CHEMISTRY
A EUROPEAN JOURNAL

DOI: 10.1002/chem.200903564

Recyclable Solid Ruthenium Catalysts for the Direct Arylation of Aromatic C–H Bonds

Hiroki Miura, Kenji Wada,* Saburo Hosokawa, and Masashi Inoue[a]

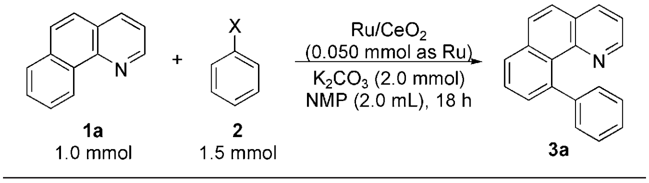
The development of new environmentally benign processes for synthesizing organic compounds is one of the most important issues currently facing synthetic chemists.[1] If efficiencies comparable to those achieved with homogeneous catalysis can be realized, heterogeneous catalysis is quite attractive, because the catalysts can be readily separated from the reaction media and re-used.[2] On the other hand, the formation of C–C bonds by the direct activation of less reactive hydrocarbon C–H bonds by using homogeneous, transition-metal catalysts has also attracted considerable attention in modern synthetic chemistry.[3] Several solid catalysts have been reported to be effective for use in conventional C–C bond-forming reactions;[4] the arylation of heteroarenes or phenols over heterogeneous Ni, Pd, or Ru catalysts have been reported.[5] However, to the best of our knowledge, there have been no previous reports of C–C bond formation by using chelation-assisted activation of stable aromatic C–H bonds by solid ruthenium catalysts. Recently, we reported a heterogeneous Ru/CeO_2-catalyzed transfer-allylation of homoallyl alcohols into aldehydes,[6] in which the active species was considered to be a low-valent Ru species generated in situ from a Ru^{IV} oxide species on CeO_2.

In this communication, we report the first example of Ru/CeO_2-catalyzed nitrogen-directed arylation of aromatic C–H bonds with aryl halides. This reaction, for which low-valent Ru-complex catalysts are quite effective,[7] is one of the most ecological and economical methods available for preparing unsymmetrical biaryls.[7–9] The results in this communication imply that solid Ru/CeO_2 can be a good alternative to homogeneous Ru catalysts, which are known to be effective for a wide range of C–C bond-forming reactions.

Supported-Ru catalysts were prepared as follows; an oxide support was added to a solution of a Ru-catalyst precursor in THF at room temperature. After impregnation by Ru, the resulting powder was calcined in air at 400 °C for 30 min to afford Ru (2.0 wt %)/support.

The reaction of benzo[*h*]quinoline (**1a**) with chlorobenzene (**2a**) in *N*-methyl-2-pyrrolidone (NMP) at 170 °C for 18 h in the presence of a Ru/CeO_2 catalyst prepared by using $[Ru_3(CO)_{12}]$ as a catalyst precursor gave the arylated product **3a** selectively in a yield of 61 % (Table 1, entry 1). The addition of a small amount of PPh_3 to the reaction mixture facilitated the reaction and gave **3a** quantitatively (entry 2). The reactions of **1a** with bromobenzene (**2a′**) or iodobenzene (**2a″**) also produced **3a** quantitatively (Table 1, entries 3 and 4). The catalytic activity was greatly affected by the use of different Ru precursors. Catalysts prepared from Cl-containing Ru precursors such as $RuCl_3{\cdot}nH_2O$, $[\{RuCl_2(CO)_3\}_2]$, or $[\{RuCl_2(p\text{-cymene})\}_2]$ gave **3a** in higher yields than that prepared from [Ru(cod)(cot)] (cod = 1,5-cyclooctadiene; cot = 1,3,5-cyclooctatriene; Table 1, entries 5–8). The reaction that was carried out at 150 °C gave only a

Table 1. Effect of the ruthenium precursor.[a]



