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High performance liquid chromatography for facile analytical separation of the enantiomers of chiral organometallic complexes

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Dedicated to Professor Henri Brunner on the occasion of his 65th birthday

Abstract

The applicability of chiral HPLC for the rapid analysis of the enantiopurity of organoiridium and -molybdenum complexes is demonstrated. Halogen-substituted metal complexes showed the best separation and the longest elution times. Separation of enantiomers of planar chiral zirconium and titanium complexes was also attempted although unsuccessfully. Preparative-scale columns were shown to be useful for the separation of racemic material into synthetically useful amounts of pure enantiomers.

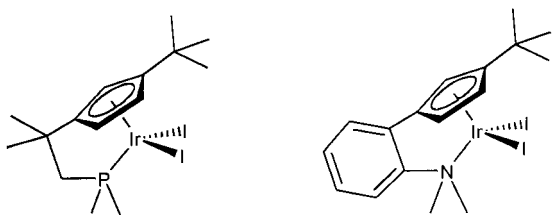
Keywords: Planar chiral; High performance liquid chromatography; Iridium; Molybdenum

1. Introduction

In the majority of enantioselective catalysts, chirality is provided by the attachment of ligands that are optically stable as free ligands and retain their dissymmetry when bound to the metal center [1]. However, the growing utility of such catalysts has stimulated interest in exploring complexes having local chirality at the metal center, provided by the presence of so-called 'planar chirality' or by a metal center that is stereogenic [2–6]. The present study was stimulated by recent work in our group that has focused on planar chiral organometallic complexes of the type shown in Fig. 1. The compound Cp^PIrH_2 (**1**) has been shown to C–H activate cyclohexane diastereoselectively [7].

Understanding and improving reactions catalyzed by chiral-at-metal complexes requires efficient methods for establishing the enantiopurity of such materials. The classical method for achieving this with organic compounds involves chemical conversion (through a series of reactions for which the stereochemistry has been reliably established) of a resolved or partially resolved complex to a substance of known absolute configuration. The structural identity and optical rotation of the correlated compound are then compared with those of the known material. Because the stereochemistry of many organometallic reactions is not firmly established, determining ee's and absolute configurations by this method is much less reliable for metal complexes. Therefore, analytical methods for measuring enantiomeric excess (ee) in organometallic compounds are generally limited to the use of chiral shift reagents in NMR spectroscopy, or X-ray diffraction for materials that can be crystallized.

Recently high performance liquid chromatography (HPLC) using chiral columns has made ee determina-



2 **7**

Fig. 1. The structure of compounds **2** (Cp^PIrI_2) and **7** (Cp^NIrI_2).

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Table 1
Organometallic compounds separated successfully using chiral HPLC

Compound	Hex/2-propanol (v/v) [a]	t_1 (min)	t_2 (min)	α [b]
Iridium complexes				
Cp^PIrH_2 (**1**)	99/1	7.15	9.36	1.59
Cp^PIrI_2 (**2**)	90/10	16.07	17.98	1.16
	95/5	32.94	37.26	1.18
Cp^PIr(binol) (**3**) [c]	90/10	14.15	16.62	1.23
Cp^PIrCl_2 (**4**)	95/5	30.94	40.78	1.38
Cp^PIr(pin) (**5**) [d]	90/10	18.84	21.69	1.19
$Cp^PIr(Me)(I)$ (**6**)	95/5	33.6	35.79	1.08
Cp^NIrI_2 (7)	90/10	3.06	3.24	0.82
$Cp^NIr(PMe_3)I_2$ (**8**)	90/10	6.79	7.45	1.24
$Cp^*(PMe_3)Ir(H)(C(O)Tol)$ (**9**)	90/10	3.12	3.46	0.73
Molybdenum complexes				
$Cp^NMo(CO)_3Cl$ (**10**)	97/3	5.6	6.04	1.21
$Cp^NMo(CO)_3Me$ (**11**)	99/1	4.5	4.81	1.32
$Cp^NMo(CO)_2(PMe_3)(C(O)Me)$ (**12**)	99/1	7.91	8.62	1.16
$Cp^NMo(O)_2Cl$ (**13**)	99.5/0.5	7.23	8.598	1.37
(Salen) complexes				
(salen)MnCl (**14**) [e]	90/10 (hex/EtOH)	10.77 (*S*,*S*)	11.85 (*R*,*R*)	1.12

[a] Solvent flow rate = 1.0 ml min^{-1}.
[b] $\alpha = (t_2 - t_m)/(t_1 - t_m)$, (m = solvent front).
[c] Binol = 2,2′-binapthol.
[d] Pin = 2,3-dimethyl-2,3-butanediol.
[e] Salen = [1,2-cyclohexanediamino-*N*,*N*′-bis(3,5-di-*t*-butylsalicylidene)].

tions in organic chemistry rapid and routine [8,9]. HPLC offers the advantage of mild separation conditions, high speed and efficiency, and the method can be used with sensitive, small-volume liquid-phase detectors [10]. The use of HPLC for preparative and analytical separations of achiral organometallic compounds has been established [9,11], but relatively little work has been published on the separation of enantiomers of organometallic complexes by this method [8,9,12]. Previous work in this area has involved chromium and rhenium complexes [5,11], while recently planar chiral ferrocene complexes have also been separated using chiral HPLC [13]. In this communication we describe the separation of a variety of chiral racemic organometallic complexes using chiral HPLC. Our work extends this technique to a wider range of organometallic functionalities than had been reported earlier.

