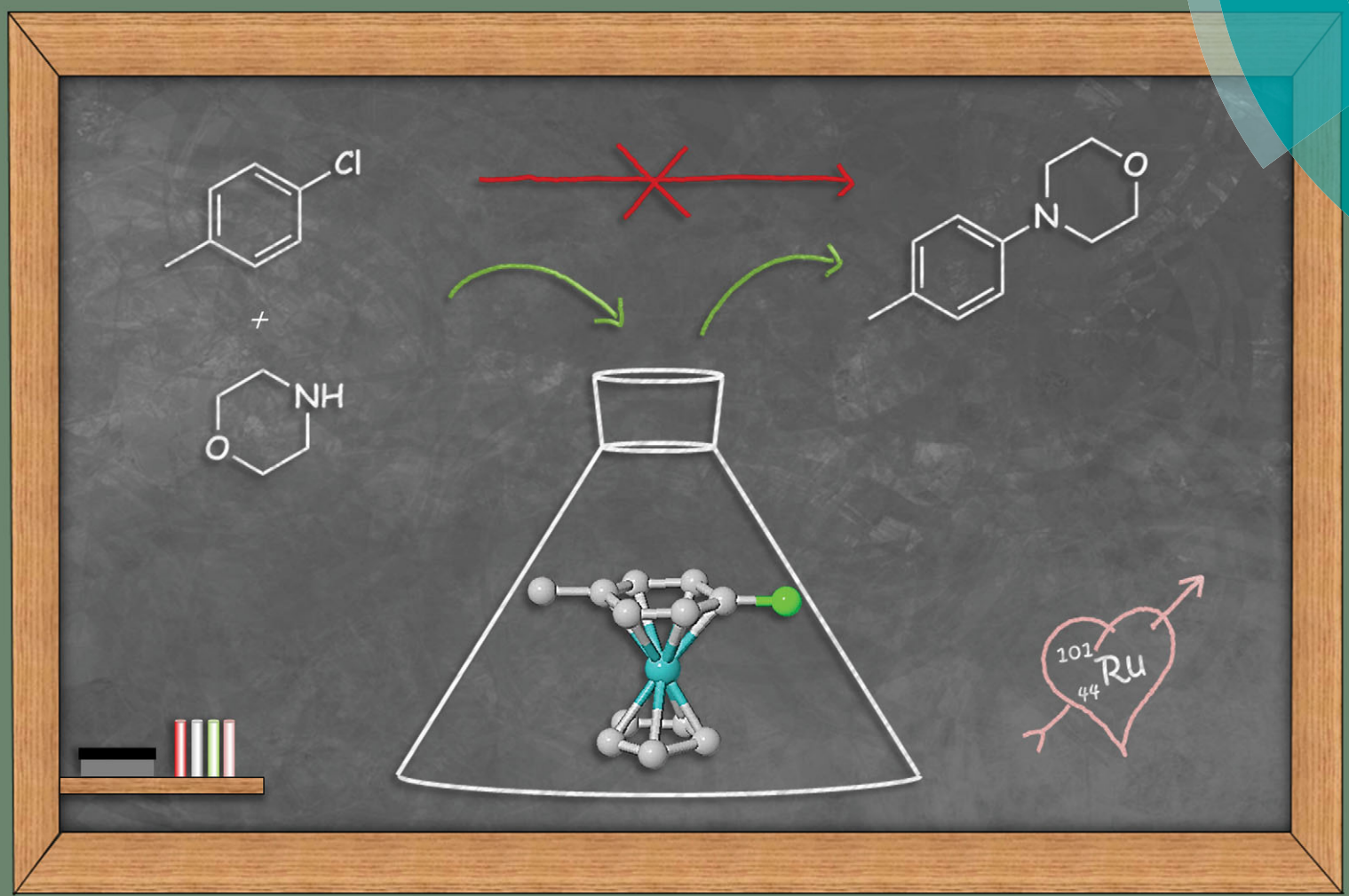
Volume 51 | Number 14 | 18 February 2015 | Pages 2737–3004

