Pergamon

Tetrahedron Letters 42 (2001) 2809–2812

TETRAHEDRON LETTERS

Chiral tricarbonyl(η^6-arene)chromium complexed diphosphanes. Highly enantioselective rhodium-mediated hydrogenation of ketones

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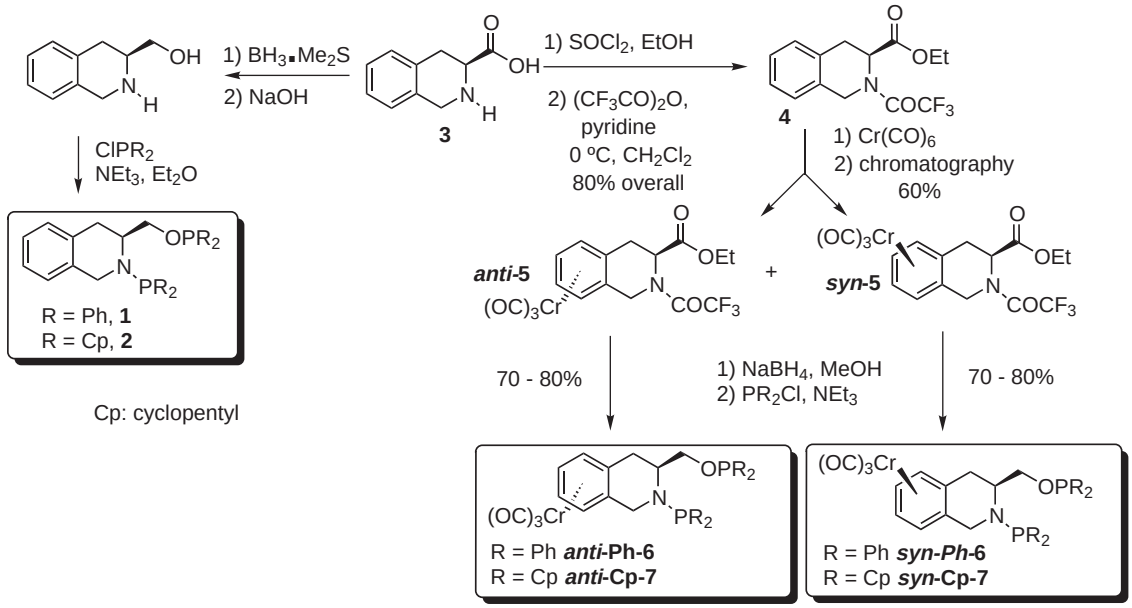
Received 15 February 2001; revised 21 February 2001; accepted 23 February 2001

Abstract—Arenechromium complexed diastereomeric aminophosphine–phosphinite ligands derived from tetrahydroisoquinoline have been synthesised and examined as chiral auxiliaries in the hydrogenation of functionalised ketones. A cyclopentyl-substituted *anti*-stereoisomer is providing the highest enantioselectivities (up to >99% ee).

Chiral chelating phosphines containing a ferrocene have encountered great success in asymmetric catalysis.[1] On the contrary, and although the tricarbonyl chromium unit has proven its utility as a stereodirecting group in chiral catalysts,[2] the use of arenechromium based chiral phosphines has obtained increased interest only in recent years.[3]

As part of an ongoing exploration of various synthetic approaches to aminophosphine–phosphinite ligands (AMPP),[4] we previously utilised the tricarbonyl chromium moiety to vary the stereo-electronic properties during ligand tuning.[5] In our example, the nitrogen atom of the AMPP was directly connected to the complexed *ortho*-substituted arene ring. Consequently,



Scheme 1.

Keywords: enantioselective hydrogenation; rhodium; ketones; aminophosphine–phosphinites; tricarbonylarenechromium.

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0040-4039/01/$ - see front matter
PII: S0040-4039(01)00325-2

the $Cr(CO)_3$ unit brought about steric and electronic control onto the corresponding AMPP ligands and a beneficial effect was observed in several cases.

