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Catalytic Direct Arylations in Polyethylene Glycol (PEG): Recyclable Palladium(0) Catalyst for C−H Bond Cleavages in the Presence of Air

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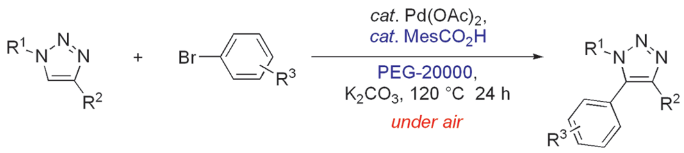
ABSTRACT



Two protocols for ruthenium- or palladium-catalyzed direct arylations in user-friendly polyethylene glycol (PEG) were devised, which set the stage for the development of user-friendly palladium(0)-catalyzed C−H bond functionalizations in the presence of air with a recyclable phosphine ligand-free palladium complex.

Catalytic direct arylations through C−H bond cleavages are increasingly viable alternatives to traditional cross-coupling reactions.[1,2] Thereby, the often difficult to prepare organometallic reagents can be replaced by simple (hetero)arenes, which allows for a streamlining of organic synthesis, as well as a reduction of undesired byproduct formation.

Among procedures for transition-metal-catalyzed direct arylations, strategies relying on a palladium(0)/palladium(II)[3−6] manifold, or the use of ruthenium catalysts,[7] arguably proved to be most versatile. However, despite significant recent progress,[1,2] protocols for such C−H bond functionalizations often continued to lack operational simplicity, in that vigorous anaerobic reaction conditions were required. Recently, an important advance was accomplished by Greaney, who discovered elegantly the high efficiency of palladium(0)-catalyzed direct arylations when being performed on water.[8,9] However, this protocol called for the use of deionized water under anaerobic reaction conditions, as, to the best of our knowledge, holds true for all reported palladium(0)-catalyzed direct arylations.

During studies directed toward the use of more sustainable reaction media for C−H bond functionalizations, we found that convenient ruthenium- or palladium(0)-catalyzed direct arylations could be conducted in inexpensive, nontoxic polyethylene glycol (PEG).[10] Herein, we wish to report on these findings, which resulted in the development of a recyclable phosphine ligand-free palladium catalyst for direct arylations in the presence of air.

In initial experiments, we observed that efficient ruthenium-catalyzed direct arylations could be accomplished in nonvolatile, nontoxic PEG-2000 as a benign reaction medium, provided that carboxylic acid MesCO$_2$H (**4a**)[11] was employed in cocatalytic amounts (Scheme 1). Thereby, various arenes

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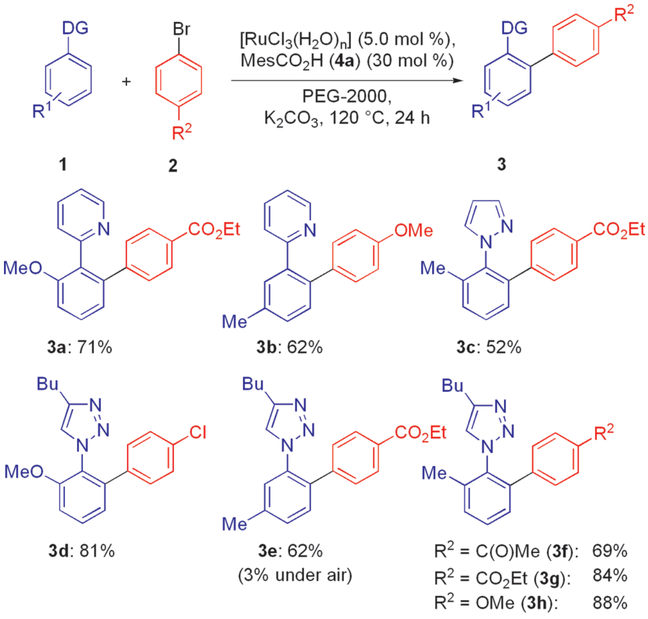
(1) (a) Ackermann, L., Ed. *Modern Arylation Methods*; Wiley-VCH: Weinheim, Germany, 2009. (b) Dyker, G., Ed. *Handbook of C−H Transformations*; Wiley-VCH: Weinheim, Germany, 2005.

