ChemComm

2009 'Catalysis in Organic Synthesis' web theme issue

Showcasing high quality research in organic chemistry

Please see our website
(http://www.rsc.org/chemcomm/organicwebtheme2009)
to access the other papers in this issue.

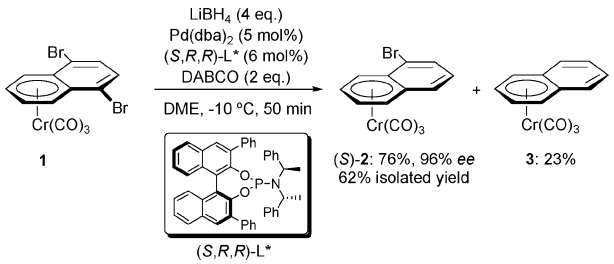
Synthesis of highly enantiomerically enriched planar chiral ruthenium complexes *via* Pd-catalysed asymmetric hydrogenolysis†‡

Audrey Mercier, Wee Chuan Yeo, Jingyu Chou, Piyali Datta Chaudhuri, Gérald Bernardinelli and E. Peter Kündig*

Received (in Cambridge, UK) 4th June 2009, Accepted 21st July 2009
First published as an Advance Article on the web 5th August 2009
DOI: 10.1039/b910977c

Key elements in this communication are a very efficient microwave synthesis of [RuCp(naphthalene)][PF_6], the precursor of [RuCp(CH_3CN)$_3$][PF_6], and a Pd-catalysed asymmetric hydrogenolysis to afford planar chiral ruthenium complexes with high levels of enantioselectivity using a bulky chiral phosphoramidite ligand.

Efficient access to optically pure planar chiral complexes is of interest in asymmetric synthesis and catalysis. The complexes can notably serve as the chiral source in asymmetric reactions and as catalysts or chiral ligands in a variety of organic transformations.[1] The most widely applied strategies to access enantiomerically enriched forms of these compounds are based either on resolution of racemates or on diastereoselective and enantioselective reactions. These approaches require a stoichiometric amount of chiral reagents or auxiliaries. A very attractive alternative, recently developed in our laboratory, is the Pd-catalysed enantioselective hydrogenolysis of the prochiral chromium complex **1** (Scheme 1).[2] We here report on the first application of this desymmetrisation process to the isoelectronic [Ru(η^5-C_5R_5)(η^6-5,8-dibromonaphthalene)][PF_6] (**5**) as well as to the neutral analogues [Ru(η^5-C_5R_5)(η^5-4,7-dibromoindene)] (**6**).



Scheme 1 Palladium-catalysed asymmetric hydrogenolysis of complex **1**.

In contrast to planar chiral ferrocenes[3] and chromium[1] complexes, ruthenium sandwich complexes have received scarce attention in terms of applications in catalysis.[4,5] Both cationic (η^6-arene)ruthenium and neutral(η^5-indenyl) ruthenium species are more resistant than [Cr(η^6-arene)(CO)$_3$] complexes to oxidative, thermal and photolytic cleavage of the metal–arene bond. To date, enantiopure members of planar chiral Ru sandwich complexes have been synthesised either *via* chiral precursors[5] or by resolution *via* (semi)-preparative HPLC.[6] To the best of our knowledge, catalytic desymmetrisation processes have been applied exclusively to prochiral [Cr(η^6-arene)(CO)$_3$] complexes.[7]

Before investigating dibromonaphthalene complexes of Ru(II), we deemed it important to further develop an efficient access to multi-gram quantities of starting material. We thus revisited the synthetic protocol of the pivotal precursor [RuCp(CH_3CN)$_3$][PF_6] (**4a**). In 2004, we reported an operationally safe and simple method for the synthesis of **4a**[8a] that avoids the use of both highly toxic thallium reagents[8b] and photolytic quartz apparatus.[8b,c] The procedure still suffers from practical limitations, notably a long reaction time and large excess of naphthalene. Focusing on the Cp–arene exchange, we now find that using microwave irradiation[9] allows us to reduce the amount of naphthalene from 10 to 2 equivalents. More importantly, the reaction time can be drastically shortened from 3 days to 15 minutes! This reaction was carried out conveniently on a 10 mmol scale, leading to 3.7 g of [RuCp(naphthalene)][PF_6] (**8**) after purification (Scheme 2).§

