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Stereoselective Synthesis and Use in Catalytic Asymmetric Addition of Diethylzinc to Benzaldehyde of New Chiral Amino Alcohol Complexes: Influence of the Chromium Complexation on the Enantioselectivity

Stéphane Malfait, Lydie Pélinski and Jacques Brocard*

Laboratoire de Catalyse Hétérogène et Homogène, Groupe de Synthèse Organométallique URA CNRS 402, C4
Université des Sciences et Technologies de Lille, 59655 Villeneuve d'Ascq, France

Abstract: The optically active amino alcohol (arene)chromium (+)-(*S*,1*S*)-**3**–**6** complexes were synthesized from enantiomerically pure indanone complex. As well as their uncomplexed counterparts, they have been used as chiral catalysts in the asymmetric addition of diethylzinc to benzaldehyde : 1-Phenylpropanol has obtained in up to 70% enantiomeric excess. A beneficial effect of the tricarbonyl chromium tripod on the enantioselectivity has been shown.

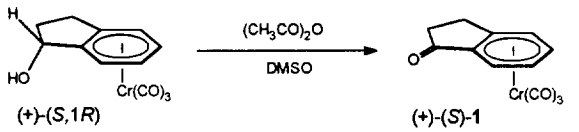
The synthesis of optically active secondary alcohols through the enantioselective addition of organometallic reagents to aldehydes has seen widespread use in stereoselective organic synthesis.[1] Among the organometallic reagents, dialkylzincs have received special attention due to the development of chiral catalysts that enable the improvment of chemoselectivity, activity and enantioselectivity of the addition.[1,2] Thus, chiral amino alcohols have been shown to be particularly suitable catalysts for such transformations.[1,2,3] Recently, 1,2-disubstituted ferrocenyl amino alcohols have been reported allowing the evaluation of not only the effect of the stereogenic center in the ligand but also that of the planar chirality of the ferrocenyl unit.[4] Such a planar chirality can also been introduced through tricarbonyl(η^6-arene)chromium complexes of amino alcohols.[5] However such investigations have received only scant attention.

We have had an ongoing interest in the synthesis and application in catalysis of chromium complexes.[6] Thus, we have sought to study the effect of a tricarbonyl chromium tripod on the addition of dialkylzinc to aldehydes. In this communication, we report the synthesis of novel chiral substituted indanol chromium complexes and their application as catalysts for the addition of diethylzinc to benzaldehyde.

We first established a synthesis of the homochiral 1-indanone-chromium complex (+)-(*S*)-**1**.[7,8] Thus, the thermolysis of chromium hexacarbonyl with enantiomerically pure (-)-(*R*)-1-indanol led to an 80/20 mixture of syn [(+)-(*S*,1*R*)] and anti [(+)-(*R*,1*R*)]-1-indanol complexes in 70% yield. Both diastereoisomers[9] were

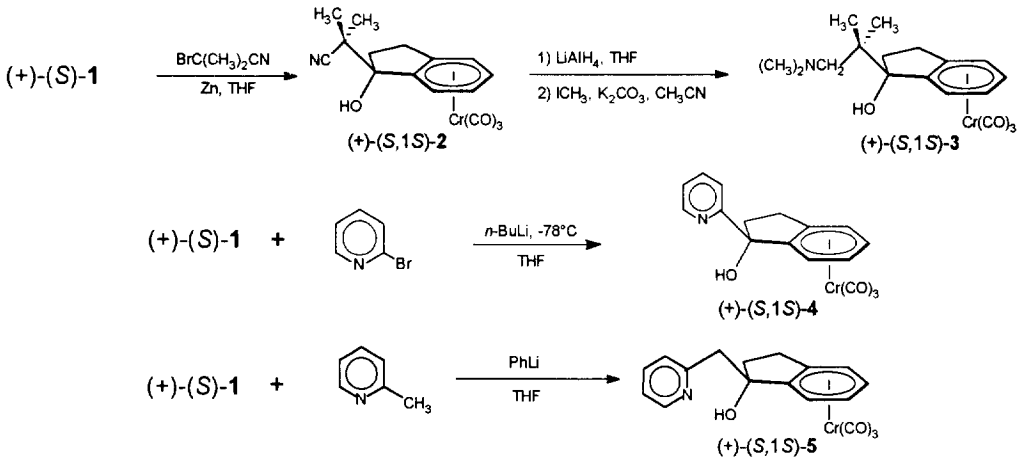
separated by a silica gel colomn chromatography and quantitative oxidation of the (+)-(*S*,1*R*) complex of 1-indanol in presence of DMSO/Ac_2O[10] gave indanone complex (+)-(*S*)-**1** in ee>98%[11] (Scheme 1).

