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Ruthenium-Catalyzed C−H Bond Arylations of Arenes Bearing Removable Directing Groups via Six-Membered Ruthenacycles

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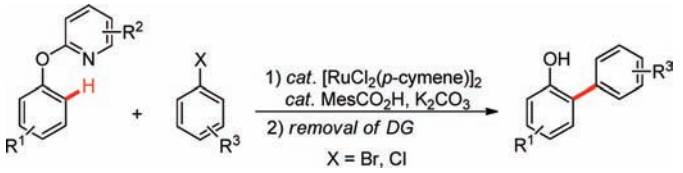
ABSTRACT



Ruthenium-catalyzed direct arylations of phenols bearing removable directing groups were accomplished through carboxylate assistance via six-membered ruthenacycles as key intermediates.

In recent years, transition-metal-catalyzed direct arylations have emerged as increasingly viable alternatives to traditional cross-coupling reactions.[1] Particularly, ruthenium catalysts have proven to be valuable tools for sustainable C−H bond arylations, with recent applications to step economical syntheses of bioactive compounds in academia and pharmaceutical industries.[2,3] However, despite this remarkable recent progress, ruthenium-catalyzed C−H bond arylations of arenes with aryl halides continue to lack generality, as illustrated by their severe limitation to substrates that form five-membered ruthenacycles (Scheme 1).[2,3] As a direct consequence, ruthenium-catalyzed[4] direct arylations with aryl (pseudo)halides were thus far unfortunately not viable with arenes[5] displaying removable directing groups. Recently, we introduced carboxylates as effective cocatalysts for most generally

(1) Selected recent reviews on C−H bond functionalizations: (a) Yeung, C. S.; Dong, V. M. *Chem. Rev.* **2011**, *111*, 1215–1292. (b) Ackermann, L.; Potukuchi, H. K. *Org. Biomol. Chem.* **2010**, *8*, 4503–4513. (c) Daugulis, O. *Top. Curr. Chem.* **2010**, *292*, 57–84. (d) Sun, C.-L.; Li, B.-J.; Shi, Z.-J. *Chem. Commun.* **2010**, *46*, 677–685. (e) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 624–655. (f) Ackermann, L. *Chem. Commun.* **2010**, *46*, 4866–4877. (g) Fagnou, K. *Top. Curr. Chem.* **2010**, *292*, 35–56. (h) Giri, R.; Shi, B.-F.; Engle, K. M.; Maugel, N.; Yu, J.-Q. *Chem. Soc. Rev.* **2009**, *38*, 3242–3272. (i) Ackermann, L.; Vicente, R.; Kapdi, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 9792–9826. (j) Thansandote, P.; Lautens, M. *Chem.—Eur. J.* **2009**, *15*, 5874–5883. (k) Satoh, T.; Miura, M. *Chem. Lett.* **2007**, *36*, 200–205 and references cited therein.

(2) A review: Ackermann, L.; Vicente, R. *Top. Curr. Chem.* **2010**, *292*, 211–229.

(3) For illustrative examples, see: (a) Lakshman, M. K.; Deb, A. C.; Chamala, R. R.; Pradhan, P.; Pratap, R. *Angew. Chem., Int. Ed.* **2011**, *50*, 11400–11404. (b) Seki, M.; Nagahama, M. *J. Org. Chem.* **2011**, *76*, 10198–10206. (c) Doherty, S.; Knight, J. G.; Addyman, C. R.; Smyth, C. H.; Ward, N. A. B.; Harrington, R. W. *Organometallics* **2011**, *30*, 6010–6016. (d) Seki, M. *ACS Catal.* **2011**, *1*, 607–610. (e) Yu, B.; Yan, X.; Wang, S.; Tang, N.; Xi, C. *Organometallics* **2010**, *29*, 3222–3226. (f) Miura, H.; Wada, K.; Hosokawa, S.; Inoue, M. *Chem.—Eur. J.* **2010**, *16*, 4186–4189. (g) Ackermann, L.; Born, R.; Vicente, R. *ChemSusChem.* **2009**, 546–549. (h) Özdemir, I.; Demir, S.; Cetinkaya, B.; Gourlaouen, C.; Maseras, F.; Bruneau, C.; Dixneuf, P. H. *J. Am. Chem. Soc.* **2008**, *130*, 1156–1157. (i) Oi, S.; Sasamoto, H.; Funayama, R.; Inoue, Y. *Chem. Lett.* **2008**, *37*, 994–995. (j) Ackermann, L.; Althammer, A.; Born, R. *Tetrahedron* **2008**, *64*, 6115–6124. (k) Ackermann, L.; Althammer, A.; Born, R. *Synlett* **2007**, 2833–2836. (l) Ackermann, L.; Born, R.; Álvarez-Bercedo, P. *Angew. Chem., Int. Ed.* **2007**, *46*, 6364–6367. (m) Ackermann, L. *Org. Lett.* **2005**, *7*, 3123–3125. (n) Oi, S.; Aizawa, E.; Ogino, Y.; Inoue, Y. *J. Org. Chem.* **2005**, *70*, 3113–3119 and references cited therein.