ChemComm

Chemical Communications

www.rsc.org/chemcomm



ISSN 1359-7345

ROYAL SOCIETY OF CHEMISTRY

COMMUNICATION

James W. Walton and Jonathan M. J. Williams

Catalytic S_NAr of unactivated aryl chlorides

ChemComm

COMMUNICATION

View Article Online
View Journal | View Issue

Catalytic S_NAr of unactivated aryl chlorides†

James W. Walton*[ab] and Jonathan M. J. Williams[a]

Cite this: *Chem. Commun.*, 2015, **51**, 2786

Received 9th September 2014,
Accepted 6th October 2014

DOI: 10.1039/c4cc07116f

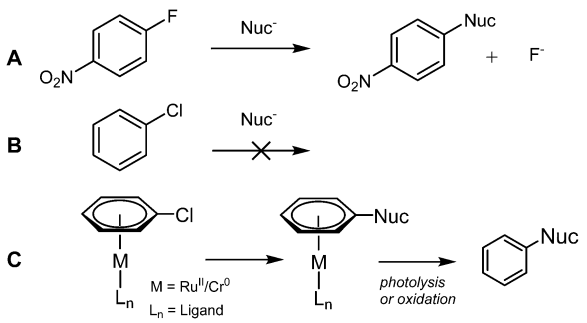
www.rsc.org/chemcomm

We present nucleophilic aromatic substitution of unsubstituted aryl chlorides *via* a mechanism that is catalytic in [CpRu(*p*-cymene)]PF_6 and involves a Ru(η^6-arylchloride) intermediate. From the spectroscopic evidence we infer that arene exchange is the rate limiting step in this process and develop several new Ru(II) complexes that lower the activation barrier to arene exchange.

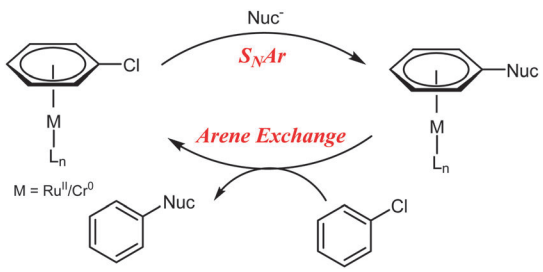
Nucleophilic aromatic substitution (S_NAr) is one of the building blocks of synthetic chemistry, and is used far and wide in industry and academia. However, limitations restrict the use of S_NAr to certain substrates. Activated arenes are required (incorporating an electron withdrawing group to stabilise the negatively charged intermediate, Scheme 1A) and the C–X bond must be polarised; the rate of reaction follows the order X = F > Cl ≫ Br. Alternative arylation methods include metal[1a,b] and non-metal[1c] catalysed coupling reactions of Ar–X and Ar–H.

Fluorobenzene can undergo S_NAr with strong alkoxide nucleophiles[2] but chlorobenzene does not undergo S_NAr (Scheme 1B). One method by which *unactivated* aryl halides (*i.e.* those without an electron withdrawing group) can undergo S_NAr is *via* η^6-coordination to a transition metal (*e.g.* Ru(II),[3] Cr(0),[4] Fe(II),[5] Mn(I),[6] Scheme 1C). It is well established that π-complexation of an arene to a transition metal increases its reactivity towards nucleophilic attack[7] and deprotonation.[8] More recently, activation of a Cr(0) η^6-aryl C–H bond towards Pd insertion and subsequent arylation has been achieved.[9] The drawback to these reactions is that the η^6-arene–metal bond is strong and stoichiometric metal is required; liberation of the aryl product is carried out by photolysis[10] or oxidation.[11]

Semmelhack *et al.* propose a catalytic cycle in which an unactivated aryl chloride binds η^6 to Cr(0), facilitating S_NAr, before exchange between the bound product and free aryl chloride



Scheme 1



Scheme 2

takes place, completing the catalytic cycle (Scheme 2).[12] Despite demonstrating an increase in the rate limiting step (arene exchange), no catalytic S_NAr was reported.