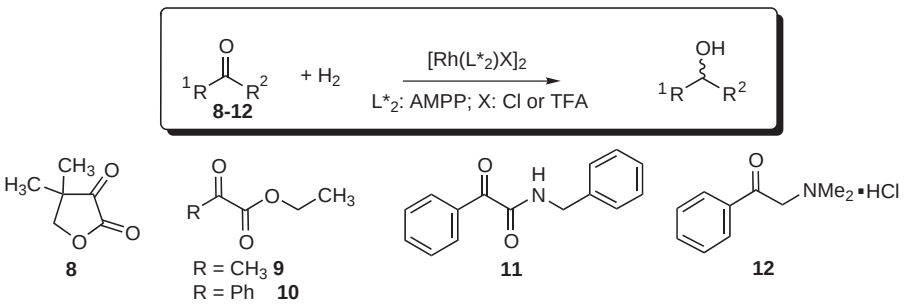
Considering the steric crowding provided by the $Cr(CO)_3$ when complexed on an aromatic precursor and taking into account the beneficial outcome expected while varying judiciously only the steric characteristic of chiral ligands, we thought to utilise the $Cr(CO)_3$ unit to accomplish specifically a steric tuning of AMPP ligands. The ligand precursor derived from tetrahydroisoquinoline carboxylic acid, which eludes the immediate proximity of the complexed arene and the nitrogen atom of the future AMPP ligand, appears particularly relevant for such a study. In addition, the uncomplexed ligands (*S*)-Cp,Cp-QuinoNOP and (*S*)-Cy,Cy-QuinoNOP induced already high enantioselectivities in ketone hydrogenation.[5] In this communication, we report the synthesis of isoquinoline based diastereomeric diphosphanes bearing a $Cr(CO)_3$ moiety and their use in asymmetric hydrogenation of functionalised ketones.

The parent ligands (*S*)-Ph,Ph-QuinoNOP **1** and (*S*)-Cp,Cp-QuinoNOP **2** (Scheme 1) have already been synthesised previously starting from (*S*)-1,2,3,4-tetrahydro-3-isoquinolinecarboxylic acid **3**.[5b] In order to synthesise and separate the corresponding $Cr(CO)_3$ complexed diastereomeric precursors possessing opposite face aromatic chiralities, the methodology developed earlier by us and others did not apply.[2a,5b] We have therefore devised the strategy given below. First, acid **3** was converted into its ethyl ester followed by a reaction with trifluoroacetic anhydride providing compound **4** in 80% overall yield. The latter was then thermolysed in the presence of hexacarbonylchromium in dibutylether/tetrahydrofuran producing the mixture of diastereomers ***anti*-5** and ***syn*-5** as a result of the $Cr(CO)_3$ complexation below and above the arene plane with nevertheless no diastereoselectivity (*anti*/*syn*: 54/46). Both diastereomers could be separated through silica gel chromatography (60% overall yield). Assignments of all protons of both isolated complexes were obtained easily by use of standard NMR techniques. Hence, the pairs of methylene protons attached to a given carbon atom were identified. The protons positioned to the side of the carbonyl ligands of $Cr(CO)_3$ can be markedly deshielded.[6] Consequently, in both diastereomers, the protons on the carbons connected to the complexed arene ring and lying on the side of the chromium tripod were deshielded (average $\Delta\delta = 0.2$ ppm) compared to the uncomplexed ligand. The remaining protons, opposite to the $Cr(CO)_3$ were not or only slightly deshielded ($\Delta\delta < 0.1$ ppm). Next, the *anti* and *syn* compounds, ***anti*-5** and ***syn*-5**, were reduced with $NaBH_4$ providing the corresponding amino-alcohols, which were converted through the standard procedure into the *anti* (***anti*-Ph-6** and ***anti*-Cp-7**) and *syn* (***syn*-Ph-6** and ***syn*-Cp-7**) complexed AMPP ligands in 70–80% overall yields.[7]

These new ligands were then evaluated in the rhodium catalysed hydrogenation of 5 typical ketones possessing various functionalities, i.e. 4,4-dimethyl-2,3-furandione **8**, ethyl pyruvate **9**, ethyl phenylglyoxylate **10**, *N*-benzylbenzoylformamide **11**, and 2-(*N*,*N*-dimethyl)-aminoketone hydrochloride **12** (Scheme 2). The results of the hydrogenation are summarised in Table 1. Earlier results are also reported in Table 1 for comparison.