(2) Recent reviews: (a) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094–5115. (b) Kakiuchi, F.; Kochi, T. *Synthesis* **2008**, 3013–3039. (c) Li, B.-J.; Yang, S.-D.; Shi, Z.-J. *Synlett* **2008**, 949–957. (d) Lewis, J. C.; Bergman, R. G.; Ellman, J. A. *Acc. Chem. Res.* **2008**, *41*, 1013–1025. (e) Satoh, T.; Miura, M. *Chem. Lett.* **2007**, *36*, 200–205. (f) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174–238. (g) Seregin, I. V.; Gevorgyan, V. *Chem. Soc. Rev.* **2007**, *36*, 1173–1193. (h) Pascual, S.; de Mendoza, P.; Echavarren, A. M. *Org. Biomol. Chem.* **2007**, *5*, 2727–2734. (i) Campeau, L.-C.; Stuart, D. R.; Fagnou, K. *Aldrichimica Acta* **2007**, *40*, 35–41. (j) Ackermann, L. *Synlett* **2007**, 507–526. (k) Daugulis, O.; Zaitsev, V. G.; Shabashov, D.; Pham, Q. N.; Lazareva, A. *Synlett* **2006**, 3382–3388.

10.1021/ol9020354 CCC: $40.75

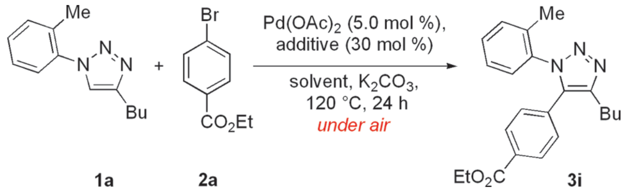
Scheme 1. Ruthenium-Catalyzed Direct Arylations in PEG-2000



1 bearing Lewis basic directing groups (DG) could be regioselectively arylated with $[\mathrm{RuCl_3(H_2O)}_n]$[12] as an inexpensive ruthenium source. Unfortunately, attempts to perform these ruthenium-catalyzed direct arylations under an atmosphere of air provided thus far unsatisfactory results.

Therefore, we focused our attention on the development of palladium(0)-catalyzed direct arylations of 1,2,3-triazole[13,14] in the presence of air (Table 1).

Table 1. Palladium(0)-Catalyzed Direct Arylations under Air[a]



entry	solvent	additive	yield
1	NMP		25%
2	NMP	MesCO$_2$H (**4a**)	42%
3	DMA	MesCO$_2$H (**4a**)	42%
4	1,4-dioxane	MesCO$_2$H (**4a**)	45%
5	PEG-400	MesCO$_2$H (**4a**)	
6	PEG-2000	MesCO$_2$H (**4a**)	39%
7	PEG-20000		39%
8	PEG-20000	MesCO$_2$H (**4a**)	74%
9	PEG-20000	*t*-BuCO$_2$H (**4b**)	62%

[a] Reaction conditions: **1a** (0.50 mmol), **2a** (0.75 mmol), Pd(OAc)$_2$ (5.0 mol %), additive (30 mol %), solvent, K$_2$CO$_3$ (1.00 mmol), 120 °C, 24 h, under air, yields of isolated products.

While commonly employed organic solvents gave rise to low conversions (entries 1−4), the use of high molecular weight PEGs, in combination with carboxylic acids **4**, improved catalytic efficacy significantly (entries 5−9). Interestingly, optimal reaction conditions, hence, involved the use of a phosphine ligand-free palladium catalyst modified with carboxylic acid MesCO$_2$H (**4a**)[15] in PEG-20000 (entry 8).