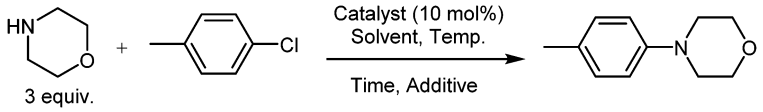
Rh(III) catalysed intramolecular S_NAr based on this catalytic cycle has been reported but is limited to aryl fluorides.[13] Intermolecular S_NAr of aryl fluorides (Ru(II) catalysed) has also appeared[14] but requires a large excess of arene and is unsuccessful with aryl chlorides. Anti-Markovnikov hydroamination of styrene *via* catalytic π-complexation to Ru(II) has also been reported.[15]

In this report we present the first example of catalytic S_NAr of unactivated aryl chlorides. Experimental evidence suggests that our method proceeds *via* a η^6-coordination mechanism. In an effort to reduce the high reaction temperature and long

[a] *Department of Chemistry, University of Bath, Claverton Down, Bath, BA2 7AY, UK*
[b] *Department of Chemistry, Durham University, South Road, Durham, DH1 3LE, UK. E-mail: james.walton@durham.ac.uk*

† Electronic supplementary information (ESI) available. See DOI: 10.1039/c4cc07116f

Table 1 S_NAr reaction between morpholine and chlorotoluene under a variety of conditions (see ESI for full list of conditions). Conversions were determined by ^{1}H-NMR. (Cp* = pentamethylcyclopentadienyl, DMI = 1,3-dimethylimidazolinone, DPPPent = 1,5-bis(diphenylphosphino)pentane)



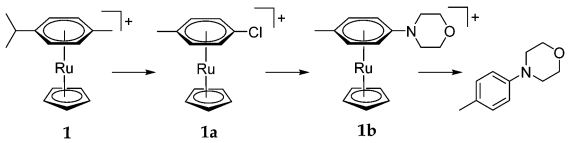
Entry	Catalyst	Solvent	Temp. (°C)	Time	Additive	Conversion (%)
1	—	MeCN	80	18 h	—	0
2	—	Toluene	110	18 h	—	0
3	—	Cyclohexanone	150	18 h	—	0
4	$[CpRu(MeCN)_3]PF_6$	Cyclohexanone	150	18 h	—	6
5	$[Cp^*Ru(MeCN)_3]PF_6$	Cyclohexanone	150	18 h	—	5
6	[CpRu(*p*-cymene)]PF_6	Cyclohexanone	150	18 h	—	10
7	[CpRu(*p*-cymene)]PF_6	Cyclohexanone	180	18 h	—	18
8	[CpRu(*p*-cymene)]PF_6	DMI	180	18 h	—	17
9	[CpRu(*p*-cymene)]PF_6	Cyclohexanol	180	18 h	—	16
10	[CpRu(*p*-cymene)]PF_6	*p*-Xylene	180	18 h	—	0
11	[CpRu(*p*-cymene)]PF_6	1-Octanol	180	18 h	—	25
12	[CpRu(*p*-cymene)]PF_6	1-Octanol	180	18 h	Mol. sieves	25
13	[CpRu(*p*-cymene)]PF_6	1-Octanol	180	18 h	Et_3N	21
14	[CpRu(*p*-cymene)]PF_6	1-Octanol	180	18 h	Na_2CO_3	11
15	$[Ru(p\text{-cymene})Cl_2]_2$	1-Octanol	180	18 h	DPPPent	0
16	[CpRu(*p*-cymene)]PF_6	1-Octanol	180	4 d	—	45
17	[CpRu(*p*-cymene)]PF_6	1-Octanol	180	7 d	—	75
18	**[CpRu(*p*-cymene)]PF_6**	**1-Octanol**	**180**	**14 d**	**—**	**90**

reaction time, several new catalysts were synthesised with a view to lowering the activation barrier of the rate limiting step.

Our initial investigation focussed on the reaction between morpholine and chlorotoluene under a variety of reaction conditions (selected results are given in Table 1, see ESI† for a complete set of reaction conditions). In the absence of a catalyst no product formed, despite attempts over a range of temperatures and in several solvents (Table 1, entries 1–3).

Based on the work of Woodgate *et al.*,[3a] we anticipated that catalysts incorporating a $[CpRu]^+$ fragment (Cp = cyclopentadienyl) would expedite the S_NAr reaction, *via* η^6-coordination of chlorotoluene. A number of catalysts were investigated (Table 1, entries 4–6). Each catalyst led to conversion into the desired product, providing that high temperatures were employed, with [CpRu(*p*-cymene)]PF_6 performing best. In a solvent screen at 180 °C, 1-octanol was found to give the highest conversion (Table 1, entries 7–11). If the reaction mixture was left for 14 days the product conversion reached 90% (Table 1, entries 16–18). The effect of additives on the rate of reaction was examined (Table 1, entries 12–15). No increase in product conversion was observed for a variety of additives, including base, molecular sieves and ligands. In summary, catalytic S_NAr between morpholine and chlorotoluene can be achieved with 90% yield in 1-octanol at 180 °C in 14 days.