Entry	Ru precursor	X		*T* [°C]	Yield [%][b]
1	$[Ru_3(CO)_{12}]$	Cl	(**2a**)	170	61
2[c]	$[Ru_3(CO)_{12}]$	Cl	(**2a**)	170	99
3[c]	$[Ru_3(CO)_{12}]$	Br	(**2a′**)	170	99
4[c]	$[Ru_3(CO)_{12}]$	I	(**2a″**)	130	99
5	$RuCl_3{\cdot}nH_2O$	Cl	(**2a**)	170	89
6	$[\{RuCl_2(CO)_3\}_2]$	Cl	(**2a**)	170	84
7	$[\{RuCl_2(p\text{-cymene})\}_2]$	Cl	(**2a**)	170	69
8	[Ru(cod)(cot)]	Cl	(**2a**)	170	25
9	$[Ru_3(CO)_{12}]$	Cl	(**2a**)	150	trace

[a] CeO_2 was prepared by using an aqueous solution of NH_3. [b] Determined by GLC based on **1a**. [c] 0.10 mmol of PPh_3 were added.

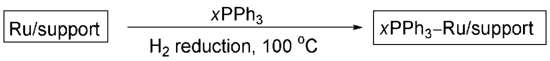
---

[a] H. Miura, Dr. K. Wada, Dr. S. Hosokawa, Prof. Dr. M. Inoue
Department of Energy and Hydrocarbon Chemistry
Kyoto University, Katsura, Nishikyo-ku
Kyoto 615-8510 (Japan)
Fax: (+81) 75-383-2479
E-mail: wadaken@scl.kyoto-u.ac.jp

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.200903564.

trace amount of the biaryl product (Table 1, entry 9); this indicates that a high reaction temperature is required to generate the highly active catalytic species in situ from the ruthenium(IV) species supported on CeO_2.[6,10]

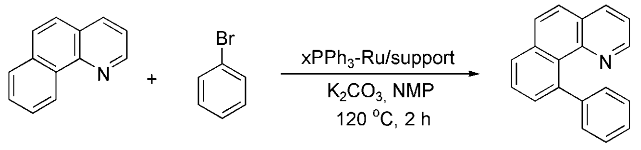
Next, we examined the effect of pretreatment of the Ru/CeO_2 catalyst and found that the PPh_3 modification of Ru/CeO_2 greatly increased the catalytic activity. PPh_3-modified solid Ru catalysts were prepared as follows; treatment of Ru/support at 100 °C for 20 min in the presence of PPh_3 in an H_2 atmosphere afforded PPh_3-modified Ru catalysts, designated as $x$$PPh_3$–Ru/support ($x$ = molar ratio of PPh_3:Ru; Scheme 1).



Scheme 1. Preparation of PPh_3–Ru/support catalysts.

In the presence of the PPh_3-modified Ru/CeO_2 catalyst, 3 PPh_3–Ru/CeO_2, the reaction of **1a** with **2a′** gave **3a** in a yield of 81 % under much milder conditions: 120 °C for 2 h (Table 2, entry 1). The PPh_3-modified solid Ru catalyst supported on ZrO_2 gave **3a** in a good yield (Table 2, entry 2), but catalysts supported on SiO_2, TiO_2, Al_2O_3, or MgO (Table 2, entries 3–6) did not show any catalytic activity.[11] The precipitant used for the preparation of the CeO_2 support also affected the catalytic activity, with KOH giving the best results (Table 2, entry 9). Furthermore, the molar ratio of PPh_3 used for the modification, as well as the pretreatment conditions, significantly affected the catalytic activity; 3 PPh_3–Ru/CeO_2 showed the highest activity (Table 2, entries 9–11). Note that it has also been reported that homogeneous ruthenium-complex-catalyzed C–H alkylation is also affected by the number of phosphine ligands coordinated to the Ru center.[12] Catalysts reduced in the absence of PPh_3 did not produce **3a** at all (Table 2, entry 12) even if PPh_3 was added to the reaction mixture (Table 2, entry 13). Note that the quantity of Ru species that leached into the solution after the reaction shown in Table 2, entry 9 was 0.00065 mmol (2.6 % of Ru species in the fresh catalyst), as calculated by ICP-AES analysis.