Having identified reaction conditions for user-friendly direct arylations in the presence of air, we probed the scope of this C−H bond functionalization protocol (Table 2).[16] Valuable functional groups were tolerated by the catalytic

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(3) For representative recent examples of palladium(0)-catalyzed direct arylations with aryl (pseudo)halides, see: (a) Miyasaka, M.; Fukushima, A.; Satoh, T.; Hirano, K.; Miura, M. *Chem.—Eur. J.* **2009**, *15*, 3674–3677. (b) Campeau, L.-C.; Stuart, D. R.; Leclerc, J.-P.; Bertrand-Laperle, M.; Villemure, E.; Sun, H.-Y.; Lasserre, S.; Guimond, N.; Lecavallier, M.; Fagnou, K. *J. Am. Chem. Soc.* **2009**, *131*, 3291–3306. (c) Bellina, F.; Benelli, F.; Rossi, R. *J. Org. Chem.* **2008**, *73*, 5529–5535. (d) Caron, L.; Campeau, L.-C.; Fagnou, K. *Org. Lett.* **2008**, *10*, 4533–4536. (e) Lebrasseur, N.; Larrosa, I. *J. Am. Chem. Soc.* **2008**, *130*, 2926–2927. (f) Laleu, B.; Lautens, M. *J. Org. Chem.* **2008**, *73*, 9164–9167. (g) Bedford, R. B.; Betham, M.; Charmant, J. P. H.; Weeks, A. L. *Tetrahedron* **2008**, *64*, 6038–6050. (h) Iwasaki, M.; Yorimitsu, M.; Oshima, K. *Chem. Asian J.* **2007**, *2*, 1430–1435. (i) Chiong, H. A.; Pham, Q.-N.; Daugulis, O. *J. Am. Chem. Soc.* **2007**, *129*, 9879–9884. (j) Chuprakov, S.; Chernyak, N.; Dudnik, A. S.; Gevorgyan, V. *Org. Lett.* **2007**, *9*, 2333–2336. (k) García-Cuadrado, D.; de Mendoza, P.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M. *J. Am. Chem. Soc.* **2007**, *129*, 6880–6886, and references cited therein.

(4) For selected examples of palladium(0)-catalyzed direct arylations from our laboratories, see: (a) Ackermann, L.; Althammer, A.; Fenner, S. *Angew. Chem., Int. Ed.* **2009**, *48*, 201–204. (b) Ackermann, L.; Barfüsser, S. *Synlett* **2009**, 808–812. (c) Ackermann, L.; Althammer, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 1627–1629.

(5) Miura, M.; Satoh, T. In *Modern Arylation Methods*; Ackermann, L., Ed.; Wiley-VCH: Weinheim, Germany, 2009; pp 335−362.

(6) For representative examples of the development of C−H bond functionalizations that were proposed to proceed through palladium(II)/palladium(IV) catalysis, see: (a) Tremont, S. J.; Rahman, H. U. *J. Am. Chem. Soc.* **1984**, *106*, 5759–5760. (b) Byers, P. K.; Canty, A. L.; Skelton, B. W.; White, A. H. *J. Chem. Soc., Chem. Commun.* **1986**, 1722–1724. (c) Catellani, M.; Frignani, F.; Rangoni, A. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 119–122. (d) Canty, A. L.; Denney, M. C.; van Koten, G.; Skelton, B. W.; White, A. H. *Organometallics* **2004**, *23*, 5432–5439. (e) Kalyani, D.; Deprez, N. R.; Desai, L. V.; Sanford, M. S. *J. Am. Chem. Soc.* **2005**, *127*, 7330–7331. (f) Daugulis, O.; Zaitsev, V. G. *Angew. Chem., Int. Ed.* **2005**, *44*, 4046–4048. (g) Giri, R.; Liang, J.; Lei, J.-G.; Li, J.-J.; Wang, D.-H.; Chen, X.; Naggar, I. C.; Guo, C.; Foxman, B. M.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2005**, *44*, 7420–7424. (h) Deprez, N. R.; Kalyani, D.; Krause, A.; Sandford, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 4972–4973. (i) Racowski, J. M.; Dick, A. R.; Sanford, M. S. *J. Am. Chem. Soc.* **2009**, *131*, 10974–10983, and references cited therein.