(4) For representative examples of *palladium*-catalyzed C−H bond functionalizations of arenes bearing removable directing groups, see: (a) Huang, C.-H.; Chattopadhyay, B.; Gevorgyan, V. *J. Am. Chem. Soc.* **2011**, *133*, 12406–12409. (b) Chu, J.-H.; Lin, P.-S.; Wu, M.-J. *Organometallics* **2010**, *29*, 4058–4065. (c) Chernyak, N.; Dudnik, A. S.; Huang, C.; Gevorgyan, V. *J. Am. Chem. Soc.* **2010**, *132*, 8270–8272. (d) Gu, S.; Chen, C.; Chen, W. *J. Org. Chem.* **2009**, *74*, 7203–7206 and references cited therein.

(5) For direct arylations of heteroarenes, see: Ackermann, L.; Lygin, A. V. *Org. Lett.* **2011**, *13*, 3332–3335.

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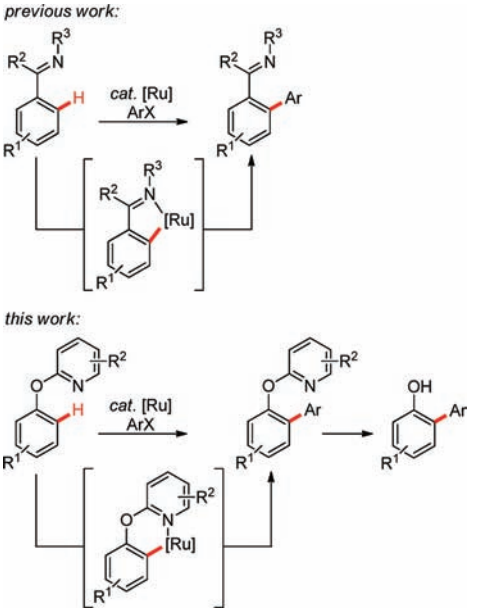
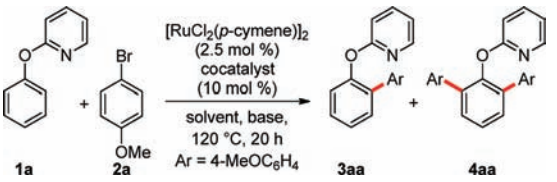
applicable ruthenium(II)-catalyzed direct arylations in various solvents.[6,7] In continuation of our studies,[8] we devised first ruthenium-catalyzed direct arylations of arenes *via* six-membered ruthenacycles that set the stage for a removable directing group strategy, the development of which we report herein.

Scheme 1. Removable Directing Group Strategy *via* Six-Membered Ruthenacycles



At the outset, we tested representative *in situ* generated ruthenium catalysts in the direct arylation of 2-phenoxypyridine[9] (**1a**) (Table 1). Interestingly, the most efficient catalysis was achieved with catalysts derived from secondary phosphine oxide[10] **5** or carboxylic acid **6**,[8a] while unsatisfactory results were obtained with either N-heterocyclic carbene precursors or tertiary phosphines (entries 1−5). The catalytic C−H bond arylation occurred in NMP as the solvent, yet proceeded also efficiently in H_2O as a sustainable reaction medium (entries 6−8). Furthermore, carboxylate assistance enabled high-yielding direct arylations in toluene, with K_2CO_3 being the optimal base (entries 9−17).

