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Synthesis and application in enantioselective hydrogenation of new free and chromium complexed aminophosphine–phosphinite ligands

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Abstract

A straightforward synthesis of new free and $Cr(CO)_3$ complexed AMPP ligands (**4**–**7**) is described starting from (*S*)-indoline-2-carboxylic acid. The ligands were applied successfully in the asymmetric hydrogenation of α-functionalized ketones i.e. a ketolactone **8**, a ketoamide **9** and an aminoketone **10** leading to the corresponding optically active alcohols in 99, 97, and 99% ee respectively.

There has been great interest devoted to asymmetric synthesis catalyzed by optically active transition metal complexes and the access to chiral bisphosphines which are capable of bringing very high enantioselectivities plays a critical role in the development of homogeneous asymmetric catalytic processes.[1] On the other hand, arene–$Cr(CO)_3$ complexes have frequently proven their value for organic synthesis.[2] Further, due to their plane of chirality, $Cr(CO)_3$ complexes of unsymmetrically *ortho*-disubstituted arenes have become valuable chiral reagents in stereoselective synthesis.[3] Such complexes, presenting a planar metallocene chirality, have found applications as ligands when transformed into phosphines in catalytic processes. In particular, ferrocenyl derivatives exhibiting this type of chirality have been the most studied and used in asymmetric catalysis.[4] Despite their interesting electronic and steric properties, chiral (η^6-arene)–chromium moieties have been less studied as chiral auxiliaries.[5]

We have an ongoing interest in the synthesis and application in asymmetric catalysis of both chromium complexes[6] and aminophosphine–phosphinite diphosphines (AMPP).[7] Thus, we set out to synthesise and evaluate new AMPP ligands possessing a benzene coordinated with $Cr(CO)_3$ with the hope of combining the unique properties provided by both classes of compounds. In this communication, we

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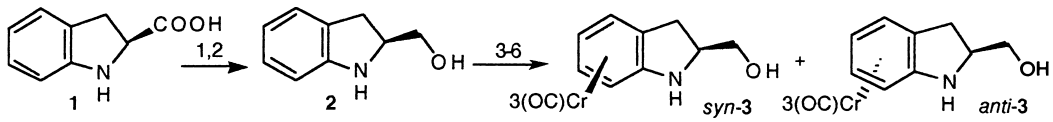
report the synthesis of novel homochiral AMPP ligands derived from (*S*)-indoline-2-carboxylic acid **1** and of the corresponding diphosphines coordinated with $Cr(CO)_3$ as well as their use in enantioselective hydrogenation.

As shown in Scheme 1, (*S*)-2-hydroxymethyl-indoline **2** was easily obtained through standard procedures starting from the corresponding acid. Thus, **1** was first reduced in the presence of borane–methylsulfide complex[8] and the resulting oxazaborolidine was hydrolysed in situ with sodium hydroxide leading to the β-aminoalcohol **2** as a white powder in ca. 100% overall yield after workup.[9]

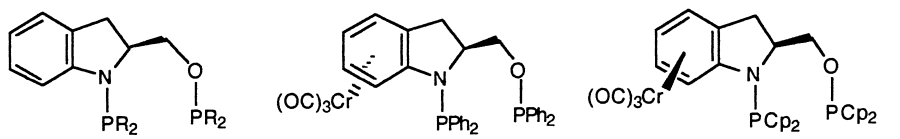


1: $BH_3{\cdot}Me_2S$, 2: NaOH, 3: TBDMSCl, 4: $Cr(CO)_6$, 5: chromatography, 6: nBu$_4$NF

Scheme 1.

The aminoalcohol **2** was then converted into two diastereomers bearing the $Cr(CO)_3$ moiety coordinated to each enantioface of the indoline ring. However, in order to separate the two $Cr(CO)_3$ complexes, a prior substitution of the primary alcohol was necessary. Thus, **2** was reacted first with *t*-butyldimethylsilyl chloride in dichloromethane giving the silylether. Then, chromium complexation took place in the presence of $Cr(CO)_6$ in THF providing a mixture of the *syn* and *anti* diastereomers (24:76 ratio) which were isolated as yellow powders in 70% global yield after a silica gel chromatographic workup. Finally, in separate experiments, the *syn* and *anti* isomers were treated with nBu$_4$NF to generate *syn*-**3** and *anti*-**3** aminoalcohols subsequently isolated in quantitative yield (Scheme 1).[9]