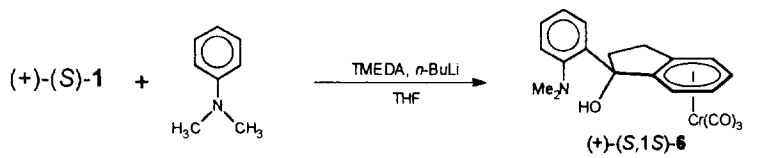
Scheme 1



This complex was converted to four amino alcohol (η^6-arene)chromium complexes (Scheme 2). Thus, the complex (+)-(*S*,1*S*)-**3** was obtained in three steps. First, a Reformatsky reaction was conducted with (+)-(*S*)-**1** that gave, after workup, a single complex (+)-(*S*,1*S*)-**2** in 69% yield. The ketone was reduced from the unhindered antiface[12] leading accordingly to the (*S*,1*S*) isomer. Then, a reduction with lithium aluminium hydride followed by a bis methylation with methyl iodide led to the complex (+)-(*S*,1*S*)-**3** in 30% overall yield[13]. The three complexes (+)-(*S*,1*S*)-**4**–**6** were obtained in one step through reaction of (+)-(*S*)-**1** with the appropriate nucleophile. Accordingly, (+)-(*S*,1*S*)-**4**[14] was synthesized in 71% yield at -78 °C through reaction between of (+)-(*S*)-**1** and 2-lithiopyridine obtained from 2-bromopyridine and *n*-butyllithium.[15] Addition with 2-picolyllithium[16] gave after workup (+)-(*S*,1*S*)-**5** in 30% yield.[17] Finally, addition of 2-(N,N-dimethylamino)phenyllithium obtained from reaction of dimethylaniline and *n*-butyllithium/TMEDA[16] gave (+)-(*S*,1*S*)-**6** in 40% yield.[18] The moderate yields have been attributed to the enhance acidity of the methylene group adjacent to the ketone.

Scheme 2





The complexes synthesized above as well as the corresponding chromium free amino alcohols have been applied to the addition of diethylzinc to benzaldehyde (Scheme 3).[19] The results are summarized in the table.

Scheme 3

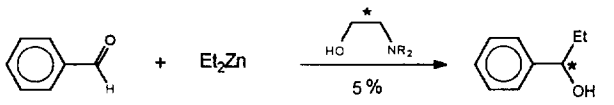


Table: Enantioselective addition of diethylzinc to benzaldehyde in presence of chiral catalyst

Entry[a]	Catalyst	Time (h)	yield (%)[b]	ee (%)[c]	configuration[d]
1	(+)-(*S*,1*S*)-**3**	25	96	57	R
2	**3** uncomplexed[e]	25	74	0	-
3	(+)-(*S*,1*S*)-**4**	90	92	47	R
4	**4** uncomplexed[e]	90	89	9	R
5	(+)-(*S*,1*S*)-**5**	18	97	70	R
6	**5** uncomplexed[e]	18	96	10	R
7	(+)-(*S*,1*S*)-**6**	18	92	42	S
8	**6** uncomplexed[e]	18	77	19	S

[a] the reactions were performed at room temperature. [b] determined by ^{1}H NMR. [c] determined by GC analysis on FS-Cyclodex β-I/P (30 m x 0.24). [d] determined by specific rotation. [e] obtained by photodecomplexation.