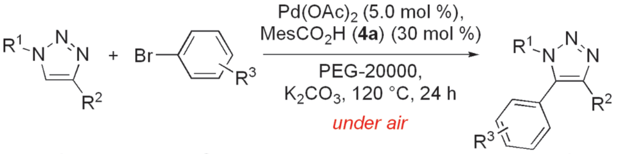
(7) For selected examples of ruthenium-catalyzed direct arylations, see: (a) Kitazawa, K.; Kochi, T.; Sato, M.; Kakiuchi, F. *Org. Lett.* **2009**, *11*, 1951–1954. (b) Ackermann, L.; Born, R.; Vicente, R. *ChemSusChem* **2009**, *2*, 546–549. (c) Ackermann, L.; Mulzer, M. *Org. Lett.* **2008**, *10*, 5043–5045. (d) Özdemir, I.; Demir, S.; Cetinkaya, B.; Gourlaouen, C.; Maseras, F.; Bruneau, C.; Dixneuf, P. H. *J. Am. Chem. Soc.* **2008**, *130*, 1156–1157. (e) Oi, S.; Funayama, R.; Hattori, T.; Inoue, Y. *Tetrahedron* **2008**, *64*, 6051–6059. (f) Ackermann, L.; Born, R.; Álvarez-Bercedo, P. *Angew. Chem., Int. Ed.* **2007**, *46*, 6364–6367. (g) Ackermann, L.; Althammer, A.; Born, R. *Angew. Chem., Int. Ed.* **2006**, *45*, 2619–2622. (h) Kakiuchi, F.; Matsuura, Y.; Kan, S.; Chatani, N. *J. Am. Chem. Soc.* **2005**, *127*, 5936–5945. (i) Oi, S.; Aizawa, E.; Ogino, Y.; Inoue, Y. *J. Org. Chem.* **2005**, *70*, 3113–3119. (j) Ackermann, L. *Org. Lett.* **2005**, *7*, 3123–3125 and references cited therein.

(8) Turner, G. L.; Morris, J. A.; Greaney, M. F. *Angew. Chem., Int. Ed.* **2007**, *46*, 7996–8000.

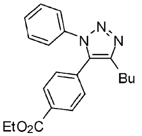
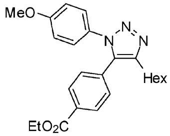
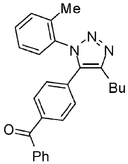
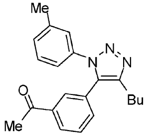
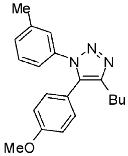
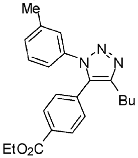
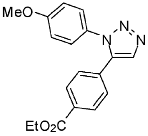
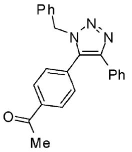
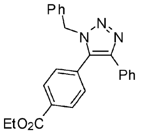
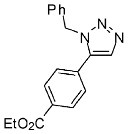
(9) Ohnmacht, S. A.; Mamone, P.; Culshaw, A. J.; Greaney, M. F. *Chem. Commun.* **2008**, 1241–1243.

