ORGANIC LETTERS

2008
Vol. 10, No. 11
2299−2302

Assisted Ruthenium-Catalyzed C−H Bond Activation: Carboxylic Acids as Cocatalysts for Generally Applicable Direct Arylations in Apolar Solvents

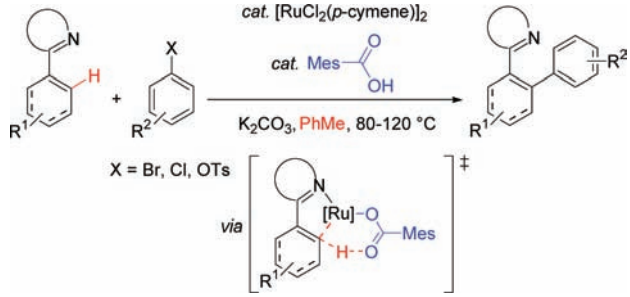
Lutz Ackermann,* Rubén Vicente, and Andreas Althammer

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

lutz.ackermann@chemie.uni-goettingen.de

Received April 4, 2008

ABSTRACT



Catalytic amounts of aromatic carboxylic acid $MesCO_2H$ enabled efficient ruthenium-catalyzed direct arylations in apolar solvents with unparalleled broad scope via a concerted deprotonation−metalation mechanism.

The arylation of (hetero)arenes through the functionalization of C−H bonds is an attractive alternative to cross-couplings with organometallic reagents because of its ecologically and economically benign nature.[1] While most of these direct arylations are accomplished with palladium-based catalysts,[1–3] recent studies highlight the potential of ruthenium complexes in these challenging transformations.[1a] Unfortunately, experimental studies on the working mode of these promising ruthenium complexes are thus far not available.[1a,4] Recently, we found that efficient direct arylations of arenes are achieved with ruthenium complexes derived from air-stable (heteroatom-substituted) secondary phosphine oxide (HA)SPO[1b,5] preligands.[6–9] Since ruthenacycles of substituted arenes were prepared stoichiometrically in the presence of sodium acetate under mild reaction conditions,[10] we

(1) Recent reviews on C–H bond functionalizations: (a) Ackermann, L. *Top. Organomet. Chem.* **2007**, *24*, 35–60. (b) Ackermann, L. *Synlett* **2007**, 507–526. (c) Satoh, T.; Miura, M. *Top. Organomet. Chem.* **2007**, *24*, 61–84. (d) Satoh, T.; Miura, M. *Chem. Lett.* **2007**, *36*, 200–205. (e) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174–238. (f) Seregin, I. V.; Gevorgyan, V. *Chem. Soc. Rev.* **2007**, *36*, 1173–1193. (g) Bergman, R. G. *Nature* **2007**, *446*, 391–393. (h) Campeau, L.-C.; Stuart, D. R.; Fagnou, K. *Aldrichim. Acta* **2007**, *40*, 35–41. (i) Daugulis, O.; Zaitsev, V. G.; Shabashov, D.; Pham, Q. N.; Lazareva, A. *Synlett* **2006**, 3382–3388. (j) Yu, J.-Q.; Giri, R.; Chen, S. *Org. Biomol. Chem.* **2006**, 4041–4047.

(2) Selected recent rhodium-catalyzed direct arylations: (a) Lewis, J. C.; Wu, J. Y.; Bergman, R. G.; Ellman, J. A. *Angew. Chem., Int. Ed.* **2006**, *45*, 1589–1591. (b) Yanagisawa, S.; Sudo, T.; Noyori, R.; Itami, K. *J. Am. Chem. Soc.* **2006**, *128*, 11748–11749. (c) Proch, S.; Kempe, R. *Angew. Chem., Int. Ed.* **2007**, *46*, 3135–3138. (d) Vogler, T.; Studer, A. *Org. Lett.* **2008**, *10*, 129–131, and references cited therein.

(3) Copper-catalyzed direct arylations: (a) Do, H.-Q.; Daugulis, O. *J. Am. Chem. Soc.* **2008**, *130*, 1128–1129. (b) Do, H.-Q.; Daugulis, O. *J. Am. Chem. Soc.* **2007**, *1292*, 1404–12405.

(4) Ruthenium-catalyzed direct arylations were recently studied computationally: Özdemir, I.; Demir, S.; Cetinkaya, B.; Gourlaouen, C.; Maseras, F.; Bruneu, C.; Dixneuf, P. H. *J. Am. Chem. Soc.* **2008**, *130*, 1156–1157.