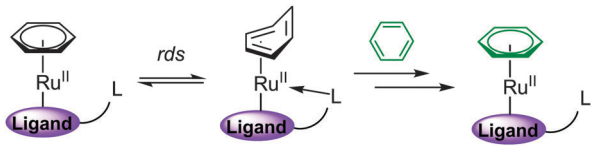
We sought to understand why such long reaction times and high reaction temperatures were required. Under the optimised reaction conditions, positive mode electrospray mass spectrometry (ESI-MS^+) showed a peak at m/z = 344 with the characteristic Ru isotope pattern, corresponding to the η^6-bound product (complex **1b** in Scheme 3). ^{1}H-NMR showed a pair of doublets in the range 5.5–5.7 ppm, also corresponding



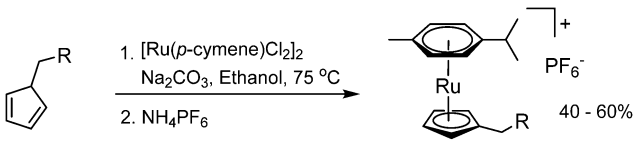
Scheme 3

to **1b**; no η^6-bound chlorotoluene (**1a**) was observed by ES-MS^+ or ^{1}H-NMR. We postulate, therefore, that the reaction occurs *via* the mechanism shown in Scheme 2 and that arene exchange is the rate limiting step; S_NAr is fast so that no bound chlorotoluene is observed but arene exchange is slow so that bound product is observed.

The mechanism by which arene exchange takes place in $[Cr(CO)_3(\eta^6\text{-arene})]$ complexes has been well studied.[16] It was determined that the rate-determining step is an initial change in arene bonding from $\eta^6 \rightarrow \eta^4$ (Scheme 4). While similar analysis has not been carried out for $Ru^{II}(\eta^6\text{-arene})$ complexes, we assume the same mechanism for arene exchange and propose that the success found for our catalytic system with 1-octanol as a solvent is due to coordination of the hydroxyl group during the slow $\eta^6 \rightarrow \eta^4$ step. This maintains an 18 e^- complex and lowers the activation energy.



Scheme 4

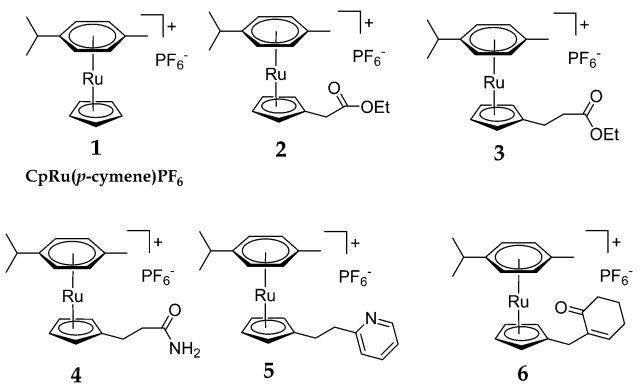


Scheme 5

This theory is supported by the reasonable product conversion in solvents such as cyclohexanol and DMI (Table 1, entries 8 and 9) and the lack of conversion in the non-coordinating solvent *p*-xylene (Table 1, entry 10). It has previously been noted that addition of ketones, such as cyclohexanone, lowers the activation barrier to arene exchange in Cr(0) systems *via* coordination of the carbonyl lone pair during the $\eta^6 \rightarrow \eta^4$ process.[17]

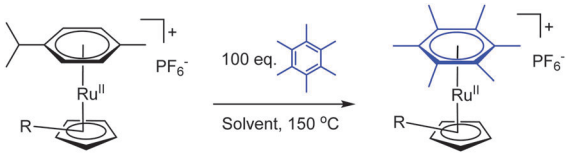
To test this theory, several new catalysts were synthesised (**2–6**), each incorporating a tether, covalently bound to the Cp ring, capable of coordinating to Ru during the $\eta^6 \rightarrow \eta^4$ step (Scheme 4).[18] Our expectation was that intramolecular coordination of the tether to the Ru centre would lower the activation barrier to arene exchange and, subsequently, increase the rate of the S_NAr reaction.