This new efficient preparation removes a bottleneck in the preparation of the widely used catalyst [RuCp(CH_3CN)$_3$][PF_6].[10] We also note that it can be more convenient to use the air-stable catalyst precursor [RuCp(naphthalene)][PF_6] (**8**) in place of the air-sensitive [RuCp(CH_3CN)$_3$][PF_6] (**4a**).[11]

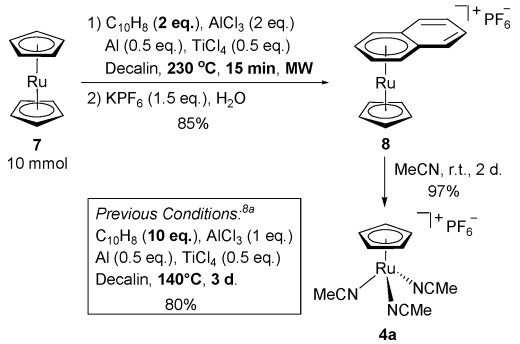
Complexes **5a**, **b** and **6a**, **b** were synthesised starting from [RuCp(CH_3CN)$_3$][PF_6] (**4a**) and [RuCp*(CH_3CN)$_3$][PF_6] (**4b**),[12] respectively, according to literature procedures.[13,14] Similarly, complex **6c** was prepared from **4c** (Scheme 3).

Initial desymmetrisation studies started with cationic [Ru(η^5-C_5R_5)(η^6-5,8-dibromonaphtahlene)][PF_6] (**5**) as substrates (Table 1). The optimal conditions developed for chromium complex **1** were applied first. $LiBH_4$ was employed as the hydride source and DABCO was used as the borane scavenger to prevent the formation of the BH_3–ligand adduct.[15] The reaction of **5a** in DME gave only moderate conversion and asymmetric induction (Table 1, entry 1). Using dichloromethane, adjusting the temperature to −50 °C and the amount of $LiBH_4$ to one equivalent afforded mono-halogenated **9a** in

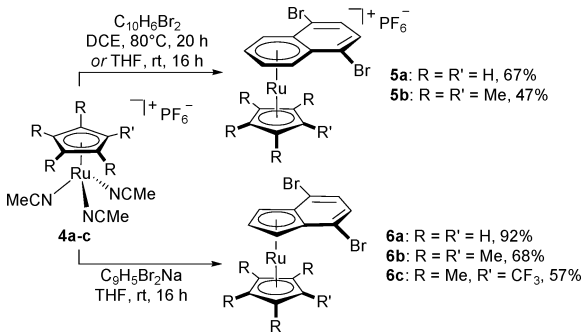
Department of Organic Chemistry, University of Geneva, Quai Ernest Ansermet 30, 1211 Geneva 4, Switzerland. E-mail: Peter.Kundig@unige.ch

† This article is part of a ChemComm 'Catalysis in Organic Synthesis' web-theme issue showcasing high quality research in organic chemistry. Please see our website (http://www.rsc.org/chemcomm/organicwebtheme2009) to access the other papers in this issue.

‡ Electronic supplementary information (ESI) available: Experimental details for the reported compounds and spectroscopic data (28 pages). CCDC 735050. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b910977c



Scheme 2 Improved protocol for the synthesis of **4a** *via* microwave-assisted Cp–arene exchange.