2. Results and discussion

2.1. General conditions

As shown in Table 1, the enantiomers of a range of middle and late organotransition metal compounds, including planar chiral cyclopentadienyl complexes, were separated successfully using chiral HPLC. In a typical run, 20 μl of 0.1 M solution of the sample was injected and eluted with the appropriate solvent mixture. A Chiralcel OD column, which derives its chirality from cellulose carbamate adsorbed onto silica (Fig. 2), was used. In addition to the majority of complexes analyzed that have not yet been enantiomerically resolved on a preparative scale, chromatograms were run of separate and mixed samples of two known compounds available in both racemic and optically active form. In the case where successful resolution was achieved (**10**; see below), the one major peak observed for the active material co-eluted with one of the two peaks observed for the racemic system. This supports our conclusion that the two peaks of equal area observed in these analyses are enantiomers. This technique worked well for moderately air sensitive middle and late transition series metal complexes but poorly for early metals.

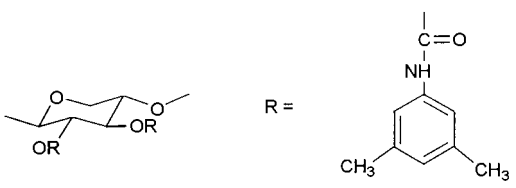

Fig. 2. The chiral phase of HPLC on a chromatographic column is packed with 3,5-dimethylphenyl carbamate derivative of cellulose (Chiracell OD).

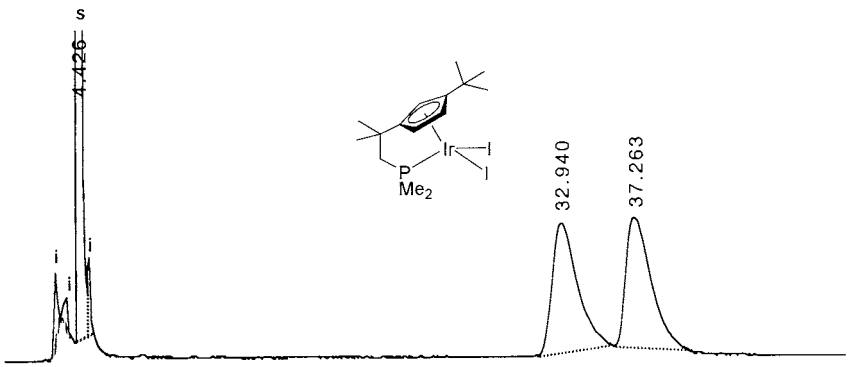

Fig. 3. A representative chromatogram. The two peaks integrate to 50.3:49.7: conditions as per Table 1; s = injection solvent; i = impurities.

2.2. Iridium complexes

The chiral HPLC technique successfully separated racemic Cp^P and Cp^N (see Fig. 1 for ligand abbreviations) iridium complexes bearing halogen (**2**, **4**), alkoxy (**3**, **5**), and even hydride (**1**, **9**) functionalities. The stability of the hydride complexes **1** and **9** on the column is notable, given the air sensitivity of these complexes. The Cp^P complexes had a longer retention time than the Cp^N complexes (see Fig. 3 for typical chromatograms) due possibly to the decreased polarity of the Cp^N metal complexes as compared to the Cp^PIrX_2 (X = I or Cl) complexes.

2.3. Molybdenum complexes

The molybdenum complexes listed in Table 1 proved to be more difficult to separate because of their rapid elution from the column. In addition, the air sensitivity of these complexes required that the injection be made immediately upon dissolution of the complex into the eluent. Compounds **10**, **11**, **12** and **13** all eluted in less than 10 min ranging from 4.50 (earlier enantiomer of **11**) to 8.60 min (later enantiomer of **13**). While the retention times of most of the molybdenum complexes were determined successfully, the dimer $[Cp^NMo(CO)_3]_2$ decomposed too quickly for meaningful analysis. In all cases, allowing the molybdenum complexes to stand in solution for more than a few minutes resulted in the formation of an unidentified insoluble blue precipitate. The substituents on the molybdenum center affected the retention time, but these difference were smaller than those observed in the iridium complexes. A sample of **10** was separated using a semi-preparative scale chiral HPLC column. The retention times were similar to those observed on the analytical column and the major peak observed for optically active material co-eluted with one of the two peaks of equal area observed for the racemic system (Fig. 4).