Table 2. Direct arylation by PPh_3-modified solid Ru catalysts.[a]



1a **2a'** **3a**

Entry	x	Ru precursor	Support[b]		Yield [%][c]
1	3	$[Ru_3(CO)_{12}]$	CeO_2	(NH_3)	81
2	3	$[Ru_3(CO)_{12}]$	ZrO_2	(JRC-ZRO-3)	60
3	3	$[Ru_3(CO)_{12}]$	SiO_2	(Cabosil)	0
4	3	$[Ru_3(CO)_{12}]$	TiO_2	(JRC-TIO-4)	0
5	3	$[Ru_3(CO)_{12}]$	Al_2O_3	(JRC-ALO-8)	0
6	3	$[Ru_3(CO)_{12}]$	MgO	(NH_3)	0
7	3	$[\{RuCl_2(CO)_3\}_2]$	CeO_2	(NH_3)	68
8	3	$[Ru_3(CO)_{12}]$	CeO_2	(KOH)	76
9	3	$[\{RuCl_2(CO)_3\}_2]$	CeO_2	(KOH)	98 (99)[d]
10	2	$[\{RuCl_2(CO)_3\}_2]$	CeO_2	(KOH)	39
11	4	$[\{RuCl_2(CO)_3\}_2]$	CeO_2	(KOH)	63
12	0	$[\{RuCl_2(CO)_3\}_2]$	CeO_2	(KOH)	0
13[e]	0	$[\{RuCl_2(CO)_3\}_2]$	CeO_2	(KOH)	0

[a] Reaction conditions: **1a** (0.50 mmol), **2a′** (0.75 mmol), $x$$PPh_3$–Ru/$CeO_2$ (0.025 mmol with respect to Ru), K_2CO_3 (1.0 mmol), NMP (2.0 mL). [b] The support or precipitant used to prepare the support is shown in parenthesis. [c] Determined by GLC based on **1a**. [d] Reaction conditions: **1a** (1.0 mmol), **2a′** (1.5 mmol), $x$$PPh_3$–Ru/$CeO_2$ (0.50 mmol with respect to Ru), K_2CO_3 (2.0 mmol), NMP (2.0 mL). [e] 0.075 mmol of PPh_3 was added to the reaction mixture.

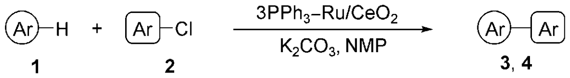
The catalytic reactions of chloroarenes were examined by using the 3 PPh_3–Ru/CeO_2 catalyst, which showed the highest activity in Table 2 (entry 9), and the results are summarized in Table 3. While the reaction with chlorobenzene at 120 °C provided arylated product **3a** in a moderate yield (Table 3, entry 1), the reaction at 140 °C proceeded efficiently to afford **3a** in 94 % yield within 6 h (Table 3, entry 2). Various chloroarenes with *para* functional groups (**2a**–**f**) and 2-chloronaphthalene (**2g**) could also be used in this reaction and the desired products **3b**–**g** were obtained in excellent yields (Table 3, entries 3–8). Also, the reactions of heterocyclic chlorides, 2-chlorothiophene (**2h**) and 2-chloropyridine (**2i**), gave **3h** and **3i**, respectively, with satisfactory yields (Table 3, entries 9 and 10). The reactions with other directed C–H activation substrates were also examined; treatment of 2-phenylpyridine (**1b**) and 1-phenyl-2-pyrazol (**1c**) with 4-chloroacetophenone (**2d**) produced mixtures of the mono- (**3j** and **k**) and diarylated (**4j** and **k**) products (Table 3, entries 11 and 12).

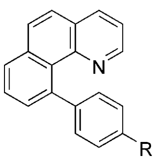
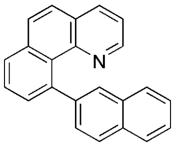
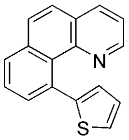
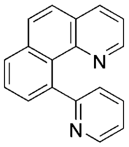
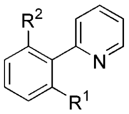
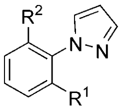
It is important to investigate whether or not the reaction actually occurs on the solid surface. To this end, hot filtration of the solid catalyst after the reaction of **1a** and **2a′** in the presence of 3 PPh_3–Ru/CeO_2 at 120 °C had proceeded for 0.5 h completely suppressed further progress of the reaction. This result strongly suggests that the catalyst works heterogeneously.

