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Kinetic Resolution of Racemic Tricarbonyl(2-chloroanisole)chromium via Palladium-Catalysed Asymmetric Alkoxycarbonylation

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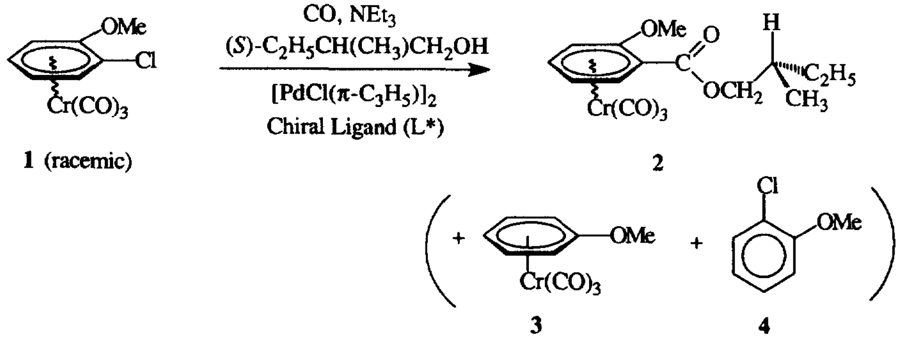
Abstract *: Tricarbonyl(o-chloroanisole)chromium was treated with an alcohol and carbon monoxide in the presence of triethylamine and a chiral palladium catalyst to give (o-methoxybenzoate ester)Cr(CO)$_3$ complexes in high selectivity with up to 30% ee. Starting tricarbonyl(o-chloroanisole)chromium was recovered in up to 39% ee. The Pd / PPFA catalytic system exhibited high reactivity and selectivity for the carbonylation reaction.*

The activation of the C-Cl bond of chloroarenes in palladium-catalysed reactions by coordination of a tricarbonylchromium moiety to the aromatic ring is nowadays a well documented process.[1] In this field, much attention has been devoted to the formation of carbon-carbon bond through either carbonylation or cross-coupling reactions. Among these examples, an asymmetric synthesis of optically active (arene)chromium complexes was achieved by asymmetric cross-coupling of a *meso* (arene)chromium complex with vinylic metals in the presence of a chiral palladium catalyst.[1c] Namely, the selective mono-substitution of one of the enantiotopic chlorine atoms of tricarbonyl(*o*-dichlorobenzene)chromium resulted in the formation of mono-coupling products in up to 44% ee.[1c] Although this process should be theoretically transposable to a palladium-catalysed carbonylation reaction, the low selectivities we observed during alkoxycarbonylation of (dichlorobenzene)chromium complexes[2] led us to study a different process. Since good yields of esters can be obtained provided that the chloroarene is substituted by an electron-donating group, especially at the *ortho* position,[3] we have investigated the kinetic resolution of racemic (*o*-chloroanisole)chromium complex **1** in the presence of chiral palladium catalysts. For analytical reasons, an optically active alcohol, (*S*)-2-methyl-1-butanol, was first used as the alkoxy source, thus leading to the formation of the diastereomeric esters **2** (Scheme 1).

Scheme 1

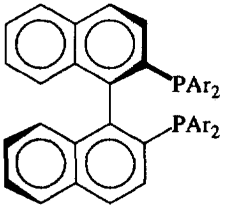


Our preliminary results are summarized in Table 1. An evaluation with the simple triphenylphosphine ligand first revealed that good yields of **2** can be obtained under quite mild conditions, starting equally either from the preformed $PdCl_2(PPh_3)_2$ complex or the *in situ* combination $[PdCl(\pi\text{-}C_3H_5)]_2$ / PPh_3 (entry 1). Under these conditions, the product of reduction of the C-Cl bond **3** and uncomplexed starting compound **4** were also obtained in variable amounts, and account for the balance of data reported in Table 1.

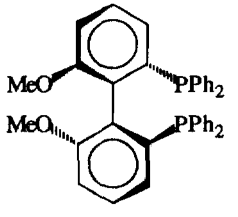
Table 1. Catalytic Asymmetric Carbonylation of (*o*-chloroanisole)$Cr(CO)_3$ with (*S*)-2-methyl-1-butanol[a]