2.4. Manganese and cobalt salen complexes

To demonstrate the scope of this analytical technique, we explored the use of HPLC for the separation of the commercially available chiral organometallic complexes (salen)MnCl (**14**) and (salen)Co (**15**) (salen = [1,2 - cyclohexanediamino - *N*,*N*′ - bis(3,5 - di - *t* - butylsalicylidene)]). Analysis of compound **14** showed distinguishable retention times for each enantiomer (with the *S*,*S* enantiomer eluting earlier) using 90/10 hexane/EtOH as the solvent mixture. However, the

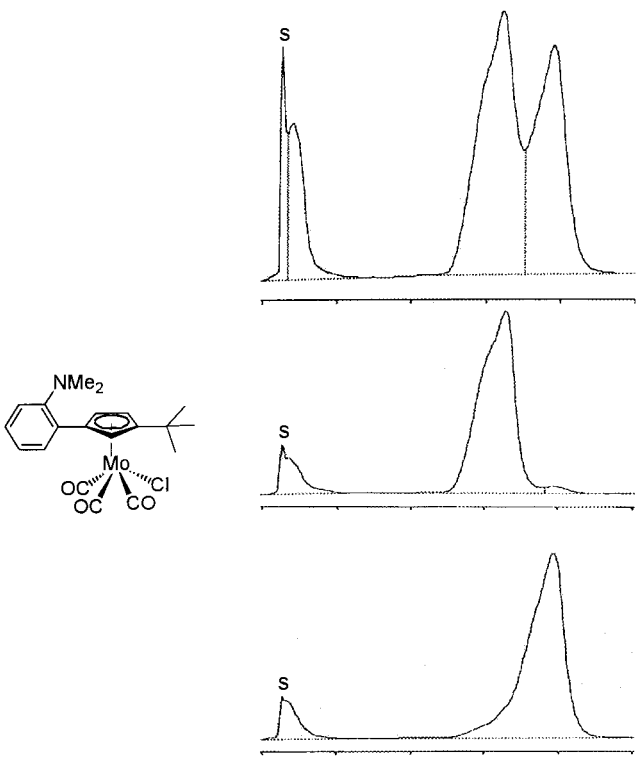

Fig. 4. Chiral HPLC traces of compound **10** after separation (a) racemic, (b) faster-moving enantiomer (c) slower-moving enantiomer. Conditions as per Table 1; s = injection solvent.

racemate showed a single peak under the same conditions. We suspect that this may be due to oligomerization of the enantiomeric pairs in solution, although we have not pursued this question further. For complex **15**, the racemic mixture did not separate using even the most non-polar solvent system available (99.5/0.5 hexane/2-propanol).

3. Summary and conclusion

In this work we have established that chiral HPLC can dramatically reduce the amount of time and material required for the determination of enantiopurity of a reasonably wide range of chiral organometallic complexes. We have demonstrated the applicability of this technique for the rapid analysis of the enantiopurity of organoiridium and -molybdenum complexes. Halogen-substituted metal complexes showed the best separation and the longest elution times. Separation of enantiomers of planar chiral zirconium and titanium complexes ($Cp^NCp^*ZrCl_2$, $Cp^PCp^*ZrCl_2$, $(Cp^P)_2TiCl_2$) was also attempted. Limitations imposed by the nature of the chiral column unfortunately resulted in decomposition in these cases. Preparative-scale columns have been shown to be useful for the separation of racemic material into synthetically useful amounts of pure enantiomers. We are presently attempting to extend the generality of this analytical technique.

4. Experimental

4.1. General

Manipulations of air sensitive compounds were performed in a vacuum atmospheres recirculating inert atmosphere glove box. The synthesis of compounds **1**–**2** [7], **3**–**8** [14], **9** [15] and **10**–**13** [16] are described elsewhere. Both enantiomers of **14** (*S*,*S* and *R*,*R*) and **15** (*S*,*S* and *R*,*R*) were purchased from STREM and used without further purification. Hexanes used in the glove box were passed through a column of activated alumina collected under and sparged with N_2 prior to use. All elution solvents for chiral HPLC were filtered through Nylon-66 (0.45 μm/47 mm) filters prior to use.

4.2. HPLC analysis

HPLC analysis was performed on a Chiracel OD column attached to a Rainin Instrument HPXL solvent delivery system and pressure moderator. UV detection was monitored at 254 nm using a Rainin instrument dynamics absorbance detector. Compounds were weighed out into 5 ml scintillation vials under N_2, dissolved in dry hexanes, capped with a plastic septum and brought out of the box. A 1.0-ml syringe with a needle was used to pierce the cap and extract the solution which was then filtered through a Milled-LG syringe driven filter unit (0.20 μm/4 mm) before being injected onto the column. In cases where the compound was not sufficiently soluble in hexanes, 2-propanol was syringed into the vial before filtration. A 20 μl sample of the filtered solution was then immediately injected onto the column.

For separations of larger amounts of material, the semi-preparative scale Chiracel OD column was used under the same conditions as used for the analytical samples. A solution of **10** (0.7 ml, 4.4 M in hexanes/2-propanol, 97/3) was filtered through a Milled-LG syringe driven filter unit (0.20 μm/4 mm) before being injected onto the column. The fast and slow enantiomers were collected separately after they passed through the UV detector. To isolate larger amounts of material, the injections were repeated and the fractions combined. The solvent was then removed in vacuo to result in the desired two enantiomers in enantiopure form.

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