(5) Ackermann, L. *Synthesis* **2006**, 1557–1571.

(6) Ackermann, L. *Org. Lett.* **2005**, *7*, 3123–3125.

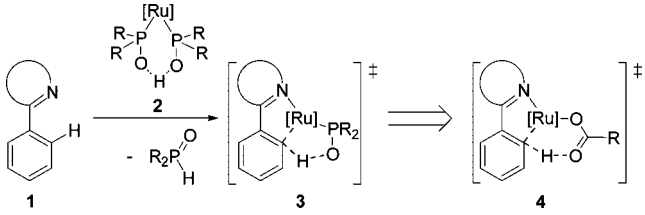
(7) Ackermann, L.; Althammer, A.; Born, R. *Angew. Chem., Int. Ed.* **2006**, *45*, 2619–2622.

(8) For the use of complexes derived from *N*-heterocyclic carbenes, see: refs 4 and 6: Ackermann, L.; Born, R.; Álvarez-Bercedo, P. *Angew. Chem., Int. Ed.* **2007**, *46*, 6364–6367.

10.1021/ol800773x CCC: $40.75
Published on Web 04/26/2008

wondered whether the high catalytic efficacy of (HA)SPO preligands originated from an assisted intramolecular proton abstraction mechanism,[11] illustrated as transition-state model **3** in Scheme 1. By analogy, a concerted cyclometalation−

Scheme 1. Cooperative Metalation−Deprotonation

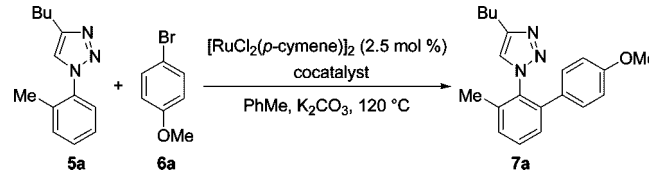


deprotonation process should be also accessible through the use of substoichiometric amounts of carboxylates[12] via transition state **4**. Consequently, we probed the use of acids as cocatalysts in ruthenium-catalyzed direct arylations with aryl (pseudo)halides[13] as electrophiles.

Methodologies for copper-catalyzed regioselective syntheses of 1,2,3-triazoles **5**[14] recently enabled their widespread applications in various research areas, ranging from bioorganic chemistry to material sciences.[15] Therefore, we set out to probe this valuable heterocyclic scaffold in novel ruthenium-catalyzed direct arylations.

All ruthenium-catalyzed direct arylations with organic electrophiles were limited to the use of the highly polar solvent *N*-methylpyrrolidinone (NMP).[1a] Consequently, we focused on the use of significantly less polar toluene as solvent (Table 1). As expected, no reaction occurred in

Table 1. Ruthenium-Catalyzed Direct Arylation of Triazole **5a** in PhMe[a]



entry	cocatalyst	isolated yield (%)
1		
2	HIPrCl[b]	9
3	PPh_3[b]	20
4	$(1\text{-Ad})_2P(O)H$[b]	85
5	$(1\text{-Ad})CO_2H$[c]	85
6	$t\text{-BuCO}_2H$[c]	66
7	$i\text{-PrCO}_2H$[c]	69
8	$(PhO)_2P(O)OH$[c]	50
9	$MesCO_2H$[c]	93
10	$MesCO_2H$[b]	89

[a] Reaction conditions: $[RuCl_2(p\text{-cymene})]_2$ (2.5 mol %), cocatalyst (10.0−30.0 mol %), K_2CO_3 (1.0 mmol), **5a** (0.50 mmol), **6a** (0.75 mmol), PhMe (2 mL), 120 °C, 22 h. [b] 10.0 mol %. [c] 30 mol %. HIPrCl = *N*,*N*′-bis-(2,6-diisopropyl phenyl)imidazolium chloride.

toluene[16] in the absence of an additive (entry 1). Various *N*-heterocyclic carbene precursors[4,8] or phosphines[9] failed to provide satisfactory results as well (entries 2, and 3).

On the contrary, an efficient ruthenium-catalyzed direct arylation of triazole **5a** was achieved with air-stable SPO $(1\text{-Ad})_2P(O)H$[6] as preligand (entry 4). Thus, triazole **7a** was exclusively formed with a regioselectivity that is complementary to the one observed in palladium-catalyzed[17] direct arylations of the heterocyclic moiety in 1,2,3-triazoles. Remarkably, carboxylic (entries 5−7) or phosphoric acids (entry 8) enabled efficient C−H bond functionalizations of triazole **5a** in toluene as well. Among a variety of cocatalysts, aromatic sterically hindered carboxylic acid $MesCO_2H$ proved superior (entry 9), thus allowing for a reduction of cocatalyst loading (entry 10).