entry	ligand (L*)	1/L*/Pd mol. ratio	°C, hrs	1 conv[b] (%)	2 yield[c] (%)	2 sel[d] (%)	2 ee[e] (%)
1	PPh_3	50 : 2 : 1	90, 2	98	76	88	0
2	PPh_3	20 : 2 : 1	85, 0.5	28	17	68	<2
3	(*R*)-BINAP	20 : 2 : 1	90, 2	10	4	50	28
4	(*R*)-BINAP	20 : 2 : 1	90, 5	43	28	76	31
5	(*R*)-BINAP	20 : 2 : 1	80, 5	22	10	59	29
6	(*S*)-BINAP	20 : 2 : 1	90, 5	65	30	46	-34
7	(*R*)-Tol-BINAP	20 : 2 : 1	90, 5	26	8	50	26
8	(*S*)-MeO-BIPHEP	20 : 2 : 1	90, 1	25	17	94	21
9	(*S*)-MeO-BIPHEP	20 : 2 : 1	90, 3	66	42	93	21
10	(*S*)-(*R*)-PPFA	20 : 1 : 1	60, 1	81	72	92	7
11	(*S*)-(*R*)-PPFA	20 : 1 : 1	50, 0.5	45	24	88	14
12	(*S*)-(*R*)-PPFA	20 : 2 : 1	50, 0.5	57	49	92	12
13	(*S*)-(*R*)-BPPFA	20 : 1 : 1	70, 1	31	20	79	8

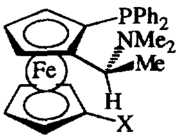
[a] For a typical procedure, see reference 4. [b] Conversion based on **1** and determined by ^1H NMR. [c] Isolated yield by chromatography. [d] Selectivity of carbonylated product *vs* reduced product = [2]/([2] + [3]). [e] Enantiomeric excess was determined by HPLC (Daicel Chiralcel OD eluted with 7% isopropanol in hexane). Positive ee values refer to an excess of the first eluted diastereomer.



Ar = C_6H_5 : (*R*)-BINAP
Ar = 4-MeC_6H_4 : (*R*)-Tol-BINAP



(*S*)-MeO-BIPHEP



X = H : (*S*)-(*R*)-PPFA
X = PPh_2 : (*S*)-(*R*)-BPPFA

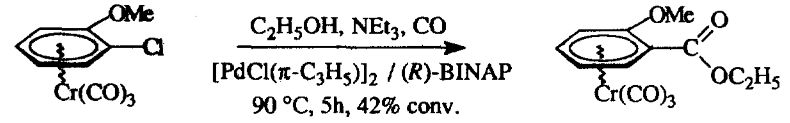
We have next investigated this carbonylation reaction in the presence of chiral ligands using $[PdCl(\pi\text{-}C_3H_5)]_2$ as the catalyst precursor. Reaction of **1** catalyzed by palladium complexes coordinated with BINAP proceeded slower than with PPh_3 (entries 3-6).[4] The palladium-(*R*)-BINAP system afforded systematically ~ 30% ee of **2** without appreciable change with temperature and conversion in the 0-50% range. The use of the antipodal ligand, (*S*)-BINAP (entry 6), resulted in an almost similar ee value, thus suggesting that the kinetic resolution is mainly controlled by the chirality of the palladium complex, probably during the oxidative addition of the C-Cl bond to the zerovalent palladium catalytic species.[1c] This trend is reinforced by the absence of enantioselectivity with PPh_3, the experimental value of ee being within the accuracy of the chromatographic measurements (entry 2).

Comparable enantioselectivity was observed in the reaction with the closely related chiral ligand Tol-BINAP (entry 7). Nevertheless, the yield and the selectivity into ester **2** were rather low. The latter could be significantly improved by using another atropoisomeric chiral ligand, MeO-BIPHEP (entries 8-9). In that case, excellent selectivities into **2** could be obtained, despite a somewhat lower enantioselectivity.

The asymmetric reaction catalyzed by the $[PdCl(\pi\text{-}C_3H_5)]_2$ / (*S*)-(*R*)-PPFA combination gave at best only 14% ee of **2** (entries 10-12). As for the previous catalytic systems described, the enantioselectivity was almost not affected in the 0-50% conversion range, and slowly decreased as expected beyond this barrier (10% ee at 64% conversion, 7% ee at 81% conv., and 4% ee at 93% conv.). However, one of the most interesting feature of this catalytic system is its very high reactivity and selectivity for the carbonylation reaction. Namely, carbonylation occurs since 50 °C and a 72% yield of ester **2** could be obtained in half an hour at 60 °C, leaving unreacted starting material **1** in 15% yield and 38% ee[5] (entry 10). Interestingly, the L*/Pd ratio had almost no influence on the enantioselectivity nor on the catalytic activity, but an increase of the amount of PPFA allowed to reduce side reactions, especially decomplexation of the arene ring in **1** (compare entries 11 and 12). A possible explanation of the high reactivity of the Pd / PPFA system for the carbonylation reaction lies in the *P,N* chelating character of the ligand. Actually, it is known that amines play a crucial role in alkoxycarbonylation processes, not only for trapping the hydrogen chloride removed by the reaction, but also probably for assisting elementary steps like alcoholysis of the intermediary aroyl-palladium species.[6] The presence of the amino group of PPFA directly in the coordination sphere of palladium is undoubtedly a determining factor. This possibility is reinforced by the results obtained in the presence of (*S*)-(*R*)-BPPFA, a bis(diphenylphosphino) chelate closely related to PPFA (entry 13); In the presence of this *P,P* chelating ligand, the catalytic activity is greatly reduced compared to that of the Pd / PPFA system, although it is still better than with the classical systems. The enantioselectivity remains low.