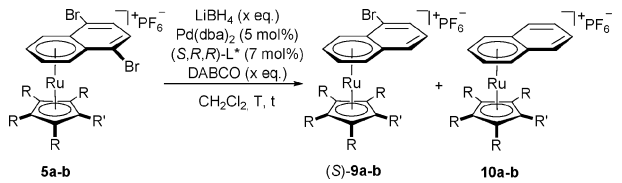


Scheme 3 Synthesis of cationic and neutral complexes **5** and **6** (DCE = dichloroethane).

90% ee with an excellent selectivity between **9a** and the over-reduced complex **10a** (Table 1, entry 2). With complex **5b**, bearing the bulky, electron-rich Cp* ligand, the optimal temperature for the desymmetrisation was −40 °C. After 3 h, full conversion and high **9b**/**10b** selectivity were attained and the ee reached 96% (Table 1, entry 3). Taking advantage of the kinetic resolution at play in this reaction, **9b** can be obtained in 99% enantiomeric excess, albeit at the expense of a larger amount of over-reduced complex **10b** (Table 1, compare entries 3 and 4, faster conversion of the minor enantiomer (*R*)-**9** into **10** leads to further enrichment in (*S*)-**9**).[16] When the reaction was performed on a larger scale (3 mmol), as low as 1 mol% of Pd and 4 mol% of chiral ligand were sufficient to achieve complete conversion and high enantioselectivity (Table 1, entry 5). Attempts to separate complexes **9** and **10** were not successful. Conversion of **9b** into **13b** by a microwave-assisted cross-coupling reaction was performed without erosion of enantioselectivity (Scheme 4). Separation of **13b** from remaining **10b** posed no problem. The (*S*) absolute configuration of **13b**, and by analogy **9b**, was determined *via* X-ray crystallographic analysis.[17]

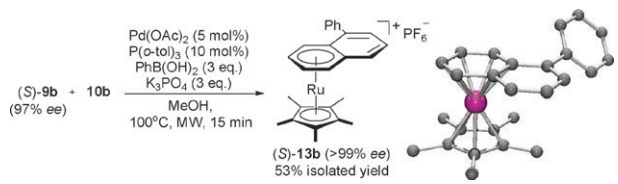
We next tested this desymmetrisation procedure on the neutral analogues **6**. These are more stable and easier to handle than the cationic derivatives (Table 2). Reaction conditions had to be modified from those optimal for **5**. The temperature was raised to 10 °C, $Pd(dba)_2$ was used in place of $[Pd(allyl)Cl]_2$, and the solvent was changed to DME. Substantial over-reduction to give **12a** remained a problem, however (Table 2, entry 1). In toluene the **11a**/**12a** selectivity was improved (Table 2, entry 2). At −20 °C complete conversion

Table 1 Palladium-catalysed asymmetric hydrogenolysis of cationic complexes[a]



Entry	5	T/°C	$LiBH_4$ (eq.)	t/h	5 (%)[b]	9 (%)[b]	10 (%)[b]	ee 9 (%)[c]
1[d,e]	**5a**	−20	2	1.7	27	56	17	74
2[d,f]	**5a**	−50	1	1.7	2	75	19	90
3[g]	**5b**	−40	1.5	3.0	0	92	8	96
4[g]	**5b**	−40	1.5	4.0	0	88	12	99
5[h]	**5b**	−40	1.5	2.5	0	90	10	97

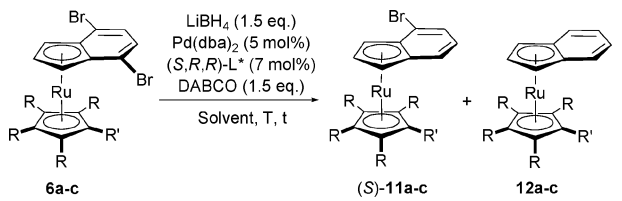
[a] Reaction conditions (unless otherwise stated): 0.2 mmol of **5**, $LiBH_4$ added dropwise as a DME solution, 0.025 M in dry and degassed CH_2Cl_2. [b] Determined by ^1H NMR. [c] Determined by ^1H NMR in the presence of $[n\text{-}Bu_4N][\Delta\text{-TRISPHAT}]$.[18] [d] 20 mol% of L*, no DABCO. [e] Reaction carried out in DME. [f] 3% of decomplexation product. [g] 2.5 mol% $[Pd(allyl)Cl]_2$. [h] Run on 3 mmol of **5**; 0.5 mol% $[Pd(allyl)Cl]_2$, 4 mol% L*; 92% isolated yield of a 9 : 1 mixture of **9**: **10**.



