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A Catalytic-Enantioselective Entry to Planar Chiral π-Complexes: Enantioselective Methoxycarbonylation of 1,2-Dichlorobenzene–$Cr(CO)_3$

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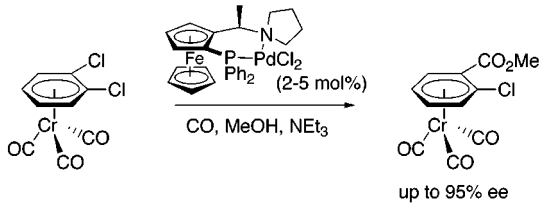
ABSTRACT



The palladium-catalyzed mono-methoxycarbonylation of 1,2-dichlorobenzene tricarbonylchromium(0) has been achieved with up to 95% ee in the presence of the chiral ferrocene ligand (*R*,*S*)-PPF-pyrrolidine. It was found that the enantioselectivity strongly depends on the reaction time (conversion). Obviously, the initial enantioselectivity is enhanced by a subsequent kinetic resolution connected to the formation of the bis-methoxycarbonylated byproduct.

Planar chiral transition metal π-complexes such as ferrocenes[1] and arene−$Cr(CO)_3$ complexes[2] with two different substituents at the 1,2- or 1,3-position (Figure 1) have found

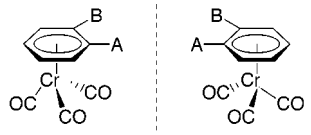


Figure 1. Arene−$Cr(CO)_3$ complexes with two different substituents at the 1,2-position represent planar chiral structures.

widespread application in organic synthesis, especially as chiral architectures for the design of new ligands for asymmetric catalysis[1,3,4] and as chiral building blocks for natural product synthesis.[5]

While most methods for the preparation of planar chiral π-complexes are based either on the resolution of racemic mixtures or on stereoselective transformations using stoichiometric amounts of chiral reagents or auxiliaries, very few cases of catalytic-enantioselective entries to such compounds have been reported.[6,7]

One of the conceptually most appealing approaches to nonracemic arene−$Cr(CO)_3$ complexes is the desymmetri-

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(2) For recent reviews, see: (a) Schmalz, H.-G.; Siegel, S. In *Transition Metals for Organic Synthesis Vol. 1*; Beller, M., Bolm, C., Eds.; Wiley-VCH: Weinheim, 1998; p 550. (b) Hegedus, L. S. *Transition Metals in the Synthesis of Complex Organic Molecules*; University Science Books, Sausalito, CA, 1999; Chapter 10.

(3) For a review, see: Richards, C. J.; Locke, A. J. *Tetrahedron: Asymmetry* **1998**, *9*, 2377.

(4) (a) For a review, see: Bolm, C.; Muniz, K. *Chem. Soc. Rev.* **1999**, *28*, 51. (b) For a recent example, see: Jang, H.-Y.; Seo, H.; Han, J. W.; Chung, Y. K. *Tetrahedron Lett.* **2000**, *41*, 5083.

(5) See, for instance: (a) Schellhaas, K.; Schmalz, H.-G.; Bats, J. W. *Chem. Eur. J.* **1998**, *4*, 57. (b) Geller, T.; Schmalz, H.-G.; Bats, J. W. *Tetrahedron Lett.* **1998**, *39*, 1537. (c) Kamikawa, K.; Uemura, M. *Synlett* **2000**, 938. (d) Monovich, L. G.; Le Huerou, Y.; Ronn, M.; Molander, G. A. *J. Am. Chem. Soc.* **2000**, 122. (e) Ratni, H.; Kündig, E. P. *Org Lett.* **1999**, *1*, 1997.

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Table 1. Results of the Methoxycarbonylation Experiments According to Scheme 1. As Catalysts $(PPh_3)_2PdCl_2$ as Well as the $PdCl_2$ Complexes of the Chiral Ligands (**4**−**9**, See Figure 2) Were Employed