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



entry	cocatalyst	base	solvent	**3aa** (%)	**4aa** (%)
1	–	K_2CO_3	NMP	–	–
2	HIPrCl	K_2CO_3	NMP	4	6
3	PPh_3	K_2CO_3	NMP	17	–
4	$(1\text{-Ad})_2P(O)H$ (**5**)	K_2CO_3	NMP	54	44
5	$MesCO_2H$ (**6**)[b]	K_2CO_3	NMP	14	73
6	–	K_2CO_3	H_2O	–	–
7	KPF_6[c]	K_2CO_3	H_2O	–	–
8	$MesCO_2H$ (**6**)[b]	K_2CO_3	H_2O	50	31
9	–	K_2CO_3	PhMe	–	–
10	HIPrCl	K_2CO_3	PhMe	–	–
11	PPh_3	K_2CO_3	PhMe	–	–
12	KPF_6[c]	K_2CO_3	PhMe	–	–
13	$MesCO_2H$ (**6**)[b]	KOAc	PhMe	–	–
14	$MesCO_2H$ (**6**)[b]	NaOAc	PhMe	–	–
15	$MesCO_2H$ (**6**)[b]	Na_2CO_3	PhMe	32	–
16	$MesCO_2H$ (**6**)[b]	Ag_2CO_3	PhMe	20	–
17	$MesCO_2H$ (**6**)[b]	K_2CO_3	PhMe	66	24

[a] Reaction conditions: **1a** (1.50 mmol), **2a** (0.50 mmol), $[RuCl_2(p\text{-cymene})]_2$ (2.5 mol %), cocatalyst (10 mol %), K_2CO_3 (1.00 mmol), solvent (2.0 mL), 120 °C, 20 h; HIPr = *N*,*N*′-bis(2,6-di-isopropylphenyl)-imidazolium, yields of isolated products. [b] **6** (30 mol %). [c] 40 mol %.

To further explore the influence of the additive and the base on catalytic efficacy, we probed the direct arylation of *ortho*-fluoro-substituted arene **1b** (Table 2). Thus, the most effective catalysis was again achieved with $MesCO_2H$ (**6**) as the cocatalyst and K_2CO_3 as the base, while KO_2CMes as the stoichiometric base was found to be ineffective.[8a] Generally, the ruthenium(II) carboxylate catalysts displayed a remarkably high chemoselectivity, and products stemming from catalytic C−F[11] bond functionalizations were hence not observed.

The scope of the optimized catalytic system was thereafter explored in the direct arylation of differently substituted 2-aryloxypyridines **1** (Scheme 2).

(6) (a) Ackermann, L.; Vicente, R.; Althammer, A. *Org. Lett.* **2008**, *10*, 2299–2302. (b) Ackermann, L.; Mulzer, M. *Org. Lett.* **2008**, *10*, 5043–5036. (c) Ackermann, L.; Novák, P. *Org. Lett.* **2009**, *11*, 4966–4969. (d) Ackermann, L.; Vicente, R. *Org. Lett.* **2009**, *11*, 4922–4925. (e) Ackermann, L.; Jeyachandran, R.; Potukuchi, H. K.; Novák, P.; Büttner, L. *Org. Lett.* **2010**, *12*, 2056–2059. (f) Ackermann, L.; Vicente, R.; Potukuchi, H. K.; Pirovano, V. *Org. Lett.* **2010**, *12*, 5032–5035. (g) Ackermann, L.; Novák, P.; Vicente, R.; Pirovano, V.; Potukuchi, H. K. *Synthesis* **2010**, 2245–2253. (h) Ackermann, L.; Hofmann, N.; Vicente, R. *Org. Lett.* **2011**, *13*, 1875–1877. Oxidative transformations: (i) Ackermann, L.; Lygin, A. V.; Hofmann, N. *Angew. Chem., Int. Ed.* **2011**, *50*, 6379–6382. (j) Ackermann, L.; Pospech, J. *Org. Lett.* **2011**, *13*, 4153–4155. (k) Ackermann, L.; Fenner, S. *Org. Lett.* **2011**, *13*, 6548–6551.