Scheme 4 Suzuki–Miyaura coupling of **9b**. ORTEP view of the crystal structure of (*S*)-**13b**.

was achieved, affording **11a** in up to 96% ee along with a good **11a**/**12a** ratio (Table 2, entries 3 and 4).[19] Complex **6b**, incorporating the bulky, electron-rich Cp* ligand, was proved more problematic. **11b** was obtained in 68% ee, with a 2 : 1 ratio between **11b** and **12b** (Table 2, entry 5). The reaction was

Table 2 Palladium-catalysed asymmetric hydrogenolysis of neutral complexes[a]



Entry	6	Solvent	T/°C	t/h	6 (%)[b]	11 (%)[b]	12 (%)[b]	ee 11 (%)[c]
1	**6a**	DME	10	1.5	0	30	70	96
2	**6a**	Toluene	10	1.5	0	65	35	89
3	**6a**	Toluene	−10	2.5	2	72	26	91
4	**6a**	Toluene	−20	18.0	0	72 (72)[d]	28	96
5	**6b**	Toluene	−20	22.5	0	69 (62)[d]	31	68
6	**6c**	Toluene	−20	24.0	3	77 (71)[d]	20	78

[a] Reaction conditions (unless otherwise stated): 0.1 mmol of **6**, $LiBH_4$ added dropwise as a DME solution, 0.025 M in dry and degassed solvent. [b] Determined by ^1H NMR. [c] Determined by chiral HPLC. [d] Isolated yield after flash chromatography.

also carried out with **6c** (R = Me, R′ = CF_3), isosteric to **6c** and isoelectronic to **6a**.[20] Complex **11c** was obtained with an intermediate 78% ee (Table 2, entry 6), indicating that both steric and electronic properties affect the enantioselectivity outcome of the process. This trend had not been observed for the cationic complexes.

In conclusion, we have established a convenient, high yield, microwave-assisted synthesis for the preparation of $[RuCp(CH_3CN)_3][PF_6]$ (**4a**) from readily available ruthenocene. We have also developed the first catalytic desymmetrisation of ruthenium complexes and demonstrated the generality of the Pd-catalysed asymmetric enantioselective hydrogenolysis. Studies are ongoing in our laboratory to apply these planar chiral complexes as chiral ligands in asymmetric catalysis.

Financial support by the Swiss National Science Foundation and the University of Geneva is acknowledged with thanks. We are grateful to M. Berthod, P. Buchgraber, D. Linder and C. Mazet for helpful discussions and technical assistance.

Notes and references

§ See caution note on the use of Al powder in the microwave experiments (ESI).

1 (*a*) C. Bolm and K. Muniz, *Chem. Soc. Rev.*, 1999, **28**, 51; (*b*) A. R. Pape, K. P. Kaliappan and E. P. Kündig, *Chem. Rev.*, 2000, **100**, 2917; (*c*) A. Salzer, *Coord. Chem. Rev.*, 2003, **242**, 59; (*d*) *Transition Metal Arene π-Complexes in Organic Synthesis and Catalysis: Topics in Organometallic Chemistry*, ed. E. P. Kündig, Springer Verlag, Heidelberg, 2004, vol. 7; (*e*) M. Ogasawara and S. Watanabe, *Synthesis*, 2009, 1761.