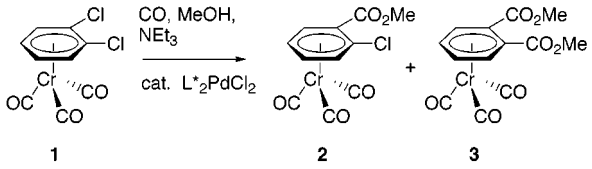
entry	catalyst	amount of catalyst (mol %)	reactn time (min)	yield[a] of recovd **1** (%)	yield[a] of **2**/**ent-2** (%)	yield[a] of **3** (%)	ee (%) of **2**/**ent-2** (config)[e]
1	$(PPh_3)_2PdCl_2$	10	150			86	
2	$(PPh_3)_2PdCl_2$	5	120	3	15	77	
3	$(PPh_3)_2PdCl_2$	5	60	22	41	36	
4	**4**−$PdCl_2$	5	60	51	37	5	19 (1*R*)
5	**4**−$PdCl_2$	5	120	35	49	10	16 (1*R*)
6	**5**−$PdCl_2$	5	60	54	38	5	12 (1*R*)
7	**5**−$PdCl_2$	5	120	18	41	31	30 (1*R*)
8	**6**−$PdCl_2$	5	120	42	43	14	<2
9	**7**−$PdCl_2$	5	120	76	22	1	6 (1*R*)
10	**8**−$PdCl_2$	5	120	30	49	17	20 (1*R*)
11	**9**−$PdCl_2$	5	60	24	47	23	63 (1*S*)[c]
12	**9**−$PdCl_2$	5	90	9	38	50	92 (1*S*)[d]
13	**9**−$PdCl_2$	5	120			84	
14	**9**−$PdCl_2$	10	30	30	48	21	64 (1*S*)
15	**9**−$PdCl_2$	2	180	5	31	48	95 (1*S*)[f]

[a] Isolated yield after chromatographic purification. [b] Determined by HPLC (DAICEL Chiralcel OJ, 2-propanol/*n*-hexane = 10:90; flow rate 0.5 mL/min, 254 nm). [c] Average of three runs. [d] Average of two runs. [e] Absolute configuration of the main enantiomer. [f] Reaction was performed on a 5 mmol scale.

zation of prochiral dichloroarene−$Cr(CO)_3$ complexes by means of Pd-catalyzed cross-coupling chemistry.[8] This was first investigated by Uemura and co-workers[7] who obtained the best results with the Suzuki reaction of 1,2-dichlorobenzene−$Cr(CO)_3$ (**1**) with phenylboronic acid in the presence of the ferrocene ligand (*S*,*R*)-PPFA. In this case the desired coupling product was formed in 40% yield and 69% ee. However, no further reports have appeared since 1994.

In the course of our research program on the use of planar chiral arene−$Cr(CO)_3$ complexes in synthesis, we were interested in the chiral bifunctional complex **2**, which we intended to prepare by enantioselective Pd-catalyzed methoxycarbonylation[9] of **1** (Scheme 1).

Scheme 1



The various experiments carried out during the optimization of this reaction (Table 1) were all performed on a 0.5 mmol scale in a degassed 2:1 mixture of MeOH and NEt_3 (4 mL) at 60 °C and a CO pressure of 1 atm. Our first attempt to achieve the desired mono-methoxycarbonylation of **1** using 10 mol % of the achiral catalyst $(PPh_3)_2PdCl_2$ failed due to exclusive formation of the bis-methoxycarbonylated product **3**. By subsequently lowering the catalyst amount and the reaction time (Table 1, entries 1−3), we were able to obtain *rac*-**2** in 41% isolated yield.

Initial experiments in the enantioselective series employing $PdCl_2$ complexes of the commercially avialable chiral ligands (*R*)-BINAP (**4**)[10] and (*S*,*R*)-PPFA (**5**)[11] (Figure 2) resulted in rather low enantioselectivities. In the case of **4**, the mono-coupling product (**2**/*ent*-**2**) was formed in 16−19% ee (Table 1, entries 4 and 5). Interestingly, a significant dependence of the enantioselectivity on the conversion was observed in

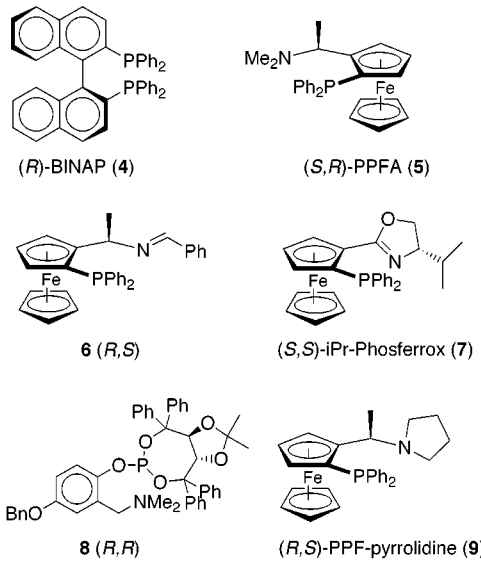


Figure 2. Chiral ligands used in the asymmetric methoxycarbonylation experiments according to Scheme 1.

