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

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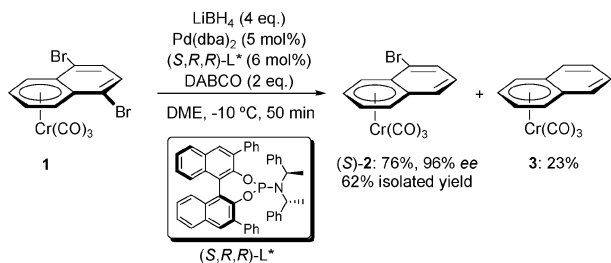
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Key elements in this communication are a very efficient microwave synthesis of [RuCp(naphthalene)][PF₆], the precursor of [RuCp(CH₃CN)₃][PF₆], and a Pd-catalysed asymmetric hydrogenolysis to afford planar chiral ruthenium complexes with high levels 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(η⁵-C₅R₅)(η⁶-5,8-dibromonaphthalene)][PF₆] (**5**) as well as to the neutral analogues [Ru(η⁵-C₅R₅)(η⁵-4,7-dibromoindene)] (**6**).



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

In contrast to planar chiral ferrocenes³ and chromium¹ complexes, ruthenium sandwich complexes have received

scarce attention in terms of applications in catalysis.^{4,5} Both cationic (η⁶-arene)ruthenium and neutral(η⁵-indenyl) ruthenium species are more resistant than [Cr(η⁶-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 precursors⁵ or by resolution *via* (semi)-preparative HPLC.⁶ To the best of our knowledge, catalytic desymmetrisation processes have been applied exclusively to prochiral [Cr(η⁶-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(CH₃CN)₃][PF₆] (**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 irradiation⁹ 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)][PF₆] (**8**) after purification (Scheme 2).§

This new efficient preparation removes a bottleneck in the preparation of the widely used catalyst [RuCp(CH₃CN)₃][PF₆].¹⁰ We also note that it can be more convenient to use the air-stable catalyst precursor [RuCp(naphthalene)][PF₆] (**8**) in place of the air-sensitive [RuCp(CH₃CN)₃][PF₆] (**4a**).¹¹

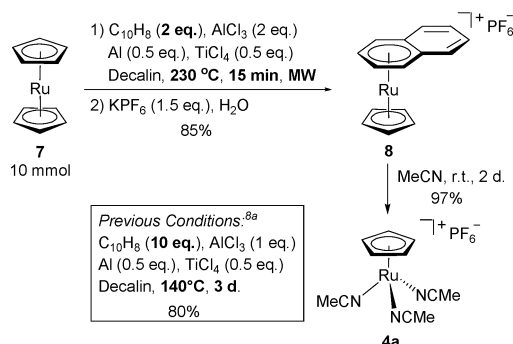
Complexes **5a**, **b** and **6a**, **b** were synthesised starting from [RuCp(CH₃CN)₃][PF₆] (**4a**) and [RuCp*(CH₃CN)₃][PF₆] (**4b**),¹² respectively, according to literature procedures.^{13,14} Similarly, complex **6c** was prepared from **4c** (Scheme 3).

Initial desymmetrisation studies started with cationic [Ru(η⁵-C₅R₅)(η⁶-5,8-dibromonaphthalene)][PF₆] (**5**) as substrates (Table 1). The optimal conditions developed for chromium complex **1** were applied first. LiBH₄ was employed as the hydride source and DABCO was used as the borane scavenger to prevent the formation of the BH₃–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 LiBH₄ to one equivalent afforded mono-halogenated **9a** in

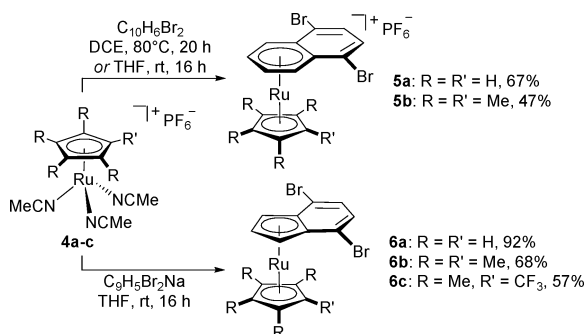
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‡ Electronic supplementary information (ESI) available: Experimental details for the reported compounds and spectroscopic data (28 pages). CCDC 735050. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b910977c



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

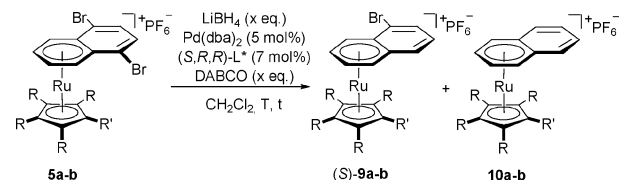


Scheme 3 Synthesis of cationic and neutral complexes **5** and **6** (DCE = dichloroethane).

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

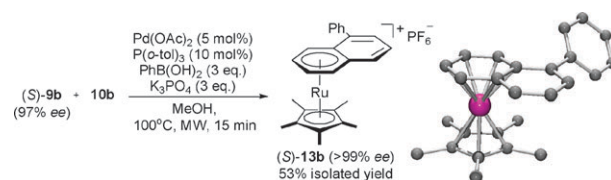
We next tested this desymmetrisation procedure on the neutral analogues **6**. These are more stable and easier to handle than the cationic derivatives (Table 2). Reaction conditions had to be modified from those optimal for **5**. The temperature was raised to 10°C , Pd(dba)₂ was used in place of [Pd(allyl)Cl]₂, 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	<i>T</i> /°C	LiBH ₄ (eq.)	<i>t</i> /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

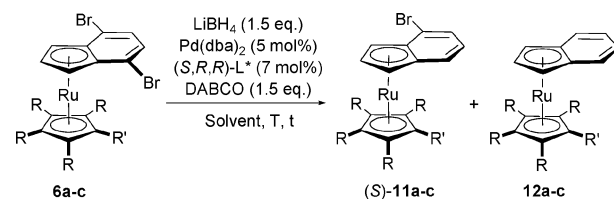
^a Reaction conditions (unless otherwise stated): 0.2 mmol of **5**, LiBH₄ added dropwise as a DME solution, 0.025 M in dry and degassed CH₂Cl₂. ^b Determined by ¹H NMR. ^c Determined by ¹H NMR in the presence of [*n*-Bu₄N][Δ-TRISPHAT].¹⁸ ^d 20 mol% of L*, no DABCO. ^e Reaction carried out in DME. ^f 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	<i>T</i> /°C	<i>t</i> /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**, LiBH₄ 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** ($R = \text{Me}$, $R' = \text{CF}_3$), 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 $[\text{RuCp}(\text{CH}_3\text{CN})_3][\text{PF}_6]$ (**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.

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

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