(7) For subsequent reports, see: (a) Flegeau, E. F.; Bruneau, C.; Dixneuf, P. H.; Jutand, A. *J. Am. Chem. Soc.* **2011**, *133*, 10161–10170. (b) Stefane, B.; Fabris, J.; Pozgan, F. *Eur. J. Org. Chem.* **2011**, 3474–3481. (c) Ouellet, S. G.; Roy, A.; Molinaro, C.; Angelaud, R.; Marcoux, J.-F.; O'Shea, P. D.; Davies, I. W. *J. Org. Chem.* **2011**, *76*, 1436–1439. (d) Li, W.; Arockiam, P. B.; Fischmeister, C.; Bruneau, C.; Dixneuf, P. H. *Green Chem.* **2011**, *13*, 2315–2319. (e) Arockiam, P. B.; Fischmeister, C.; Bruneau, C.; Dixneuf, P. H. *Angew. Chem., Int. Ed.* **2010**, *49*, 6629–6632. (f) Arockiam, P.; Poirier, V.; Fischmeister, C.; Bruneau, C.; Dixneuf, P. H. *Green Chem.* **2009**, *11*, 1871–1875.

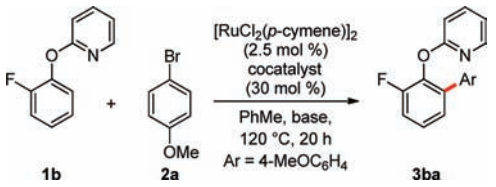
(8) For reviews, see: (a) Ackermann, L. *Chem. Rev.* **2011**, *111*, 1315–1345. (b) Ackermann, L. *Pure Appl. Chem.* **2010**, *82*, 1403–1413. (c) Ackermann, L.; Born, R.; Spatz, J. H.; Althammer, A.; Gschrei, C. J. *Pure Appl. Chem.* **2006**, *78*, 209–214.

(9) For a ruthenium-catalyzed cross-dehydrogenative silylation, see: Kakiuchi, F.; Igi, K.; Matsumoto, M.; Hayamizu, T.; Chatani, N.; Murai, S. *Chem. Lett.* **2002**, 396–397.

(10) Reviews: (a) Ackermann, L. *Isr. J. Chem.* **2010**, *50*, 652–663. (b) Ackermann, L. *Synlett* **2007**, 507–526.

(11) (a) Kawamoto, K.; Kochi, T.; Sato, M.; Mizushima, E.; Kakiuchi, F. *Tetrahedron Lett.* **2011**, *52*, 5888–5890. (b) See also: Ackermann, L.; Wechsler, C.; Kapdi, A. R.; Althammer, A. *Synlett* **2010**, 294–298.

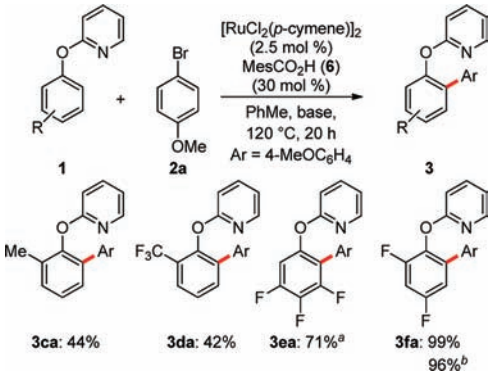
Table 2. Ruthenium-Catalyzed Direct Arylation of Arene **1b**[a]



entry	cocatalyst	base	**3ba**
1	–	K_2CO_3	–
2	–	KOAc	61%
3	KOAc	K_2CO_3	91%
4	$MesCO_2H$ (**6**)	KOAc	<5%
5	$MesCO_2H$ (**6**)	NaOAc	<5%
6	$MesCO_2H$ (**6**)	CsOAc	30%
7	**$MesCO_2H$ (6)**	**K_2CO_3**	**98%**
8	–	KO_2CMes	<5%

[a] Reaction conditions: **1b** (1.50 mmol), **2a** (0.50 mmol) [$RuCl_2$(*p*-cymene)]$_2$ (2.5 mol %), cocatalyst (30 mol %), K_2CO_3 (1.00 mmol), solvent (2.0 mL), 120 °C, 20 h; yields of isolated products.