One of the major advantages of solid catalysts is their recyclability. After performing the reaction under the conditions shown in Table 2, entry 9, the solid catalyst was separated from the reaction mixture by centrifugation and washed with diethyl ether and methanol/H_2O. The resulting solid was calcined in air at 400 °C for 30 min to recover Ru/CeO_2. Modification by PPh_3 was then performed through the aforementioned procedure to give the PPh_3–Ru/CeO_2 catalyst for reuse. As shown in Scheme 2, the catalyst was recyclable and produced the biaryl product quantitatively within short reaction periods. Furthermore, at a higher temperature of 170 °C, the reaction went to completion within 0.5 h and the catalyst could be used at least three times without any loss of activity.

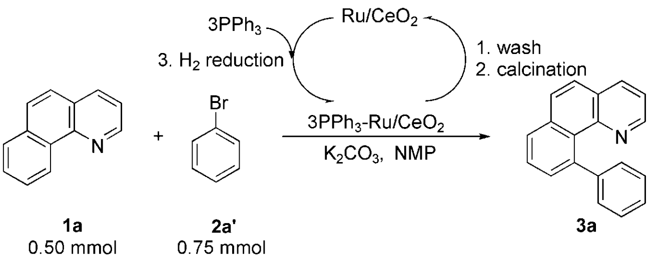
An FTIR study was used to analyse the catalytic species used in this reaction. A distinct band at 975 cm^{-1} for the fresh Ru/CeO_2 catalyst indicates the formation of a ruthenium–oxo species,[10] which would be a good precursor of the catalytically active species that is formed in situ (see Sup-

Table 3. Direct arylation with aryl chlorides.[a]



Entry	Reagents		Product		t [h]	Yield [%][b]
1[c]	**1a**	**2a**		**3a** (R=H)	12	58[d]
2	**1a**	**2a**		**3a** (R=H)	6	94[d]
3	**1a**	**2b**		**3b** (R=Me)	6	96
4	**1a**	**2c**		**3c** (R=OMe)	12	96
5	**1a**	**2d**		**3d** (R=COMe)	3	95
6	**1a**	**2e**		**3e** (R=CO_2Me)	5	91
7	**1a**	**2f**		**3f** (R=CF_3)	12	86
8	**1a**	**2g**		**3g**	5	98
9	**1a**	**2h**		**3h**	4	98
10	**1a**	**2i**		**3i**	6	53
11	**1b**	**2d**		**3j** (R^1=H, R^2=4-$MeCOC_6H_4$) **4j** (R^1, R^2=4-$MeCOC_6H_4$)	3	94 (74:26)[e]
12	**1c**	**2d**		**3k** (R^1=H, R^2=4-$MeCOC_6H_4$) **4k** (R^1, R^2=4-$MeCOC_6H_4$)	5	84 (60:40)[e]

[a] Reaction conditions: **1** (0.50 mmol), **2** (0.75 mmol), $3PPh_3$–Ru/CeO_2 (0.025 mmol with respect to Ru), K_2CO_3 (1.0 mmol) NMP (2.0 mL), 140 °C. [b] Isolated yield based on **1**. [c] Reaction at 120 °C. [d] Yield determined by GLC. [e] Molar ratio of **3**:**4**.



at 120 °C
1st run: 98% (2 h)
2nd run: 99% (3 h)

at 170 °C
1st run: 94% (0.5 h)
2nd run: 94% (0.5 h)
3rd run: 98% (0.5 h)

Scheme 2. Recycling of solid Ru catalyst.

porting Information). In contrast, there were no signs of such oxo species on the unsuccessful SiO_2-, TiO_2-, Al_2O_3-, or MgO-supported catalysts.