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(7) (a) Uemura, M.; Mishimura, H.; Hayashi, T. *Tetrahedron Lett*. **1993**, *34*, 107. (b) Uemura, M.; Mishimura, H.; Hayashi, T. *J. Organomet. Chem*. **1994**, *473*, 129.

the case of **5**. While after 1 h (ca. 45% conversion) the isolated product showed only 12% ee, the enantioselectivity increased to 30% ee when the reaction time was doubled (Table 1, entries 6 and 7).

We next tried the easily accessible chiral ferrocene P,N ligands **6**[12] and **7**,[13] but unfortunately only very poor selectivities were achieved (Table 1, entries 8 and 9). Somewhat better, but still unsatisfactory, results (20% ee) were obtained with the P,N ligand **8**[14] (Table 1, entry 10).

Because the ferrocenyl ligand **5** had so far led to the highest selectivities, we hoped that the chiral ligand **9**[11] (as a sterically more hindered analogue of PPFA) would lead to better results. Indeed, when this ligand was employed under the standard conditions (Table 1, entry 11), the product **2** was formed with 63% ee in 47% yield. With this ligand, a significant dependency of the enantioselectivity on the conversion was observed again (Table 1, entries 11 and 12). Longer reaction times led to the formation of the bis-coupled product **3** as the only isolated product (Table 1, entry 13). Increasing the amount of catalyst from 5 to 10 mol % had no significant influence on the enantioselectivity when the reactions were stopped at a comparable degree of conversion (Table 1, entries 11 and 14). With only 2 mol % of the catalyst (**9**−$PdCl_2$), the product **2**[15] was obtained in 95% ee (31% yield) after 3 h together with 48% of **3**[16] (Table 1, entry 15). To obtain more detailed information about the reaction course, a standard experiment using ligand **9** was monitored by means of HPLC.[17] The results of this experiment are depicted in Figures 3 and 4. While Figure 3 shows

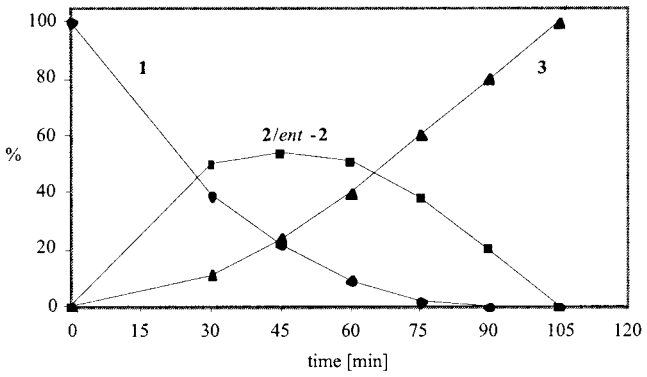


Figure 3. Time dependence of the composition of the reaction mixture using **9** as chiral ligand.

the relative composition of the reaction mixture during the reaction course, Figure 4 illustrates the constant increase of

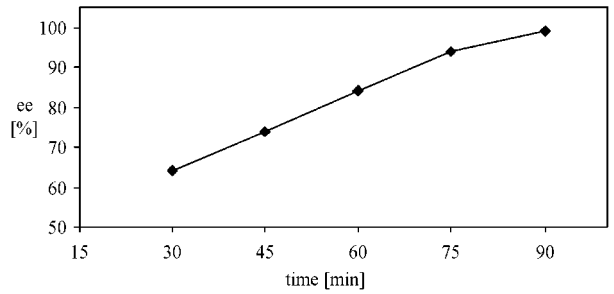
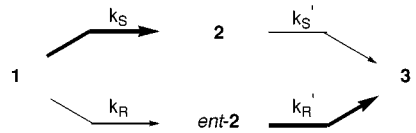


Figure 4. Time dependence of the enantiomeric purity of **2** during the reaction shown in Scheme 1 employing **9**−$PdCl_2$ as chiral catalyst.

the enantiomeric purity of the mono-coupled product (**2**) during the course of the reaction.

The fact that the initial enantioselectivity of **2** (ca. 60% ee) is greatly enhanced as the reaction proceeds (Figure 4) can only be explained by an additional kinetic resolution connected to the formation of the bis-coupled product **3** (Scheme 2).

Scheme 2



We can assume that the rates (k_S and k_R) of the two competing catalytic cycles leading to the mono-coupled products **2** and *ent*-**2** differ by a factor of about 4. The initial enantiomeric ratio (**2**/*ent*-**2** = ca. 80:20 at low conversion) is then improved because the further conversion of *ent*-**2** is faster than that of the main enantiomer ($k_S' < k_R'$).