With a highly active catalytic system in hand, we probed its scope in direct arylations of 1,2,3-triazoles **5** employing apolar toluene as solvent (Table 2).[18] A variety of functionalized electron-poor (entries 1−5) as well as electron-rich (entries 6, and 7) aryl bromides was converted with high efficacy. Additionally, a heteroaryl bromide enabled the chemo- and regioselective preparation of triazole **7i** with excellent isolated yield (entry 8).

(9) For the use of PPh_3 as ligand in ruthenium-catalyzed direct arylations with aryl bromides in NMP, see: (a) Oi, S.; Aizawa, E.; Ogino, Y.; Inoue, Y. *J. Org. Chem.* **2005**, *70*, 3113–3119. (b) Oi, S; Sakai, K.; Inoue, Y. *Org. Lett.* **2005**, *7*, 4009–4011, and references cited therein. See also: (c) Ackermann, L.; Althammer, A.; Born, R. *Synlett* **2007**, 2833–2836.

(10) (a) Davies, D. L.; Al-Duaij, O.; Fawcett, J.; Giardiello, M.; Hilton, S. T.; Russell, R. D. *Dalton Trans.* **2003**, 4132–4138. (b) For previous work on ortho-metalations of functionalized arenes, see: Fernandez, S.; Pfeffer, M.; Ritleng, V.; Sirlin, C. *Organometallics* **1999**, *18*, 2390–2394, and references cited therein.

(11) Cooperative mechanisms were previously proposed for transition metal-catalyzed C−H bond functionalizations: (a) Ryabov, A. D *Chem. Rev.* **1990**, *90*, 403–424. (b) Davies, D. L.; Donald, S. M. A. Macgregor, S. A. *J. Am. Chem. Soc.* **2005**, *127*, 13754–13755. (c) Tenn, W. J., III; Young, K. J. H.; Bhalla, G.; Oxgaard, J.; Goddard, W. A., III; Periana, R. A *J. Am. Chem. Soc.* **2005**, *127*, 14172–14173. (d) Feng, Y.; Lail, M.; Barakat, K. A.; Cundari, T. R.; Gunnoe, T. B.; Petersen, J. L. *J. Am. Chem. Soc.* **2005**, *127*, 14174–14175. (e) Garcia-Cuadrado, D.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M. *J. Am. Chem. Soc.* **2006**, *128*, 1066–1067. (f) Feng, Y.; Lail, M.; Foley, N. A.; Gunnoe, T. B.; Barakat, K. A.; Cundari, T. R.; Petersen, J. L. *J. Am. Chem. Soc.* **2006**, *128*, 7982–7994. (g) Tenn, W. J., III; Young, K. J. H.; Oxgaard, J.; Nielsen, R. J.; Goddard, W. A., III; Periana, R. A. *Organometallics* **2006**, *25*, 5173–5175. (h) Oxgaard, J.; Tenn, W. J., III; Nielsen, R. J.; Periana, R. A.; Goddard, W. A., III *Organometallics* **2007**, *26*, 1565–1567. (i) Garcia-Cuadrado, D.; de Mendoza, P.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M. *J. Am. Chem. Soc.* **2007**, *129*, 6880–6886. (j) Pascual, S.; de Mendoza, P.; Echavarren, A. M. *Org. Biomol. Chem.* **2007**, 2727–2734.

(12) Pivalic acid was used in highly efficient palladium-catalyzed direct arylations: (a) Lafrance, M.; Fagnou, K *J. Am. Chem. Soc.* **2006**, *128*, 16496–16497. (b) Lafrance, M.; Gorelsky, S. I.; Fagnou, K. *J. Am. Chem. Soc.* **2007**, *129*, 14570–14571.

(13) For ruthenium-catalyzed direct arylations and alkenylations with organometallic reagents, see: Ueno, S.; Chatani, N.; Kakiuchi, F. *J. Org. Chem.* **2007**, *72*, 3600–3602, and references cited therein.