First, the phenyl-substituted ligands **1**, ***anti*-6** and ***syn*-6** were examined in the hydrogenation of **8** (entries 1–3). As usual, the phenyl substituted AMPPs required more severe reaction conditions than the cycloalkyl substituted ones (entries 1–6). We noticed clearly a beneficial effect due to the $Cr(CO)_3$ moiety of the ***anti*-Ph-6** auxiliary as the hydrogenation product, pantolactone, was produced with 72% ee compared to 37% ee for the uncomplexed ligand (entry 2 versus 1). This is the highest enantioselectivity ever reached for the hydrogenation of **8** with Rh-based phenyl substituted AMPPs.[8] This value corresponds to an improvement of the enantiodifferenciation of 35% ee for the produced pantolactone compared to the uncomplexed ligand **1** and of 17% ee when compared to the best previously reported (*S*)-Ph,Ph-oxo-ProNOP ligand.[9] Nevertheless, a small decrease of enantioselectivity was obtained with ***anti*-Cp-7** as 87% ee were measured compared to 95% for the uncomplexed ligand **2** (entry 5 versus 4).

For the other four substrates, a beneficial effect (or clean conservation of the very high enantioselectivities) could be attributed to the presence of $Cr(CO)_3$ in the matched diastereomer ***anti*-Cp-7** mentioned above. For example, for substrate **9**, on going from uncomplexed **2**



Scheme 2.

Table 1. Asymmetric hydrogenation of functionalised ketones[a]

Entry	Substrate	Chiral ligand	Rh[b] complex	Solvent	P_{H_2} (bar)	T (°C)	Time (h)[c]	Conv. (%)[d]	Ee (%)[e] (confign)
1	**8**	**1**[f]	Rh-TFA	$PhCH_3$	50	50	89	94	37 (*R*)
2		***anti*-Ph-6**	Rh-TFA	$PhCH_3$	50	50	69	90	72 (*R*)
3		***syn*-Ph-6**	Rh-TFA	$PhCH_3$	50	50	69	85	17 (*R*)
4		**2**	Rh-TFA	$PhCH_3$	50	20	0.33	100	95 (*R*)
5		***anti*-Cp-7**	Rh-TFA	$PhCH_3$	50	20	0.5	61	87 (*R*)
6		***syn*-Cp-7**	Rh-TFA	$PhCH_3$	50	20	0.5	98	85 (*R*)
7	**9**	**2**[f]	Rh-TFA	$PhCH_3$	50	20	1	100	80 (R)
8		**2**	Rh-Cl	$PhCH_3$	50	20	6	97	70 (*R*)
9		***anti*-Cp-7**	Rh-TFA	$PhCH_3$	50	20	3	100	86 (*R*)
10		***syn*-Cp-7**	Rh-Cl	$PhCH_3$	50	20	6	93	76 (*R*)
11		**2**	Rh-TFA	MeOH	50	20	6	100	83 (*R*)
12		***anti*-Cp-7**	Rh-TFA	MeOH	50	20	6	100	95 (*R*)
13		***syn*-Cp-7**	Rh-TFA	MeOH	50	20	6	100	78 (*R*)
14	**10**	**2**[f]	Rh-TFA	$PhCH_3$	30	20	3	51	5 (*S*)
15		**2**	Rh-Cl	$PhCH_3$	30	20	4	68	11 (*S*)
16		**2**	Rh-Cl	MeOH	30	20	3	35	4 (*S*)
17		***anti*-Cp-7**	Rh-Cl	$PhCH_3$	30	20	20	100	5 (*S*)
18		***anti*-Cp-7**	Rh-Cl	MeOH	30	20	3	34	22 (*S*)
19		***syn*-Cp-7**	Rh-Cl	$PhCH_3$	30	20	3	49	4 (*S*)
20		***syn*-Cp-7**	Rh-Cl	MeOH	30	20	7	20	10 (*S*)
21	**11**	**2**	Rh-Cl	$PhCH_3$	50	20	19	100	>99 (*S*)
22		***anti*-Cp-7**	Rh-Cl	$PhCH_3$	50	20	18	100	>99 (*S*)
23		***syn*-Cp-7**	Rh-Cl	$PhCH_3$	50	20	18	100	94 (*S*)
24	**12**	**2**[f]	Rh-Cl	EtOH	50	20	18	100	>99 (*S*)
25		***anti*-Cp-7**	Rh-Cl	EtOH	50	20	18	100	>99 (*S*)
26		***syn*-Cp-7**	Rh-Cl	EtOH	50	20	18	100	95 (*S*)

[a] Hydrogenations were carried out in a 50 mL stainless steal autoclave using recrystallised **8**, **11**, and **12** and distilled **9** and **10**; substrate/Rh = 200/1.