Scheme 2. Ruthenium-Catalyzed Direct Arylations of Arenes **1**



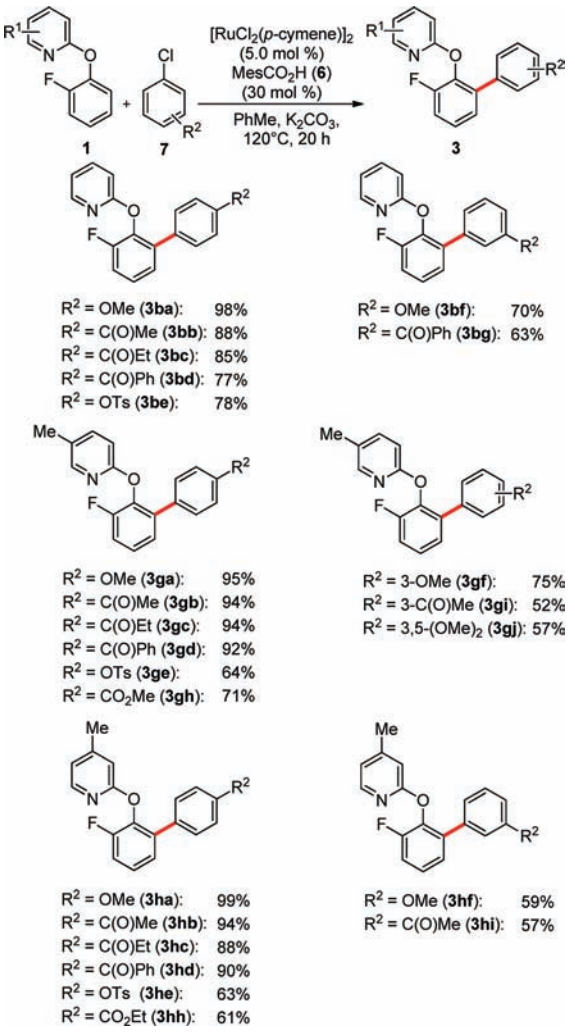
[a] Diarylated product **4ea** (11%) was also isolated. [b] [$RuCl_2$(*p*-cymene)]$_2$ (1.0 mol %).

The ruthenium(II) carboxylate complex was found to be broadly applicable and enabled the conversion of both electron-rich and electron-deficient arenes.[12] Generally, the latter substrates provided higher yields of products **3**, thus rendering a simple S_EAr-type mechanism less likely to be operative. Importantly, a satisfactory result was also obtained when using a significantly reduced catalyst loading.

Notably, the ruthenium(II) carboxylate catalyst was not restricted to the use of aryl bromides **2**, but also allowed for efficient C−H bond transformations with less expensive, yet more challenging aryl chlorides **7** as the arylating reagents (Scheme 3).

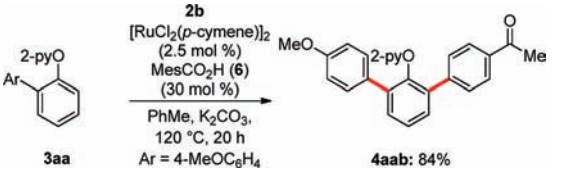
(12) The direct arylation of *ortho*-methoxy-substituted 2-phenoxypyridine with aryl bromide **2a** provided the desired product in 38% isolated yield.

Scheme 3. Scope of Direct Arylations with Aryl Chlorides **7**



The synthesis of unsymmetrically disubstituted arene **4aab** was accomplished through a sequential C−H bond functionalization strategy (Scheme 4).