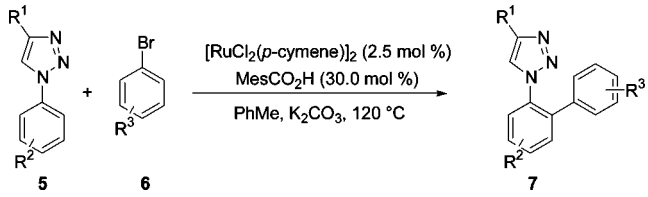
(14) (a) Huisgen, R. *Angew. Chem.* **1963**, *75*, 604–637. (b) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596–2599. (c) Tornoe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3057–3064.

(15) Selected recent reviews (a) Nandivada, H.; Jiang, X.; Lahann, J. *Adv. Mater.* **2007**, *19*, 2197–2208. (b) Angell, Y. L.; Burgess, K. *Chem. Soc. Rev.* **2007**, *36*, 1674–1689. (c) Lutz, J.-F. *Angew. Chem., Int. Ed.* **2007**, *46*, 1018–1025.

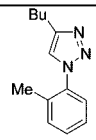
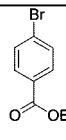
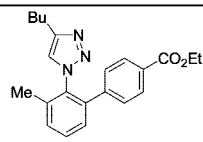
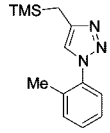
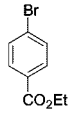
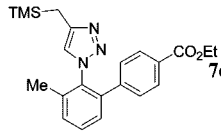
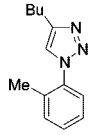
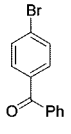
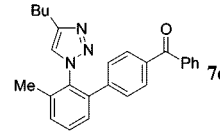
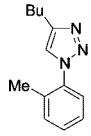
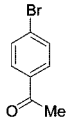
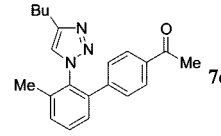
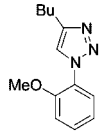
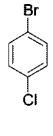
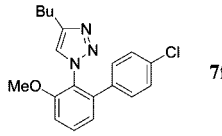
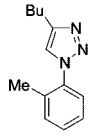
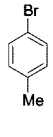
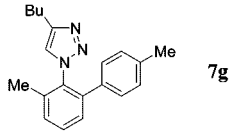
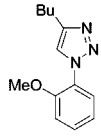
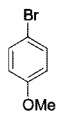
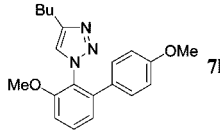
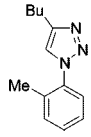
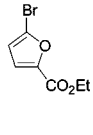
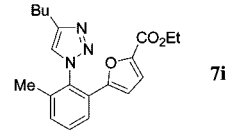
(16) Under otherwise identical reaction conditions, triazole **7a** was only isolated in 22% yield when NMP was used as solvent.

(17) (a) Ackermann, L.; Vicente, R.; Born, R. *Adv. Synth. Catal.* **2008**, *350*, 741–748. (b) Chuprakov, S.; Chernyak, N.; Dudnik, A. S.; Gevorgyan, V. *Org. Lett.* **2007**, *9*, 2333–2336. (c) Iwasaki, M.; Yorimitsu, H.; Oshima, K. *Chem. Asian J.* **2007**, *2*, 1430–1435.

Table 2. Ruthenium-Catalyzed Direct Arylations of Triazoles **5**[a]



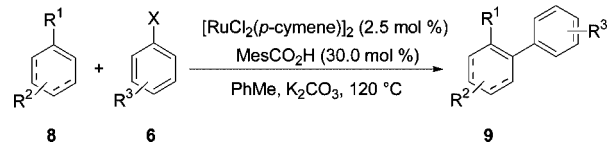
5 **6** **7**

entry	5	6	7	isolated yield
1			 **7b**	87 %
2			 **7c**	97 %
3			 **7d**	63 %
4			 **7e**	70 %
5			 **7f**	87 %
6			 **7g**	76 %
7			 **7h**	88 %
8			 **7i**	95 %