2 E. P. Kündig, P. D. Chaudhuri, D. House and G. Bernardinelli, *Angew. Chem., Int. Ed.*, 2006, **45**, 1092.

3 (*a*) *Ferrocenes*, ed. T. Hayashi and A. Togni, VCH, Weinheim, Germany, 1995; (*b*) T. J. Colacot, *Chem. Rev.*, 2003, **103**, 3101; (*c*) G. C. Fu, *Acc. Chem. Res.*, 2004, **37**, 542; (*d*) R. G. Arrayas, J. Adrio and J. C. Carretero, *Angew. Chem., Int. Ed.*, 2006, **45**, 7674; (*e*) M. Ogasawara, S. Watanabe, K. Nakajima and T. Takahashi, *Pure Appl. Chem.*, 2008, **80**, 1109.

4 (*a*) R. M. Moriarty, U. S. Gill and Y. Y. Ku, *J. Organomet. Chem.*, 1988, **350**, 157; (*b*) J. W. Janetka and D. H. Rich, *J. Am. Chem. Soc.*, 1997, **119**, 6488; (*c*) A. J. Pearson and M. V. Chelliah, *J. Org. Chem.*, 1998, **63**, 3087; (*d*) F. C. Pigge, S. Y. Fang and N. P. Rath, *Tetrahedron Lett.*, 1999, **40**, 2251; (*e*) E. Matsushima, N. Komatsuzaki, Y. Ajioka, M. Yamamoto, H. Kikuchi, Y. Takata, N. Dodo, K. Onitsuka, M. Uno and S. Takahashi, *Bull. Chem. Soc. Jpn.*, 2001, **74**, 527; (*f*) F. C. Pigge and J. J. Coniglio, *Curr. Org. Chem.*, 2001, **5**, 757.

5 (*a*) R. Pasch, U. Koelle, B. Ganter and U. Englert, *Organometallics*, 1997, **16**, 3950; (*b*) N. Komatsuzaki, H. Kikuchi, M. Yamamoto, M. Uno and S. Takahashi, *Chem. Lett.*, 1998, 445; (*c*) K. Kamikawa, M. Furusyo, T. Uno, Y. Sato, A. Konoo, G. Bringmann and M. Uemura, *Org. Lett.*, 2001, **3**, 3667; (*d*) K. Kamikawa, K. Norimura, M. Furusyo, T. Uno, Y. Sato, A. Konoo, G. Bringmann and M. Uemura, *Organometallics*, 2003, **22**, 1038; (*e*) S. Bonnet, J. Li, M. A. Siegler, L. S. von Chrzanowski, A. L. Spek, G. van Koten and R. J. M. K. Gebbink, *Chem.–Eur. J.*, 2009, **15**, 3340.

6 C. E. Garrett and G. C. Fu, *J. Am. Chem. Soc.*, 1998, **120**, 7479.

7 (*a*) M. Uemura, H. Nishimura and T. Hayashi, *Tetrahedron Lett.*, 1993, **34**, 107; (*b*) M. Uemura, H. Nishimura and T. Hayashi, *J. Organomet. Chem.*, 1994, **473**, 129; (*c*) B. Gotov and H. G. Schmalz, *Org. Lett.*, 2001, **3**, 1753; (*d*) A. Bottcher and H. G. Schmalz, *Synlett*, 2003, 1595; (*e*) K. Kamikawa, K. Harada and M. Uemura, *Tetrahedron: Asymmetry*, 2005, **16**, 1419.

8 (*a*) E. P. Kündig and F. R. Monnier, *Adv. Synth. Catal.*, 2004, **346**, 901; (*b*) T. P. Gill and K. R. Mann, *Organometallics*, 1982, **1**, 485; (*c*) B. M. Trost and C. M. Older, *Organometallics*, 2002, **21**, 2544.