To probe the suspected kinetic resolution[18,19] connected to the formation of **3**, a sample of *rac*-**2** was reacted in the

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(15) ^{1}H NMR: 3.90 (s, 3H); 5.01 (dt, 1H); 5.37 (dd, 1H); 5.56 (dt, 1H); 6.10 (dd, 1H). ^{13}C NMR: 53.1; 86.0; 89.5; 90.6; 93.9; 94.9; 113.9; 164.5; 232.9. FT-IR: 1117; 1257; 1437; 1732; 1903; 1977 cm^{-1}. HRMS: calcd 305.9387; found 305.9390. After a single recrystallization from hot *n*-hexane a sample of (1*S*)-**2** with >99% ee (HPLC) was obtained: $[\alpha]^{20}_D$ +122; $[\alpha]^{20}_{546}$ +188 (*c* = 0.10, EtOH); mp 108.5−109.0 °C (*n*-hexane). Mp of *rac*-**2**: 88−89 °C (*n*-hexane).

(16) ^{1}H NMR: 3.86 (s, 3H); 5.35 (m, 2H); 5.65 (m, 2H). ^{13}C NMR: 53.3; 90.2; 90.9; 96.7; 165.9; 232.8. FT-IR: 1119; 1275; 1445; 1724; 1902; 1977 cm^{-1}. HRMS: calcd 329.9832; found 329.9804; mp 60−61 °C (MTBE/*n*-hexane).

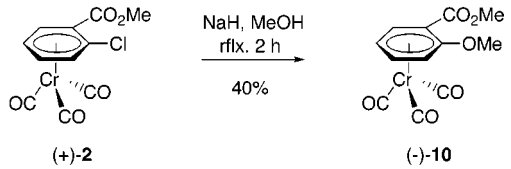
(17) Samples were taken from the reaction mixture in intervals of 15 min. After dilution with the HPLC eluent (*2*-propanol/*n*-hexane = 10: 90) and filtration through Celite, the mixtures were analyzed by HPLC (DAICEL Chiralcel OJ, external calibration).

presence of 5 mol % of **9**−$PdCl_2$ under the standard conditions. After 60% conversion, the recovered starting material (**2**) exhibited an enantiomeric excess of 10% ee. This corresponds to a selectivity factor (k_R'/k_S')[19a] of $\boldsymbol{S} = 1.25$.

Even this value seems rather low; it is well documented in the literature that only small selectivity factors are needed to significantly increase the enantiomeric purity of chiral products which are already enantiomerically enriched.[19,20] This provides a fully consistent explanation for the observed time dependency of the enantioselectivity (Figure 4), even on a semiquantitative level.

To assign the absolute configuration of the mono-methoxycarbonylated products (**2**/*ent*-**2**), a sample of (+)-**2** (ca. 90% ee) was transformed into the known methyl 2-methoxybenzoate complex **10**[21] ($[\alpha]^{20}_D$ −35; $c = 0.11$ in $CHCl_3$) by heating with MeOH in the presence of NaH (Scheme 2). As the absolute configuration of this compound (**10**) had been previously assigned,[21] it could be concluded that (+)-**2** and (−)-**10** both possess the 1*S* configuration[22] as depicted in Scheme 3.

Scheme 3



(+)-**2** (-)-**10**

In conclusion, we have demonstrated that the Pd-catalyzed methoxycarbonylation of 1,2-dichlorobenzene−$Cr(CO)_3$ can be achieved in a preparatively attractive, highly enantioselective manner in the presence of a properly chosen chiral P,N ligand. The chiral product **2** represents a bifunctional compound which should be useful as an intermediate for the synthesis of new chiral ligands and building blocks for synthesis. We are also optimistic that the methodology can be further improved and expanded to other prochiral dichlorobenzene−$Cr(CO)_3$ derivatives. Investigations in this direction are currently being carried out in this laboratory.

Acknowledgment. We thank the Fonds der Chemischen Industrie for financial support and Prof. S. Toma (Comenius University, Bratislava) for providing samples of some chiral ferrocene ligands.

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(18) The kinetic resolution of *o*-chloroanisole−$Cr(CO)_3$ through BINAP−Pd-catalyzed alkoxycarbonylation was reported; however, significant selectivities (up to 34% de) were obtained only when a chiral alcohol (3-methyl-1-butanol) was employed: Carpentier, J.-F.; Pamart, L.; Maciewjeski, l.; Castanet, Y.; Brocard, J.; Mortreux, A. *Tetrahedron Lett.* **1996**, *37*, 167.

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