[b] Catalyst precursors: Rh-Cl:$[Rh(COD)Cl]_2$, Rh-FTA:$[Rh(COD)(OCOCF_3]_2$.

[c] Reaction times were not necessarily optimised.

[d] Determined by ^1H NMR for **11** and **8** and capillary GC, FS-cyclodextrine β-I/P (25 m×0.32 m) for **8**, **9** and **10**.

[e] Determined on the basis of the specific rotation value $[\alpha]_D^{26} = +82.2$ (c 1.09, $CHCl_3$) for (*S*)-(+)-*N*-benzylmandelate[10] for the hydrogenation of **11**, by capillary GC, FS-cyclodextrine β-I/P (25 m×0.32 m) for **8**, **9**, and **10,** and HPLC analysis (chiralcel OD (Daicel)) of the free amine for **12**.

[f] Taken from Ref. 5a.

to ***anti*-Cp-7** with a parallel switch from toluene to methanol as the solvent, an increase of 15% ee was obtained (entry 12 versus 7). For the second ketoester **10**, an identical trend was observed even if the selectivity remained low (entries 14–20). For substrate **12**, for which reactions are carried out in ethanol, no loss of enantioselectivity was observed with ***anti*-Cp-7** (entry 25 versus 24) and a slight decrease was noted with ***syn*-Cp-7** (entry 26 versus 24).

We have already proposed that when hydrogenation of ketones is carried out in toluene, the non chiral ligand X (Cl or TFA) most probably remains on the rhodium during catalysis.[10] This of course is inhibiting substrate chelation onto the metal in the key catalytic hexacoordinate intermediates $Rh(P_2)(H)_2(X)(RCOR')$. However, this limitation is not an obstacle to very high enantioselectivities for the hydrogenation of substrates **8** and **11**. For the latter, the previously proposed hydrogen bond between HN and the chlorine might contribute to the high enantiodifferenciation observed. On the other side, when alcohols are used as solvents, the catalytic intermediates are most probably cationic allowing a beneficial chelation of substrates **9**, **10**, and **12**.[6c,10]

In summary, this study shows how enantioselectivity benefits from the presence of the $Cr(CO)_3$ moiety in the matched diastereomer ***anti*-Cp-7**. Nevertheless, only an increase of an average of 15% ee is achieved. Due to the C_1 and C_3 spacers between the complexed arene ring and the NP and OP functions of the ligand, respectively, a steric control is essentially effective. In addition, this study has shown that even if generally basic AMPP ligands are best examined in apolar aprotic solvents for ketones hydrogenation, switching to more polar and protic solvents can be beneficial to the enantioselective process. This approach is currently applied to the tuning of other ligands as well and extended to other enantioselective catalyses.

Acknowledgements

The authors gratefully thank the 'Ministère de la Recherche et de la Technologie' and the 'Centre National de la Recherche Scientifique' for financial support.