Each complex was synthesised by reaction between $[Ru(p\text{-cymene})Cl_2]_2$ and the corresponding Cp–tether adduct, in the presence of Na_2CO_3 and ethanol (Scheme 5).[19] The reaction mixtures were treated with NH_4PF_6 to afford complexes **2–6**. The formation of the Cp–tether adducts were specific to the various tethers. For complex **2**, CpNa and $BrCH_2CO_2Me$ were stirred in THF at 0 °C to give $CpCH_2CO_2Me$ in quantitative yield[20] before complexation with $[Ru(p\text{-cymene})Cl_2]_2$.[21] Similar protocols were used to synthesise the other Cp–tether compounds. In certain cases, it was necessary to synthesise the electrophilic component before reaction with CpNa. For example, in the synthesis of **5**, 2-Py$(CH_2)_2$OH (2-Py = 2-pyridine) was converted into 2-Py$(CH_2)_2OSO_2Me$, prior to reaction with CpNa. Each complex **2–6** was purified by column chromatography on silica and fully characterised. For full Experimental detail see ESI.†



To investigate whether the presence of the various tethers would decrease the energy barrier for the $\eta^6 \rightarrow \eta^4$ process, exchange experiments were carried out. Each complex was heated in either 1-octanol or cyclohexanone in the presence of 100 equivalents of hexamethylbenzene (C_6Me_6) for 16 h. The extent of exchange between *p*-cymene and C_6Me_6 was measured

Table 2 The percentage of arene exchange for complexes **1–6**, using either cyclohexanone or 1-octanol as the solvent after 3 and 16 h reaction times



	Arene exchange (%)			
	Cyclohexanone		1-Octanol	
Complex	3 h	16 h	3 h	16 h
1	6	38	17	92
2	(6)[a]	(50)[a]	(15)[a]	(84)[a]
3	9	51	13 (18)[b]	90 (88)[b]
4	—[c]	—[c]	(17)[d]	(85)[d]
5	44	100	36	100
6	12	50	12	65

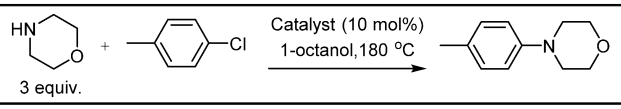
[a] Values for decarboxylated **2** ($[(MeCp)Ru(p\text{-cymene})]^+$), which forms under exchange conditions. [b] Values for the octyl ester of **3**, which forms in 1-octanol. [c] Complex **4** reacts with cyclohexanone, leading to invalid results. [d] Values for the octyl ester of **4**, which forms under the exchange conditions.

at 3 h and 16 h using ESI-MS^+ (Table 2); calibration of the ESI-MS^+ measurement was required to allow quantitative assessment (see ESI†). Relative to the parent complex, $[CpRu(p\text{-cymene})]PF_6$ (**1**), a moderate increase in the extent of arene exchange was observed for **3** and **6** in cyclohexanone after 16 h (51% and 50%, respectively *versus* 38% for **1**). Most notable, however, was the complete arene exchange in cyclohexanone for complex **5**, which incorporates a pyridyl tether. In the same solvent, **2** appeared to undergo ester hydrolysis and decarboxylation, giving $[(CpMe)Ru(p\text{-cymene})]^+$, indicated by a *m*/*z* peak at 315. This species underwent a similar amount of arene exchange to **1**. Finally, exchange for **4** in cyclohexanone could not be determined due to a side reaction with the solvent. Similar exchange behaviour was found when 1-octanol was used as the solvent. Complex **5** again displayed the greatest amount of arene exchange. The tether components in **3** and **5** rapidly reacted with the solvent to form octyl esters, which exchanged at a similar rate to the parent complex (**1**). Once again, complex **2** decarboxylated whilst **6** showed a slight reduction in the rate of exchange compared to **1**.