1-Phenylpropanol is produced with low to good enantiomeric excesses. The best selectivity was obtained with the complex (+)-(*S*,1*S*)-**5** (entry 5). A surprising result is obtained in presence of (+)-(*S*,1*S*)-**6** (entries 7–8) which led to the opposite configuration of the 1-phenylpropanol. The only uncomplexed ligand showing some significant however low enantioselectivity was derived from (+)-(*S*,1*S*)-**6** (entry 8). We observed a dramatic increase of the enantioselectivities when the tricarbonyl chromium was complexed to the catalyst (entries 1, 3, 5, 7). The gain in ee brought about by such a coordination was in the 23–60% enantiomeric excess range. Here, the effect is more pronounced than in the case reported by Jones[5b] where the uncomplexed catalyst was already highly enantioselective. Futhermore, the results confirmed a beneficial effect of complexation on the activities.

In conclusion, new chiral amino alcohols bearing arene tricarbonyl chromium moieties derived from indanol have been prepared. The presence of a tricarbonyl chromium unit, coordinated to the phenyl ring of the

aryl amino alcohol catalysts induced a significant increase of the enantioselectivity of the catalyzed addition of diethylzinc to benzaldehyde. Further studies of other chiral amino alcohols are under development and similar beneficial effects of complexation by $Cr(CO)_3$ will be presented in the future.

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13. $[\alpha]_D^{20}$ = +96 (c = 1.04, $CHCl_3$); yellow powder; m.p.: 166 - 168 °C; ^1H NMR ($CDCl_3$ + D_2O + TMS) δ 5.7 (d, J = 6.1 Hz, 1H), 5.4 (t, J = 6.1 Hz, 1H), 5.2 (d, J = 6.1 Hz, 1H), 5.1 (t, J = 6.1 Hz, 1H), 2.75 (m, 2H), 2.3 (s, 6H), 2.3 - 2.4 (m, 2H), 2.2 (m, 2H), 1.2 (s, 3H), 0.6 (s, 3H).
14. $[\alpha]_D^{20}$ = +20.7 (c = 3.35, $CHCl_3$); yellow powder ;m.p: 116 °C; ^1H NMR ($CDCl_3$ + TMS) δ 8.5 (d, J = 5.0 Hz, 1H); 7.7 (t, J = 5.0 Hz, 2H); 7.2 (t, J = 5.0 Hz, 2H); 5.5 (d, J = 6.1 Hz, 1H); 5.4 (t, J = 6.1 Hz, 1H); 5.3 (d, J = 6.1 Hz, 1H); 5.1 (t, J = 6.1 Hz, 1H); 3.0 (m, 2H); 2.5 (m, 2H).
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17. $[\alpha]_D^{20}$ = +177 (c = 2.05, Et_2O); yellow oil; ^1H NMR ($CDCl_3$ + D_2O + TMS) δ 8.5 (m, 1H); 7.6 (m, 1H); 7.2 (m, 1H); 7.0 (m, 1H); 5.3 (t, J = 6.3 Hz, 1H); 5.2 (d, J = 6.3 Hz, 1H); 5.1 (d, J = 6.3 Hz, 1H); 5.0 (t, J = 6.3 Hz, 1H); 3.1 (dd, J = 21 Hz and J = 14 Hz, 2H); 2.7 (m, 2H); 2.1 (m, 2H).
18. $[\alpha]_D^{20}$ = +80 (c = 1.4, Et_2O); yellow oil; ^1H NMR ($CDCl_3$ + TMS) δ 7.1 (m, 2H); 6.7 (m, 2H); 5.6 (d, J = 6.2 Hz, 1H); 5.5 (t, J = 6.2 Hz, 1H); 5.3 (d, J = 6.2 Hz, 1H); 5.1 (t, J = 6.2 Hz, 1H); 2.8 (s, 6H); 2.2 - 2.6 (m, 4H).
19. General Procedure: Under nitrogen, diethylzinc was added to a solution of benzaldehyde and the chiral complex (5 mol %) in dry toluene. The reaction mixture was stirred at room temperature and the progress of the reaction was monitored by GC. After work up, the residue was isoled by colomn chromatography to give 1-phenylpropanol.

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