9 D. Adam, *Nature*, 2003, **421**, 571.

10 (*a*) B. M. Trost, F. D. Toste and A. B. Pinkerton, *Chem. Rev.*, 2001, **101**, 2067; Recent reports; (*b*) E. C. Hansen and D. S. Lee, *J. Am. Chem. Soc.*, 2005, **127**, 3252; (*c*) H. Saburi, S. Tanaka and M. Kitamura, *Angew. Chem., Int. Ed.*, 2005, **44**, 1730; (*d*) B. M. Trost and A. C. Gutierrez, *Org. Lett.*, 2007, **9**, 1473; (*e*) F. C. Pigge, R. Dhanya and E. R. Hoefgen, *Angew. Chem., Int. Ed.*, 2007, **46**, 2887; (*f*) S. Constant, S. Tortoioli, J. Muller and J. Lacour, *Angew. Chem., Int. Ed.*, 2007, **46**, 2082.

11 (*a*) A. Labonne, T. Kribber and L. Hintermann, *Org. Lett.*, 2006, **8**, 5853; (*b*) T. Kribber, A. Labonne and L. Hintermann, *Synthesis*, 2007, 2809; (*c*) A. Labonne, L. Zani, L. Hintermann and C. Bolm, *J. Org. Chem.*, 2007, **72**, 5704; (*d*) D. Linder, F. Buron, S. Constant and J. Lacour, *Eur. J. Org. Chem.*, 2008, 5778.

12 B. Steinmetz and W. A. Schenk, *Organometallics*, 1999, **18**, 943.

13 (*a*) R. C. Cambie, S. A. Coulson, L. G. Mackay, S. J. Janssen, P. S. Rutledge and P. D. Woodgate, *J. Organomet. Chem.*, 1991, **409**, 385; (*b*) S. P. Nolan, K. L. Martin, E. D. Stevens and P. J. Fagan, *Organometallics*, 1992, **11**, 3947.

14 A. R. Kudinov, P. V. Petrovskii, Y. T. Struchkov, A. I. Yanovskii and M. I. Rybinskaya, *J. Organomet. Chem.*, 1991, **421**, 91.

15 The manuscript regarding the use of DABCO as BH_3-scavenger in Pd–phosphoramidite–$LiBH_4$ asymmetric hydrogenolysis of Ar–Br bonds in arene chromium complexes is in preparation.

16 Kinetic resolution: (*a*) H. B. Kagan and J. C. Fiaud, *Top. Stereochem.*, 1988, **18**, 249; (*b*) J. M. Keith, J. F. Larrow and E. N. Jacobsen, *Adv. Synth. Catal.*, 2001, **343**, 5; (*c*) For racemic [RuCp*(5-bromonaphthalene)][PF_6], a selectivity factor *S* of 3.5 was found at −40 °C.

17 *Crystal data for* (*S*)-**13**: $(C_{26}H_{27}Ru)(PF_6)$, M = 585.5, T = 150 K, MoKα, orthorhombic, space group $P2_12_12_1$, a = 7.1897(3), b = 16.1402(7), c = 20.8063(13) Å, U = 2414.4(2) Å^3, Z = 4, D_c = 1.611 g cm^{-3}, μ = 0.774 mm^{-1}, $F(000)$ = 1184, 23 582 reflections were measured of which 5188 are unique (R_{int} = 0.029) and 4261 are observed ($I > 4\sigma$). Final *R*-values are R_1 ($I > 4\sigma$) = 0.019, wR_2 ($I > 4\sigma$) = 0.020 (308 parameters, 5188 unique), Flack parameter −0.03(3). CCDC 735050.

18 J. Lacour, C. Ginglinger, F. Favarger and S. Torche-Haldimann, *Chem. Commun.*, 1997, 2285. The tris(tetrachlorobenzenediolato) phosphate(v) salt was used as a NMR chiral shift reagent to determine the enantiopurity of chiral cationic complexes **9**. We thank Prof. J. Lacour for the generous gift of [*n*-Bu_4N][Δ-TRISPHAT].

19 For racemic [RuCp(4-bromoindene)], a selectivity factor *S* of 5 was found at −20 °C.

20 P. G. Gassman, J. W. Mickelson and J. R. Sowa, *J. Am. Chem. Soc.*, 1992, **114**, 6942.