The asymmetric reaction catalyzed by the palladium-(*R*)-BINAP system in ethanol gave tricarbonyl(ethyl *o*-methoxybenzoate)chromium with an interesting selectivity but a quite poor enantioselectivity (Scheme 2).[5]

Scheme 2



1 (racemic)

21% yield, 82% sel, 8% ee (+)

This loss of enantioselectivity with ethanol (8% ee) compared to runs conducted in (*S*)-2-methyl-1-butanol (28-34% ee, entries 3-6) may imply that the alcohol also plays an important role at the oxidative addition, which is probably the enantiodetermining step. In this way, a similar dependence of enantioselectivity upon the nature of the *achiral* vinylation reagent was also observed during the asymmetric cross-coupling of tricarbonyl(*o*-dichlorobenzene)chromium.[1c]

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2. During the methoxycarbonylation of each of the three isomers of tricarbonyl(dichlorobenzene)chromium by the HCO_2Me / NaOMe / $PdCl_2(PPh_3)_2$ system, carbonylation competed with nucleophilic aromatic substitution, a source of ethers, and a mixture of monocarbonylated-monosubstituted and disubstituted products was obtained. Carpentier, J.-F.; Castanet, Y.; Brocard, J.; Mortreux, A.; Petit, F. *Tetrahedron Lett.* **1992**, *33*,-2001-2004.
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4. Typical procedure: Tricarbonyl(*o*-chloroanisole)chromium (100 mg, 0.36 mmol), $[PdCl(\pi\text{-}C_3H_5)]_2$ (3.3 mg, 0.009 mmol) and (*R*)-BINAP (22.4 mg, 0.036 mmol) were loaded in a 50 mL stainless steel autoclave which was subjected three times to a cyclic vacuum-nitrogen purge. After introduction of a solution of (*S*)-2-methyl-1-butanol (3 mL) and triethylamine (0.12 mL, 0.86 mmol), first degassed by three cycles of freeze/pump/thaw, the reactor was pressurised with CO (30 bar) and then heated with magnetic stirring at 90 °C for 5 h. The reactor was then cooled to room temperature, depressurised, and the crude reaction mixture was eluted on neutral alumina using diethyl ether to remove palladium black. After evaporation of light solvents under vacuum, an aliquot of the residue was analyzed by ^1H NMR ($CDCl_3$, 300 MHz) and HPLC (Daicel Chiralcel OD; 7% isopropanol in hexane; flow rate 1 mL/min; UV detector 315 nm; room temperature; retention times: 26.0 and 46.5 min for enantiomers of **1**, 20.1 and 30.2 min for diastereomers of **2**, 23.7 min for **3**). The residue was purified by silica gel chromatography (ether / hexane) to produce tricarbonyl((2-methyl-1-butyl) 2-methoxybenzoate)-chromium (**2**) as an oily orange solid (36 mg, 28%); ^1H NMR ($CDCl_3$) δ 0.85 (3H, t, $J = 7.5$ Hz, CH_3 Et), 0.95 (3H, d, $J = 6.8$ Hz, CH_3 Me), 1.25 (2H, m, CH_2 Et), 1.8 (1H, m, CH), 3.80 (3H, s, OCH_3), 4.05 (2H, m, OCH_2), 4.9 (1H, dd, $J(H_5,H_6) = 6.4$ Hz, $J(H_4,H_5) = 6.2$ Hz, H_5 aro), 5.05 (1H, d, $J(H_3,H_4) = 6.8$ Hz, H_3 aro), 5.7 (1H, ddd, $J(H_4,H_6) = 1.2$ Hz, H_4 aro), 6.2 (1H, dd, H_6 aro). $^{13}C\{^1H\}$ NMR δ 11.2 (CH_3 Et), 16.4 (CH_3 Me), 26.0 (CH_2 Et), 34.2 (CH), 56.1 (OCH_3), 69.4, 70.2, 72.6, ~ 83.0, 83.5, 95.0, 97.1 (OCH_2, C aro), 164.7 (COO), 231.1 ($Cr(CO)_3$); MS (EI) 358 (M^+, 7%), 302 (M^+ - 2CO, 2%), 274 (M^+ - 3CO, 72%), 189 (100%), 52 (Cr^+, 86%); IR (KBr) ν 1982-1912 ($Cr(CO)_3$), 1719 (C=O).
5. The enantiomeric excess of chiral tricarbonyl(arene)chromium complexes was determined by HPLC as described in reference 4. Bitterwolf, T. E.; Hubler, T. L. *J. Organomet. Chem.* **1995**, *487*, 119-125.
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