Having established that arene exchange could be accelerated by the presence of a coordinating tether, we proceeded to calculate half lives ($t_{1/2}$) for the initial *p*-cymene complexes of **1**, **3**, **5** and **6** under the exchange conditions described in Table 2, with cyclohexanone as the solvent. The results confirm that the pyridyl complex **5** exchanges an order of magnitude faster than the parent complex, **1** ($t_{1/2} = 2.2 \pm 0.1$ h *versus* 34 ± 0.7 h, see ESI† for details). Complexes **3** and **6** each have shorter $t_{1/2}$ than **1** (23 ± 0.3 h and 28 ± 0.4 h, respectively), confirming that the rate of arene exchange is accelerated by the coordinating tether.

Our hypothesis stated that faster arene exchange will lead to higher conversion in the S_NAr reaction between morpholine and chlorotoluene. To test this, we carried out the S_NAr reaction with three of the new potential catalysts, **1**, **3** and **5** (Table 3). As a comparison, **1** with an equivalent of free pyridine was also tested.

Table 3 S_NAr reaction between morpholine and chlorotoluene with catalysts **1**, **3** and **5**. Conversions were determined by ^{1}H-NMR



	Conversion (%)		
Catalyst	1 d	4 d	7 d
1	25	45	75
3	25	59	72
5	26	55	54
1 + Py	24	59	65

After 24 h, each catalyst gave a similar conversion. After 4 d, the catalysts incorporating a tether showed a small improvement in conversion but after 7 d the parent compound returned the highest value, due, in the case of **5**, to degradation of the catalytic species (indicated by loss of Ru species in the mass spectrum). Once again, mass spectrometric analysis after 24 h shows a *m*/*z* peak corresponding to the η^6-bound product in each of the reactions. Ultimately, it appears that although the rate of arene exchange is accelerated in the *p*-cymene → C_6Me_6 experiment described above, this acceleration does not translate into a higher conversion in the S_NAr reaction. Two explanations present themselves: (1) the η^6-bound product is more kinetically inert than $[CpRu(p\text{-cymene})]^+$, so that arene exchange is slower, (2) the η^6-bound product is more thermodynamically stable than $[CpRu(\eta^6\text{-chlorotoluene})]^+$, leading to the build-up of the product bound complex and long reaction times. Of course, a combination of both factors may be present. $[(\eta^6\text{-Dimethylaniline})Cr(CO)_3]$ is known to be more thermodynamically stable than the chlorobenzene analogue[16a,17] and a similar trend is likely in the case of $[CpRu(\eta^6\text{-arene})]^+$ – the aryl ring in the product (*e.g.* **1b** in Scheme 3) is more electron rich than *p*-cymene. In an attempt to destabilise the η^6-bound product, the nucleophile was changed from morpholine to 2,2,6,6-tetramethylmorpholine. Formation of product (either free or bound) was not observed, likely due to the steric influence of the nucleophile. Efforts are ongoing to understand and overcome the limiting factors of the reaction.

In conclusion, we have demonstrated for the first time catalytic S_NAr of unactivated aryl chlorides, albeit at high temperatures and with long reaction times. In an attempt to move to milder reaction conditions, several new Ru complexes were synthesised, incorporating tethers capable of lowering the activation barrier to dissociation. Despite achieving an 18-fold increase in the rate of arene exchange, the rate of S_NAr was not significantly increased in our test reactions. Once an efficient catalytic system based on η^6-arene exchange is realised, we envisage many applications in efficient organic synthesis.