(10) For recent selected reviews on applications of sustainable PEGs, see: (a) Candeias, N. R.; Branco, L. C.; Gois, P. M. P.; Afonso, C. A. M.; Trindade, A. F. *Chem. Rev.* **2009**, *109*, 2703–2802. (b) Bergbreiter, D. E.; Tian, J.; Hongfa, C. *Chem. Rev.* **2009**, *109*, 530–582. (c) Andrade, C. K. Z.; Alves, L. M. *Curr. Org. Chem.* **2005**, *9*, 195–218. (d) Chen, J.; Spear, S. K.; Huddleston, J. G.; Rogers, R. D. *Green Chem.* **2005**, *7*, 64–82 and references cited therein. Sigma-Aldrich: PEG-400 (380−420 g/mol, mp = 4−8 °C); PEG-2000 (1900−2200 g/mol, mp = 52−54 °C); PEG-20000 (16 000−24 000 g/mol, mp = 63−66 °C).

Table 2. Scope of Palladium(0)-Catalyzed Direct Arylations under Air[a]



1 **2** **3**

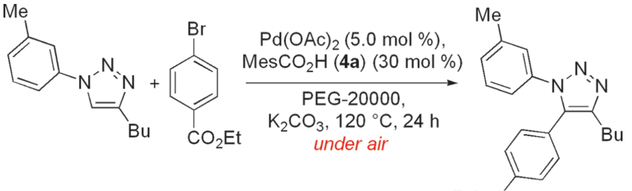
entry	R^1	R^2		2		yield
1	Ph	Bu	**1b**		**3j**	85%
2	4-MeOC$_6$H$_4$	Hex	**1c**		**3k**	70%
3	2-Tol	Bu	**1a**		**3l**	82%
4	3-Tol	Bu	**1d**		**3m**	71%
5	3-Tol	Bu	**1d**		**3n**	52%[b]
6	3-Tol	Bu	**1d**		**3o**	85%
7						77%[c]
8	4-MeOC$_6$H$_4$	H	**1e**		**3p**	70%
9	Bn	Ph	**1f**		**3q**	62%
10	Bn	Ph	**1f**		**3r**	63%
11	Bn	H	**1g**		**3s**	63%

[a] Reaction conditions: **1** (0.50 mmol), **2** (0.75 mmol), Pd(OAc)$_2$ (5.0 mol %), **4a** (30 mol %), PEG-20000 (0.50 g), K$_2$CO$_3$ (1.00 mmol), 120 °C, 24 h, under air, yields of isolated products. [b] In PEG-2000. [c] Pd(OAc)$_2$ (1.0 mol %).

system, which enabled the preparation of diversely substituted *N*-aryl triazoles **3j**−**3p** (entries 1−8). Importantly, a significantly lower loading of the in situ generated catalyst provided a comparable yield of product **3o** (entries 6 and 7). N-Benzylated triazoles **3q**−**3s** could be obtained in the presence of air, as well (entries 9−11). Further, mono-N-substituted triazoles **1e** and **1g** yielded the desired products **3p** and **3s**, respectively, with excellent C-5 regioselectivities (entries 8 and 11).

Interestingly, we found that the palladium(0) catalyst[17] derived from carboxylic acid **4a** could be conveniently recycled when employing PEG-20000 as reaction medium (Scheme 2).[18] While recycling of the catalytic system led to a slight decrease of its activity, these studies represent, to the best of our knowledge, the first example of a recyclable transition metal catalyst for direct arylations through C−H bond cleavages.

Scheme 2. Recyclability of a Direct Arylation Catalyst



1d **2a** **3o**

Cycle 1	Cycle 2	Cycle 3
85%	72%	68%

In summary, we have disclosed first transition-metal-catalyzed direct arylations in nontoxic PEGs as benign

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(11) For ruthenium-catalyzed C−H bond functionalizations with carboxylic acids as additives, see: (a) Ackermann, L.; Novák, P.; Vicente, R.; Hofmann, N. *Angew. Chem., Int. Ed.* **2009**, *48*, 6045–6048. (b) Ackermann, L.; Vicente, R.; Althammer, A. *Org. Lett.* **2008**, *10*, 2299–2302.