The three precursors **2**, *syn*-**3**, and *anti*-**3** were next converted to the corresponding diphosphines. The general method applied for the synthesis of AMPP ligands ($ClPR_2$, NEt_3)[7] was employed with success leading after workup to (*S*)-Ph,Ph–IndoNOP **4**, (*R*,2*S*)-$Cr(CO)_3$–Ph,Ph–IndoNOP **5**, (*S*)-Cp,Cp–IndoNOP **6** and (*S*,2*S*)-$Cr(CO)_3$–Cp,Cp–IndoNOP **7** in 40–80% unoptimized yields (Scheme 2).[10] The (*R*,2*S*)-$Cr(CO)_3$–Cp,Cp–IndoNOP AMPP could be obtained in some extent following an identical protocol. However, (*S*,2*S*)-$Cr(CO)_3$–Ph,Ph–IndoNOP could not be prepared by this route, (*S*,2*S*)-$Cr(CO)_3$–Ph–IndoNHOP, the intermediate amino-phosphinite,[7a] being the product formed as assayed by ^{31}P NMR. We wondered whether the use of a strong base might enable the resulting amide to undergo the expected addition to the chlorophosphine. However, a reaction of *syn*-**3** with either NaH or *n*BuLi followed by the reaction with $ClPPh_2$ gave only the amino-phosphinite.



R = Ph **4**; Cp **6**
Cp = cyclopentyl
(*S*)-R,R-IndoNOP

5
(*R*,2*S*)-$Cr(CO)_3$-Ph,Ph-IndoNOP

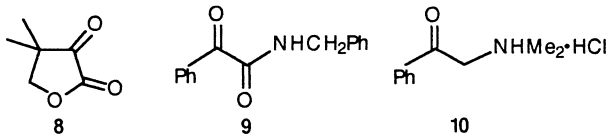
7
(*S*,2*S*)-$Cr(CO)_3$-Cp,Cp-IndoNOP

Scheme 2.

The new AMPP derivatives were then transformed onto catalyst precursors. Based on our previous studies, we chose to synthesize in situ $[Rh\{AMPP\}Cl]_2$ and $[Rh\{AMPP\}(OCOCF_3)]_2$ species.[7]

The complexes were applied in the asymmetric hydrogenation of dihydro-4,4-dimethyl-2,3-furandione **8**, *N*-benzylbenzoylformamide **9**, and 2-(*N*,*N*-dimethyl)aminoacetophenone hydrochloride **10** (Scheme 3). Selected results as well as some earlier data are summarized in Table 1.

The hydrogenations proceeded at either room temperature or 50°C under an initial hydrogen pressure of 1 or 50 bar, the chiral alcohols being produced in high yields. The reaction promoted by the rhodium



Scheme 3.

Table 1
Asymmetric hydrogenation of α-functionalized ketones[a]

Run	Substrate	AMPP	Catalyst precursor	P_{H2} (bar)	Temp. (°C)	Time[b] (h)	Conversion[c] (%)	ee (%)[d] Conf.
1[e]	**8**	*f*	"Rh-TFA"	1	20	0.1	100	98.7 (*R*)
2	**8**	**4**	"Rh-TFA"	50	50	66	81	50 (*R*)
3	**8**	**6**	"Rh-TFA"	1	20	<0.17	100	>99 (*R*)
4	**8**	**7**	"Rh-TFA"	50	20	<0.08	100	>99 (*R*)
5[g]	**9**	*f*	"Rh-Cl"	50	50	2.3	100	79.6 (*S*)
6	**9**	**6**	"Rh-TFA"	1	20	2.5	100	84 (*S*)
7	**9**	**6**	"Rh-Cl"	1	20	24	100	91 (*S*)
8	**9**	**7**	"Rh-TFA"	1	20	2	100	91 (*S*)
9	**9**	**7**	"Rh-Cl"	1	20	18	100	97 (*S*)
10[h]	**10**	*f*	"Rh^+"	50	20	17	100	96 (*S*)
11	**10**	**6**	"Rh-TFA"	50	20	18	100	>99 (*S*)

[a]Hydrogenation were carried out in the presence of 0.05 mol of substrate in deoxygenated toluene (15 mL) ; Substrate/Rh = 200/1. [b]The time was not optimized. [c]The conversions were determined by ^1H NMR. [d]Determined by GC analysis (FS-Cyclodex β-I/P 25 m x 0.32 mm column, 130 °C) on the crude reaction mixture for **8**. Based on the specific rotation value $[\alpha]_D^{26}$ = + 82.2 (*c* 1.09, $CHCl_3$) for (+)-(*S*)-*N*-benzylmandelamide. Determined by HPLC analysis (chiralcel OD (Daicel)) of the resulting *N*-benzoyl aminoalcohol for **10**. [e]Taken from reference 7b. [f](*S*)-Cp,Cp-oxoProNOP. [g]Taken from reference 11. [h]Taken from reference 12.