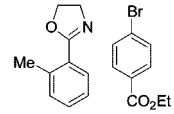
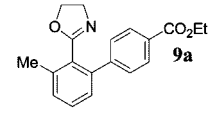
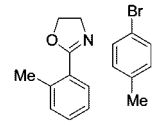
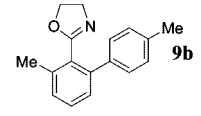
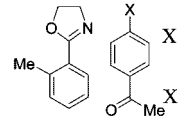
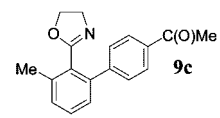
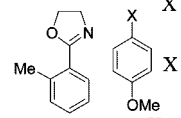
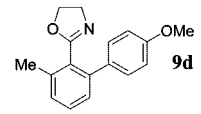
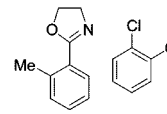
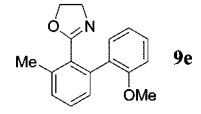
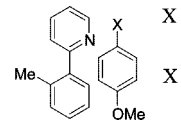
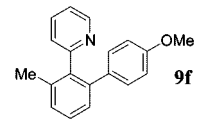
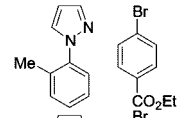
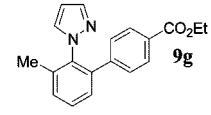
[a] Reaction conditions: **5** (0.50 mmol), **6** (0.75 mmol), $[RuCl_2(p\text{-cymene})]_2$ (2.5 mol %), $MesCO_2H$ (30.0 mol %), K_2CO_3 (2.0 equiv), PhMe (2 mL), 120 °C, 16−20 h; yields of isolated product.

Importantly, direct arylations with $MesCO_2H$ as cocatalyst were not restricted to triazoles as pronucleophiles but proved broadly applicable (Table 3). Hence, oxazolines (entries 1−10), pyridines (entries 11−13, and 16), and pyrazoles (entries 14, and 15) were directly arylated in toluene as solvent. C−H bond functionalizations with aryl bromides as electrophiles could be conveniently performed at reaction

Table 3. Scope of Ruthenium-Catalyzed Direct Arylations[a]



8 **6** **9**

entry	8	6	9	yield
1			 **9a**	99 %
2			 **9b**	96 %
3		X = Br		90 %[b]
4		X = Br	 **9c**	51 %[c]
5		X = Cl		92 %[b]
6		X = OTs		75 %
7		X = Br		95 %[b]
8		X = Cl	 **9d**	91 %
9		X = OTs		51 %
10			 **9e**	73 %
11		X = Br		99 %
12		X = Cl	 **9f**	87 %
13		X = OTs		70 %
14			 **9g**	73 %
15			**9h**	86 %
16			**9i**	59 %

[a] Reaction conditions: **8** (0.50 mmol), **6** (0.75 mmol), $[RuCl_2(p\text{-cymene})]_2$ (2.5 mol %), $MesCO_2H$ (30.0 mol %), K_2CO_3 (1.00 mmol), PhMe (2 mL), 120 °C, 16−20 h; yields of isolated product. [b] 100 °C. [c] 80 °C.

temperatures as low as 80−100 °C (entries 3, 4, and 7). Readily available, but less reactive aryl chlorides (entries 5,

8, and 12) or tosylates (entries 6, 9, and 13) provided the desired products with comparably high yields. Finally, the use of an alkene allowed for the diastereoselective formation of trisubstituted alkene **9i** (entry 16).

In conclusion, mechanistic considerations on the working mode of ruthenium-catalyzed direct arylations resulted in the development of a highly active catalyst with ample scope. Thus, substoichiometric amounts of carboxylic acid $MesCO_2H$ enabled ruthenium-catalyzed direct arylations with organic halides to be performed efficiently in an apolar solvent. With respect to both electrophiles and pronucleophiles, the catalytic system displayed an unparalleled broad scope, which allowed inter alia for the use of triazoles in ruthenium-catalyzed direct arylations.

Acknowledgment. Support by the Spanish Ministerio de Educación y Ciencia, the Alexander-von-Humboldt foundation (fellowships to R.V.), the DFG, the Fonds der Chemischen Industrie, and Sanofi-Aventis (Frankfurt) 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.

OL800773X

(18) **Representative Procedure (Table 1, Entry 9).** A suspension of $[RuCl_2(p\text{-cymene})]_2$ (7.7 mg, 0.012 mmol, 2.5 mol %), $MesCO_2H$ (25 mg, 0.15 mmol, 30 mol %), K_2CO_3 (138 mg, 1.00 mmol), **5a** (108 mg, 0.50 mmol), and **6a** (140 mg, 0.75 mmol) in PhMe (2 mL) was stirred under N_2 for 18 h at 120 °C. Thereafter, Et_2O (75 mL) and H_2O (75 mL) were added to the reaction mixture at ambient temperature. The separated aqueous phase was extracted with Et_2O (2 × 75 mL). The combined organic layers were washed with H_2O (50 mL) and brine (50 mL), dried over Na_2SO_4, and concentrated in vacuum. The remaining residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc 3:1) to yield **7a** as a colorless oil (149 mg, 93%).