ArBr > ArCl$.

Scheme 3. Intermolecular Competition Experiments



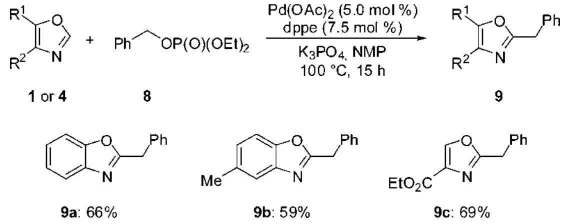
For direct C−H bond alkenylation reactions[11] we became interested in exploring the use of moisture-stable phosphates[9] **6** as convenient coupling reagents (Scheme 4). As observed for direct arylations with sulfamates **2** (vide supra), dppe was found to be the ligand of choice among different mono- or bidentate additives. Thereby, various alkenylated products **7a**−**e** could be obtained with good yields and excellent chemoselectivities.

Scheme 4. Direct Alkenylation with Phosphates **6**



Finally, the optimized protocol also set the stage for efficient regioselective benzylation reactions[12] under nonacidic reaction conditions (Scheme 5).

Scheme 5. Direct Benzylation with Phosphate **8**



In conclusion, we have developed a palladium catalyst for general direct arylations through C−H bond cleavages with moisture-stable sulfamates as electrophiles. Notably, this catalytic system derived from ligand dppe also allowed for direct benzylations and alkenylations with easily accessible phosphates as convenient coupling partners.

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Supporting Information Available: Experimental procedures, characterization data, and ^1H and ^{13}C NMR spectra for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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[10] This optimized dppe-based catalytic system proved not applicable to direct arylations of benzoxazoles with aryl tosylates.

[11] For recent examples of alkenylations with alkenyl triflates or halides as electrophiles, see: (a) Ackermann, L.; Althammer, A.; Mayer, P. *Synthesis* **2009**, 3493–3503. (b) Cruz, A. C. F.; Miller, N. D.; Willis, M. C. *Org. Lett.* **2007**, *9*, 4391–4393. (c) Ackermann, L.; Althammer, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 1627–1629. (d) Hughes, C. C.; Trauner, D. *Angew. Chem., Int. Ed.* **2002**, *41*, 1569–1572, and references cited therein.

[12] For recent reports on intermolecular transition metal-catalyzed direct benzylations through C−H bond cleavages under basic reaction conditions, see: [Ru]: (a) Ackermann, L.; Novák, P. *Org. Lett.* **2009**, *11*, 4966–4969. [Pd]: (b) Verrier, C.; Hoarau, C.; Marsais, F. *Org. Biomol. Chem.* **2009**, *7*, 647–650. (c) Lapointe, D.; Fagnou, K. *Org. Lett.* **2009**, *11*, 4160–4163. For recent examples of direct C−H bond alkylations, see: [Ru]: (d) Ackermann, L.; Novak, P.; Vicente, R.; Hofmann, N. *Angew. Chem. Int., Ed.* **2009**, *48*, 6045–6048. [Pd]: (e) Zhang, Y.-H.; Shi, B.-F.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 6097–6100.