References

1. (a) Hayashi, T. In *Ferrocenes*; Togni, A.; Hayashi, T., Eds.; VCH: Weinheim, 1995; p. 105; (b) Togni, A. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1475.
2. (a) Jones, G. B.; Heaton, S. B.; Chapman, B. J.; Guzel, M. *Tetrahedron: Asymmetry* **1997**, *8*, 3625; (b) Uemura, M.; Miyake, R.; Hayashi, Y. *J. Chem. Soc., Chem. Commun.* **1991**, 1696; (c) Uemura, M.; Miyake, R.; Nakayama, K.; Hayashi, Y. *Tetrahedron: Asymmetry* **1992**, *3*, 713; (d) Jones, G. B.; Guzel, M.; Chapman, B. J. *Tetrahedron: Asymmetry* **1998**, *9*, 901; (e) Heaton, S. B.; Jones, G. B. *Tetrahedron Lett.* **1992**, *33*, 1693; (f) Jones, G. B.; Heaton, S. B. *Tetrahedron: Asymmetry* **1993**, *4*, 261; (g) Jones, G. B.; Guzel, M.; Heaton, S. B. *Tetrahedron: Asymmetry* **2000**, *11*, 4303; (h) Malfait, S.; Pélinski, L.; Brocard, J. *Tetrahedron: Asymmetry* **1996**, *7*, 653.
3. For a recent review, see: (a) Bolm, C.; Muniz, K. *Chem. Soc. Rev.* **1999**, *28*, 51. For representative contributions, see: (b) Uemura, M.; Miyake, R.; Nishimura, H.; Matsumoto, Y.; Hayashi, T. *Tetrahedron: Asymmetry* **1992**, *3*, 213; (c) Hayashi, Y.; Sakai, H.; Kaneta, N.; Uemura, M. *J. Organomet. Chem.* **1995**, *503*, 143; (d) Vasen, D.; Salzer, A.; Gerhards, F.; Gais, H.-J.; Stürmer, R.; Bieler, N. H.; Togni, A. *Organometallics* **2000**, *19*, 539; (e) Han, J. W.; Jang, H.-J.; Chung, Y. K. *Tetrahedron: Asymmetry* **1999**, *10*, 2853; (f) Son, S. U.; Jang, H.-Y.; Lee, I. S.; Chung, Y. K. *Organometallics* **1998**, *17*, 3236; (g) Nelson, S. G.; Hilfiker, M. A. *Org. Lett.* **1999**, *1*, 1379.
4. (a) Agbossou, F.; Carpentier, J.-F.; Hapiot, F.; Suisse, I.; Mortreux, A. *Coord. Chem. Rev.* **1998**, *178–180*, 1615 and references cited therein; (b) Pasquier, C.; Eilers, J.; Reiners, I.; Martens, J.; Agbossou, F.; Mortreux, A. *Synlett* **1998**, 1162; (c) Mortreux, A.; Petit, F.; Buono, G.; Peiffer, G. *Bull. Soc. Chim. Fr.* **1987**, 631.
5. (a) Pasquier, C.; Naili, S.; Pélinski, L.; Brocard, J.; Mortreux, A.; Agbossou, F. *Tetrahedron: Asymmetry* **1998**, *9*, 193; (b) Pasquier, C.; Naili, S.; Mortreux, A.; Agbossou, F.; Pélinski, L.; Brocard, J.; Eilers, J.; Reiners, I.; Peper, V.; Martens, J. *Organometallics* **2000**, *19*, 5723.
6. The *anti* and *syn* assignment of the isolated complexed compounds was made according to: (a) Mailvaganam, B.; Perrier, R. E.; Sayer, B. G.; McCarry, B. E.; Bell, R. A.; McGlinchey, M. J. *J. Organomet. Chem.* **1988**, *354*, 325; (b) Persson, M.; Hacksell, U.; Csöregh, I. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1453.
7. The ligands have been fully characterised. ^{31}P NMR characteristics of the new ligands (121 MHz, $CDCl_3$, all singlets): ***anti*-6** 116.3 (P_O), 65.8 (P_N); ***syn*-6** 116.1 (P_O), 56.8 (P_N); ***anti*-7** 146 (P_O), 63.8 (P_N); ***syn*-7** 145.5 (P_O), 57.1 (P_N).
8. Roucoux, A.; Thieffry, L.; Carpentier, J.-F.; Devocelle, M.; Méliet, C.; Agbossou, F.; Mortreux, A.; Welch, A. J. *Organometallics* **1996**, *15*, 2440.
9. (a) Tani, K.; Suwa, K.; Tanigawa, E.; Ise, T.; Yamagata, T.; Tatsuno, Y.; Otsuka, S. *J. Organomet. Chem.* **1989**, *370*, 203; (b) Roucoux, A.; Agbossou, F.; Mortreux, A.; Petit, F. *Tetrahedron: Asymmetry* **1993**, *4*, 2279.
10. Hatat, C.; Karim, A.; Kokel, N.; Mortreux, A.; Petit, F. *New J. Chem.* **1990**, *14*, 141.