catalyst bearing the phenyl substituted AMPP **4** needed drastic conditions for a rather low rate and moderate enantioselectivity (50% ee) (run 2). In contrast, cyclopentyl substituted AMPPs **6** and **7** efficiently control the selectivity of the hydrogenation (runs 3, 4, 9 and 11). Indeed, the behaviour of phenyl versus cycloalkyl substituted AMPPs during the Rh-based hydrogenation of ketones has been established already in earlier work.[7] Importantly, the new chiral backbone introduced here brought about an interesting enhancement of selectivity compared to the more efficient AMPPs reported so far (compare runs 3 and 4 with 1, 6–9 with 5, and 11 with 10). Moreover, we hoped that ligands with a $Cr(CO)_3$–indoline chiral core might give improved enantioselectivities with respect to the uncomplexed parent diphosphine. As a matter of fact, there was no difference between **6** and **7** for the hydrogenation of **8**, the enantioselectivity being already very high (ee >99%). However, a significant ee increase was obtained when applying **7** instead of **6** in the hydrogenation of **9** (97% versus 91% ee, run 9 versus 7). Furthermore, the non-chiral ligand (Cl or TFA) also contributes to the selectivity of the hydrogenation of **9**. In this context, it is instructive to contrast the efficiency of Rh–Cl precursors with that of Rh–TFA during the catalysis. As shown in Table 1, the chromium complexed ligand **7** allowed a 6% ee enhancement when associated with the Rh–Cl moieties (compare run 9 with 8). Thus a total increase of 13% ee was accessible in combining the chromium derivative **7** with the Rh–Cl complex (run 9 versus 6). Surprisingly, the hydrogenation of **8** carried out in the presence of ligand **5** gave <1% ee.[13] Finally, we found that the new ligands reported here allowed the hydrogenation of the three substrates **8–10** with the highest enantioselectivities reported so far. Investigations for improved enantioselectivities through the syntheses of new AMPPs is still in progress and will be reported in due course.

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9. **2**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.1 (d, J=7.3 Hz, 1H), 7.0 (t, J=7.6 Hz, 1H), 6.7 (d, J=7.3 Hz, 1H), 6.65 (d, J=7.6 Hz, 1H), 4.0 (m, 1H), 3.7 (dd, J_1=10.7 Hz, J_2=3.5 Hz, 1H), 3.6 (dd, J_1=10.7 Hz, J_2=6.3 Hz, 1H), 3.1 (dd, J_1=15.9 Hz, J_2=9.0 Hz, 1H), 2.8 (dd, J_1=15.9 Hz, J_2=7.9 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 150.5, 128.9, 127.5, 124.9, 119.3, 110.1, 65.2, 60.3, 32.1, 30.6. *syn*-**3**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.6 (d, J=5.6 Hz, 1H), 5.4 (s, 1H), 5.0 (d, J=6.4 Hz, 1H), 4.8 (s, 1H), 4.1 (m, 2H), 3.6 (d, J=7.3 Hz, 1H), 3.1 (dd, J_1=10.3 Hz, J_2=14.4 Hz, 1H), 2.6 (d, J=14.4 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 237.4, 135.3, 98.7, 97.0, 96.0, 86.5, 76.2, 65.3, 60.5. *anti*-**3**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.6 (d, J=5.3 Hz, 1H), 5.4 (s, 1H), 5.0 (d, J=5.5 Hz, 1H), 4.8 (s, 1H), 4.2 (m, 2H), 3.8 (m, 2H), 3.6 (s, 1H), 2.8 (d, J=8.7 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 234.6, 133.1, 98.3, 94.6, 93.1, 84.5, 74.0, 63.9, 60.6, 30.6.
10. ^{31}P{^{1}H} NMR data at 121 MHz (ppm, $CDCl_3$) **4**: 114.2 (s, $OPPh_2$), 41.6 (s, $NPPh_2$); **5**: 116.9 (s, $OPPh_2$), 43.1 (s, $NPPh_2$); **6**: 145.9 (s, $OPCp_2$), 63 (s, $NPCp_2$); **7**: 146 (s, $OPCp_2$), 67.3 (s, $NPCp_2$).
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13. It would be premature to form conclusions regarding the relative effect on the selectivity of the chromium complexation without extending the study to the other diastereomer and thus searching for the accessibility to the latter.