Notes and references

1 (*a*) C. Liu, H. Zhang, W. Shi and A. Lei, *Chem. Rev.*, 2011, **111**, 1780; (*b*) C. S. Yeung and V. M. Dong, *Chem. Rev.*, 2011, **111**, 1215; (*c*) W. Lei, H. Cao, H. Zhang, H. Zhang, K. H. Chung, C. He, H. Wang, F. Y. Kwong and A. Lei, *J. Am. Chem. Soc.*, 2010, **132**, 16737.
2 (*a*) T. M. Koenig and D. Mitchell, *Tetrahedron Lett.*, 1994, **35**, 1339; (*b*) J. R. Rodriguez, J. Agejas and A. B. Bueno, *Tetrahedron Lett.*, 2006, **47**, 5661.
3 (*a*) R. C. Cambie, G. R. Clark, S. L. Coombe, S. A. Coulson, P. S. Rutledge and P. D. Woodgate, *J. Organomet. Chem.*, 1996, **507**, 1; (*b*) A. J. Pearson, J. G. Park, S. H. Yang and Y.-H. Chuang, *J. Chem. Soc., Chem. Commun.*, 1989, 1363.
4 K. Kamikawa, S. Kinoshita, M. Furusyo, S. Takemoto, H. Matsuzaka and M. Uemura, *J. Org. Chem.*, 2007, **72**, 3394.
5 (*a*) R. C. Cambie, S. J. Janssen, P. S. Rutledge and P. D. Woodgate, *J. Organomet. Chem.*, 1991, **420**, 387; (*b*) A. J. Pearson, J. G. Park and P. Y. Zhu, *J. Org. Chem.*, 1992, **57**, 3585.
6 A. J. Pearson and H. Shin, *J. Org. Chem.*, 1994, 2314.
7 (*a*) E. L. Velarde, R. A. Stephen, R. N. Mansour, L. T. Hoang and D. J. Burkey, *J. Am. Chem. Soc.*, 2003, **125**, 1188; (*b*) Y. K. Chung, H. S. Choi, N. G. Connelly and D. A. Sweigart, *J. Am. Chem. Soc.*, 1982, **104**, 4245.
8 (*a*) A. Schlüter, K. Bieber and W. S. Sheldrick, *Inorg. Chim. Acta*, 2002, **340**, 35; (*b*) S. Chen, V. Carperos, B. Noll, R. J. Swope and M. R. DuBois, *Organometallics*, 1995, **14**, 1221.
9 P. Ricci, K. Krämer, X. C. Cambeiro and I. Larrosa, *J. Am. Chem. Soc.*, 2013, **135**, 13258.
10 (*a*) J. W. Janetka and D. H. Rich, *J. Am. Chem. Soc.*, 1997, **119**, 6488; (*b*) F. C. Pigge, J. J. Coniglio and N. P. Rath, *J. Org. Chem.*, 2003, **69**, 1161.
11 (*a*) W. Braun, B. Calmuschi-Cula, U. Englert, K. Höfener, E. Alberico and A. Salzer, *J. Organomet. Chem.*, 2008, 2065; (*b*) R. P. Houghton, M. Voyle and R. Price, *J. Organomet. Chem.*, 1983, **259**, 183.
12 M. F. Semmelhack, A. Chlenov and D. M. Ho, *J. Am. Chem. Soc.*, 2005, **127**, 7759.
13 R. P. Houghton and M. Voyle, *J. Chem. Soc., Perkin Trans. 1*, 1984, 925.
14 (*a*) M. Otsuka, K. Endo and T. Shibata, *Chem. Commun.*, 2010, **46**, 336; (*b*) M. Otsuka, H. Yokoyama, K. Endo and T. Shibata, *Synlett*, 2010, 2601.
15 (*a*) J. Takaya and J. F. Hartwig, *J. Am. Chem. Soc.*, 2005, **127**, 5756; (*b*) M. Otsuka, H. Yokoyama, K. Endo and T. Shibata, *Org. Biomol. Chem.*, 2012, **10**, 3815.
16 (*a*) T. G. Traylor, K. J. Stewart and M. J. Goldberg, *J. Am. Chem. Soc.*, 1984, **106**, 4445; (*b*) T. G. Traylor, K. J. Stewart and M. J. Goldberg, *Organometallics*, 1986, **5**, 2062.
17 C. A. L. Mahaffy and P. L. Pauson, *J. Chem. Res., Synop.*, 1979, 126.
18 A similar approach has been shown to increase arene exchange in $Cr(\eta^6\text{-arene})$ complexes, see ref. 2*b* and (*a*) E. P. Kündig, M. Kondratenko and P. Romanens, *Angew. Chem., Int. Ed.*, 1998, **37**, 3146; (*b*) M. F. Semmelhack, W. Seufert and L. Keller, *J. Organomet. Chem.*, 1982, **226**, 183.
19 B. M. Trost and C. M. Older, *Organometallics*, 2002, **21**, 2544.
20 P.-H. Yeh, Z. Pang and R. F. Johnson, *J. Organomet. Chem.*, 1996, **509**, 123.
21 Transesterification to form the ethyl ester took place under the reaction conditions.