In summary, we have reported the first example of a chelation-assisted direct arylation of aromatic C–H bonds by solid Ru catalysts. PPh_3-modified Ru/CeO_2 showed excellent catalytic activity and various aryl chlorides could be used in the reaction. These results indicate that catalytically active species generated from Ru^{IV} oxide species on CeO_2 can be attractive alternatives to homogeneous Ru catalysts. Moreover, the present heterogeneous catalytic system is quite advantageous from both environmental and practical perspectives, since these catalysts can be easily recovered and repeatedly used. The details of the catalytically active species and further applications of Ru/CeO_2 catalytic systems for a variety of organic synthesis reactions are currently under investigation.

Experimental Section

Representative procedure: Benzo[*h*]quinoline **1a** (89.5 mg, 0.50 mmol), 4-chloroacetophenone **2d** (116 mg, 0.75 mmol), K_2CO_3 (138 mg, 1.0 mmol) and NMP (2.0 mL) were placed in a Schlenk tube (20 mL) under argon together with $3PPh_3$–Ru/CeO_2 (125 mg, 0.025 mmol with respect to Ru). The reaction mixture was stirred at 140 °C for 3 h with a cooling block. After the reaction, the catalyst was removed by centrifugation and the remaining solution concentrated under reduced pressure. The products were isolated by column chromatography (3:1; hexane/EtOAc, v/v) to give the product **3d** as a white solid (141.7 mg, 95%).

Acknowledgements

This research was supported by Ministry of Education, Culture, Sports, Science and Technology, Japan through a Grant-in-Aid for Scientific Research (No. 21360393).

Keywords: cerium · C–H activation · direct arylation · heterogeneous catalysis · ruthenium

---

[1] For green chemistry, see: a) P. T. Anastas, J. Warner in *Green Chemistry: Theory and Practice*, Oxford University Press, New York **1998**; b) R. A. Sheldon, R. S. Downing, *Appl. Catal. A* **1999**, *189*, 163–183; c) B. M. Trost, *Acc. Chem. Res.* **2002**, *35*, 695–705.

[2] For representative reviews, see: a) P. Laszlo, *Acc. Chem. Res.* **1986**, *19*, 121–127; b) Y. Izumi, M. Onaka, *Adv. Catal.* **1992**, *38*, 245–282; c) J. H. Clark, D. J. Macquarrie, *Chem. Soc. Rev.* **1996**, *25*, 303–310; d) B. F. Sels, D. E. De Vos, P. A. Jacobs, *Catal. Rev. Sci. Eng.* **2001**, *43*, 443–488; e) S. Kannan, *Catal. Surv. Asia* **2006**, *10*, 117–137; f) K. Kaneda, *Synlett* **2007**, 999–1015.

[3] For recent reviews of C–H functionalization, see: a) V. Ritleng, C. Sirlin, M. Pfeffer, *Chem. Rev.* **2002**, *102*, 1731–1769; b) F. Kakiuchi, S. Murai, *Acc. Chem. Res.* **2002**, *35*, 826–834; c) A. R. Dick, M. S. Sanford, *Tetrahedron* **2006**, *62*, 2439–2463; d) D. Alberico, M. E. Scott, M. Lautens, *Chem. Rev.* **2007**, *107*, 174–238.

[4] For recent examples, see a) S. Carrettin, J. Guzman, A. Corma, *Angew. Chem.* **2005**, *117*, 2282–2285; *Angew. Chem. Int. Ed.* **2005**, *44*, 2242–2245; b) T. Mitsudome, K. Nose, K. Mori, T. Mizugaki, K. Ebitani, K. Jitsukawa, K. Kaneda, *Angew. Chem.* **2007**, *119*, 3352–3354; *Angew. Chem. Int. Ed.* **2007**, *46*, 3288–3290; c) K. Shimizu, R. Sato, A. Satsuma, *Angew. Chem.* **2009**, *121*, 4042–4046; *Angew. Chem. Int. Ed.* **2009**, *48*, 3982–3986.

