

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

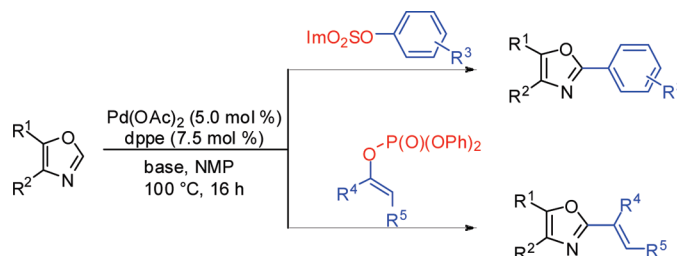
Lutz Ackermann,* Sebastian Barfüsser, and Jola Pospech

Institut fuer Organische und Biomolekulare Chemie, Georg-August-Universitaet,
Tammannstrasse 2, 37077 Goettingen, Germany

lutz.ackermann@chemie.uni-goettingen.de

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ABSTRACT



A catalytic system comprised of $\text{Pd}(\text{OAc})_2$ and bidentate ligand dppe enabled first direct arylation 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 $\text{C}(\text{sp}^2)\text{--C}(\text{sp}^2)$ 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 phenols⁵ 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.

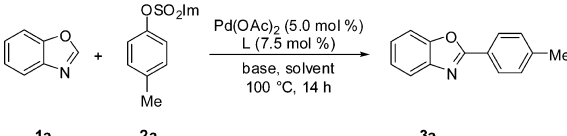
(1) Select recent reviews: (a) Ackermann, L.; Vicente, R.; Kapdi, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 9792–9826. (b) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094–5115. (c) Thansandote, P.; Lautens, M. *Chem.–Eur. J.* **2009**, *15*, 5874–5883. (d) 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.; Alvarez-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**, *2*, 546–549.

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 phosphates⁹ 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	<i>rac</i> -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

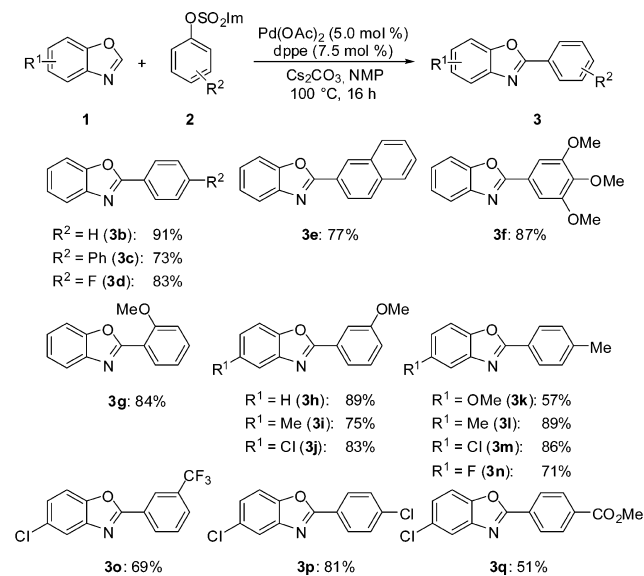
^a Reaction conditions: **1a** (0.50 mmol), **2a** (0.60 mmol), Pd(OAc)₂ (5.0 mol %), L (7.5 mol %), base (1.00 mmol), solvent (2.0 mL), 100 °C, 14 h. ^b L (15 mol %). ^c GC-conversion; HIMes = *N,N'*-bis(2,4,6-trimethylphenyl)imidazolium, (S)HIPr = *N,N'*-bis(2,6-diisopropylphenyl)imidazol(in)-ium. ^d With PdCl₂ (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 Cs₂CO₃ as base and NMP as solvent (entry 16).¹⁰ It is noteworthy that satisfactory isolated yields were also obtained with PdCl₂ 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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(9) For representative recent examples of conventional cross-coupling reactions with phosphates as electrophiles, see: (a) Gauthier, D.; Beckendorf, S.; Gögsig, 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.; Gögsig, T. M.; Skrydstrup, T. *J. Org. Chem.* **2007**, *72*, 6464–6472. (e) Ebran, J.-P.; Hansen, A. L.; Gögsig, 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.

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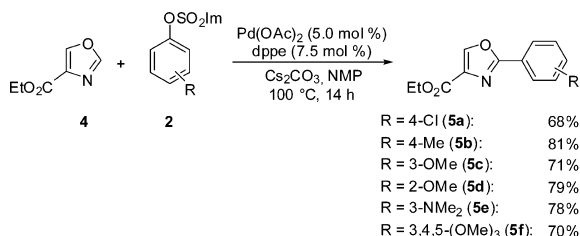
(4) Ackermann, L.; Althammer, A.; Fenner, S. *Angew. Chem., Int. Ed.* **2009**, *48*, 201–204.

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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.

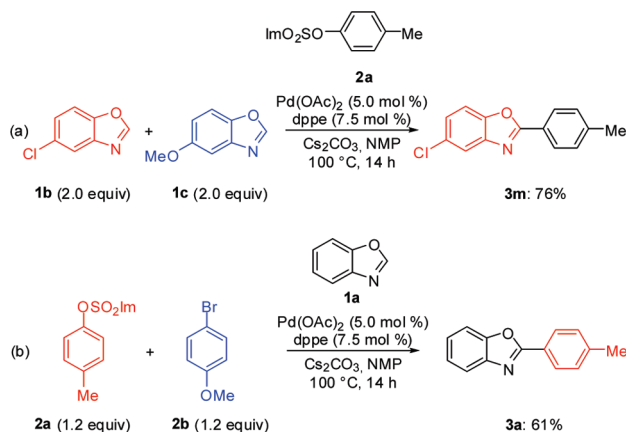
Importantly, the protocol was found not to be restricted to benzoxazoles **1**, but could be applied to C–H bond functionalizations on oxazole **4** as well (Scheme 2).

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

Scheme 3. Intermolecular Competition Experiments

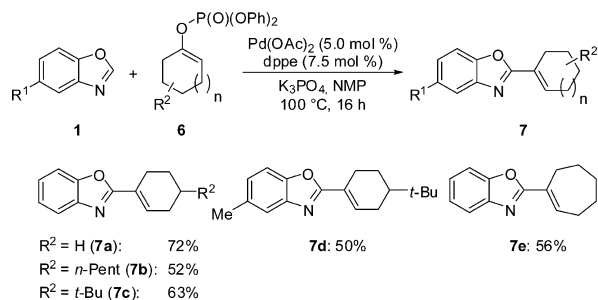


intermolecular (Scheme 3b) competition experiments indicated the following series in order of decreasing reactivity: ArOSO₂Im > ArBr > ArCl.

For direct C–H bond alkenylation reactions¹¹ we became interested in exploring the use of moisture-stable phosphates⁹ **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.

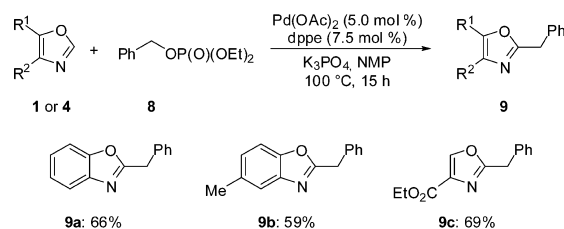
(10) This optimized dppe-based catalytic system proved not applicable to direct arylations of benzoxazoles with aryl tosylates.

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



Finally, the optimized protocol also set the stage for efficient regioselective benzylation reactions¹² 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.

Acknowledgment. Financial support by the DFG is gratefully acknowledged.

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

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