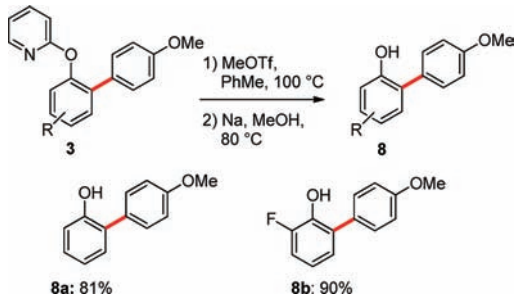
Scheme 4. Synthesis of Unsymetrically Disubstituted Arene **4aab**



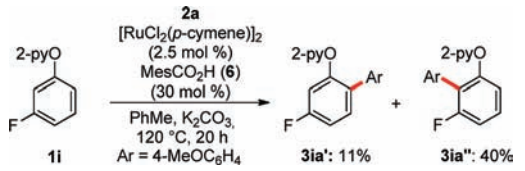
Further, we were pleased to find that the directing group could easily be removed[4b] from biaryls **3**, thereby yielding the desired phenols[13] **8** (Scheme 5).

As to the catalyst's working mode, an intramolecular competition experiment with *meta*-fluoro-substituted arene **1i** preferentially delivered product **3ia**″ through direct functionalization at the kinetically more acidic

Scheme 5. Removal of Directing Group



Scheme 6. Intramolecular Competition Experiment

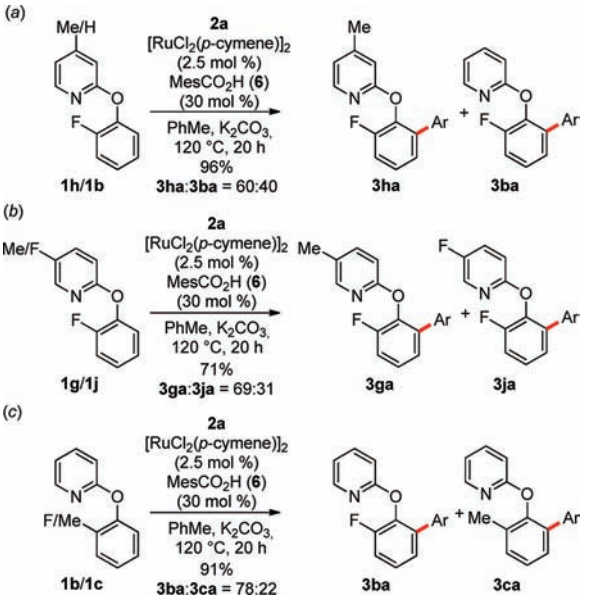


C−H bond (Scheme 6). This observation can be rationalized with a carboxylate-assisted deprotonative C−H bond ruthenation.

Intermolecular competition experiments with substrates **1** bearing different substituents on the pyridine moiety revealed that arenes with more electron-rich directing groups reacted preferentially (Scheme 7a and b). Furthermore, electron-deficient arenes were converted with higher relative rates (Scheme 7c), which contrasts with previously made observations in ruthenium-catalyzed direct arylations with aryl halides.[6f]

(13) For the elegant use of rather expensive rhodium or palladium catalysts for direct arylations of (*in situ* generated) phenol derivatives, see: (a) Bedford, R. B.; Coles, S. J.; Hursthouse, M. B.; Limmert, M. E. *Angew. Chem., Int. Ed.* **2003**, *42*, 112–114. (b) Bedford, R. B.; Limmert, M. E. *J. Org. Chem.* **2003**, *68*, 8669–8662. (c) Huang, C.; Gevorgyan, V. *J. Am. Chem. Soc.* **2009**, *131*, 10844–10845. See also: (d) Boebel, T. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2008**, *130*, 7534–7535.

Scheme 7. Intermolecular Competition Experiments (Ar = 4-MeOC$_6$H$_4$)



In summary, we have reported on the first ruthenium-catalyzed direct arylation of arenes with organic electrophiles using removable directing groups. High catalytic efficacy was ensured by ruthenium(II) carboxylate catalysts, which allowed for unprecedented ruthenium-catalyzed C−H bond arylations with aryl bromides and chlorides through six-membered ruthenacycles as the key intermediates.

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

The authors declare no competing financial interest.