[5] For examples, see: a) G. M. Badger, W. H. F. Sasse, *J. Chem. Soc.* **1956**, 616–620; b) G. A. Mines, J. Bjerrum, M. G. Hill, D. R. Casimiro, I. Chang, J. R. Winker, H. B. Gray, *J. Am. Chem. Soc.* **1996**, *118*, 1961–1965; c) S. A. Sapp, C. M. Elliott, C. Contado, S. Caramori, C. A. Bignozzi, *J. Am. Chem. Soc.* **2002**, *124*, 11215–11222; d) M. Matsushita, K. Kamata, K. Yamaguchi, N. Mizuno, *J. Am. Chem. Soc.* **2005**, *127*, 6632–6640; e) G. Cusati, L. Djakovitch, *Tetrahedron Lett.* **2008**, *49*, 2499–2502.

[6] H. Miura, K. Wada, S. Hosokawa, M. Sai, T. Kondo, M. Inoue, *Chem. Commun.* **2009**, 4112–4114.

[7] For Ru-catalyzed direct arylation with aryl halides, see: a) S. Oi, S. Fukita, N. Hirata, N. Watanuki, S. Miyano, Y. Inoue, *Org. Lett.* **2001**, *3*, 2579–2581; b) S. Oi, Y. Ogino, S. Fukita, Y. Inoue, *Org. Lett.* **2002**, *4*, 1783–1785; c) S. Oi, E. Aizawa, Y. Ogino, Y. Inoue, *J. Org. Chem.* **2005**, *70*, 3113–3119; d) S. Oi, K. Sakai, Y. Inoue, *Org. Lett.* **2005**, *7*, 4009–4011; e) L. Ackermann, *Org. Lett.* **2005**, *7*, 3123–3125; f) L. Ackermann, *Synthesis* **2006**, 1557–1571; g) L. Ackermann, A. Althammer, R. Born, *Angew. Chem.* **2006**, *118*, 2681–2685; *Angew. Chem. Int. Ed.* **2006**, *45*, 2619–2622; h) L. Ackermann, R. Born, P. Álvarez-Bercedo, *Angew. Chem.* **2007**, *119*, 6482–6485; *Angew. Chem. Int. Ed.* **2007**, *46*, 6364–6367; i) L. Ackermann, A. Althammer, R. Born, *Synlett* **2007**, 2833–2836; j) L. Ackermann, R. Vicente, A. Althammer, *Org. Lett.* **2008**, *10*, 2299–2302; k) I. Özdemir, S. Demir, B. Cetinkaya, C. Gourlaouen, F. Maseras, C. Bruneau, P. H. Dixneuf, *J. Am. Chem. Soc.* **2008**, *130*, 1156–1157; l) K. Cheng, Y. Zhang, J. Zhao, C. Xie, *Synlett* **2008**, 1325–1330; m) S. Oi, R. Funayama, T. Hattori, Y. Inoue, *Tetrahedron* **2008**, *64*, 6051–6059; n) L. Ackermann, A. Althammer, R. Born, *Tetrahedron* **2008**, *64*, 6115–6124; o) F. Požgan, P. H. Dixneuf, *Adv. Synth. Catal.* **2009**, *351*, 1737–1743.

[8] For a recent Rh-catalyzed example, see: M. Kim, J. Kwak, S. Chang, *Angew. Chem.* **2009**, *121*, 9097–9101; *Angew. Chem. Int. Ed.* **2009**, *48*, 8935–8939.

[9] For a recent Pd-catalyzed example, see: D. Kalyani, N. R. Deprez, L. V. Desai, M. S. Sanford, *J. Am. Chem. Soc.* **2005**, *127*, 7330–7331.

[10] S. Hosokawa, S. Nogawa, M. Taniguchi, K. Utani, H. Kanai, S. Imamura, *Appl. Catal. A* **2005**, *288*, 67–73.

[11] Note that Ru catalysts supported on SiO_2, Al_2O_3 and TiO_2 were also ineffective under the conditions described in Table 1.

[12] F. Kakiuchi, S. Sekine, Y. Tanaka, A. Kamitani, M. Sonoda, N. Chatani, S. Murai, *Bull. Chem. Soc. Jpn.* **1995**, *68*, 62–83.

Received: December 28, 2009