(12) (a) Ackermann, L.; Althammer, A.; Born, R. *Tetrahedron* **2008**, *64*, 6115–6124. (b) Ackermann, L.; Althammer, A.; Born, R. *Synlett* **2007**, 2833–2836.

(13) Generally, reported examples of palladium-catalyzed direct arylations with *N*-aryl 1,2,3-triazoles occurred selectively at the heteroarene: (a) Ackermann, L.; Vicente, R.; Born, R. *Adv. Synth. Catal.* **2008**, *350*, 741–748. (b) Ref. 3j.

(14) For copper-catalyzed direct arylations of 1,2,3-triazoles, see: Ackermann, L.; Potukuchi, H. K.; Landsberg, D.; Vicente, R. *Org. Lett.* **2008**, *10*, 3081–3084.

(15) Pivalic acid (**4b**) or pivalates were previously used in palladium(0)-catalyzed direct arylations: (a) Lafrance, M.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 16496–16497. (b) Campo, M. A.; Huang, Q.; Yao, T.; Tian, Q.; Larock, R. C. *J. Am. Chem. Soc.* **2003**, *125*, 11506–11507. (c) Campo, M. A.; Larock, R. C. *J. Am. Chem. Soc.* **2002**, *124*, 14326–14327.

(16) Representative procedure (Table 1, entry 8): A suspension of Pd(OAc)$_2$ (5.6 mg, 0.025 mmol, 5.0 mol %), **4a** (25 mg, 0.15 mmol, 30 mol %), K$_2$CO$_3$ (138 mg, 1.00 mmol), **1a** (108 mg, 0.50 mmol), **2a** (172 mg, 0.75 mmol), and PEG-20000 (500 mg) was stirred for 24 h at 120 °C under air. The cold crude reaction mixture was subjected directly to purification by flash column chromatography on silica gel (*n*-hexane/EtOAc 6:1) to yield **3i** (147 mg, 74%) as a yellow oil.

(17) As to the working mode of the palladium(0) catalyst, we propose the formation of palladium nanoparticles stabilized by carboxylic acid **4a** as well as by the PEG. For a review on, as well as selected examples of, palladium nanoparticles in *traditional* cross-coupling chemistry, see: (a) Reetz, M. T.; de Vries, J. G. *Chem. Commun.* **2004**, 1559–1563. (b) Reetz, M. T.; Westermann, E. *Angew. Chem., Int. Ed.* **2000**, *39*, 165–168. (c) Han, W.; Liu, C.; Jin, Z.-L. *Org. Lett.* **2007**, *9*, 4005–4007.

reaction media through the use of carboxylic acid $MesCO_2H$ (**4a**) as cocatalyst. Importantly, this allowed for unprecedented palladium(0)-catalyzed C−H bond arylations to occur under an atmosphere of air with a user-friendly recyclable phosphine ligand-free catalytic system.

Acknowledgment. Support by the DFG and the Alexander-von-Humboldt foundation (fellowship to R.V.) is gratefully acknowledged.

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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(18) Procedure for recycling studies (Scheme 2): A suspension of $Pd(OAc)_2$ (5.6 mg, 0.025 mmol, 5.0 mol %), **4a** (25 mg, 0.15 mmol, 30 mol %), K_2CO_3 (138 mg, 1.00 mmol), **1d** (108 mg, 0.50 mmol), **2a** (172 mg, 0.75 mmol), and PEG-20000 (500 mg) was stirred under air for 24 h at 120 °C. Et_2O (10 mL) was added to the cold reaction mixture, and the suspension was stirred at ambient temperature for 10 min under air. Et_2O was decanted, and the resulting residue was washed with Et_2O (3 × 10 mL). The combined organic layers were dried and purified by column chromatography on silica gel (*n*-hexane/EtOAc 6:1) to yield **3o** as a colorless oil (154 mg, 85%). Thereafter, the resulting precipitate was reused for two further catalytic direct arylations as described above.