Chemoselective Reduction of Halo-Nitro Aromatic Compounds by β-Cyclodextrin-Modified Transition Metal Catalysts in a Biphasic System

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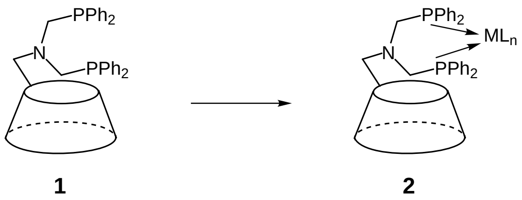
Abstract: Transition metal complexes of a water-soluble β-cyclodextrin modified diphosphine can be used in the biphasic (H_2O/organic) hydrogenation of halo-nitro aromatic compounds. The platinum complex is the most active and selective, resulting in the chemoselective formation of halo-aniline derivatives.

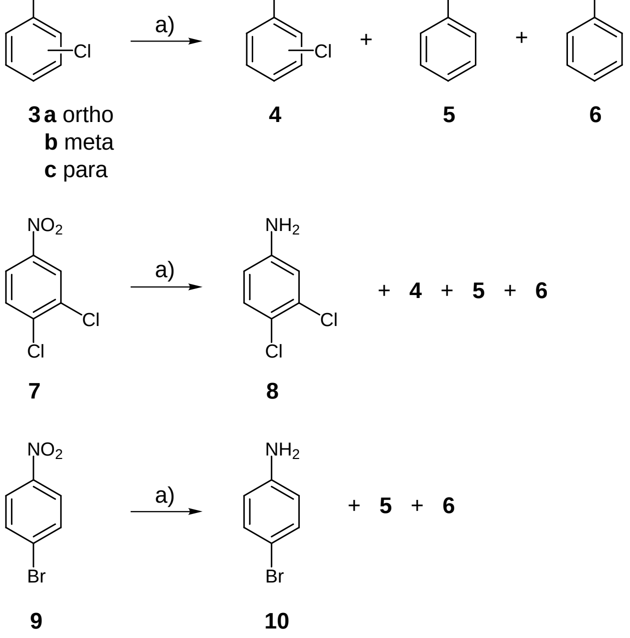
Key words: β-cyclodextrin modified diphosphine, phase transfer catalysis, catalytic reduction, supramolecular catalysis, transition metals

We have recently shown that β-cyclodextrin-modified diphosphines of the type **1** are excellent water-soluble ligands for Rh-catalyzed hydrogenation and hydroformylation of olefins in two-phase systems (aqueous/organic phases).[1] The underlying concept is based on the well-known propensity of β-cyclodextrin (β-CD) to bind reversibly organic compounds in the hydrophobic inner cavity,[2] aromatic compounds often being the preferred substrates. Host/guest phenomena also form the basis of phase transfer catalytic properties of β-CD.[2,3] In the case of water-soluble transition metal complexes **2**, the reversible formation of host/guest supramolecules not only makes phase transfer catalysis in a biphasic system[4] possible, it also sets up an entropically favorable transition metal catalyzed process such as hydrogenation or hydroformylation.[1] In this publication we demonstrate that transition metal complexes **2** derived from the ligand **1** (Scheme 1) are efficient supramolecular catalysts in the biphasic reduction of halo-nitro-aromatics with chemoselective formation of the corresponding aromatic amines.



Scheme 1

All reactions were performed in an in situ manner, i.e., the ligand **1**[1] was dissolved in a small amount of methanol and treated with the equivalent amount of a transition metal salt, the catalyst then being added to the biphasic system consisting of the halo-nitro aromatic compound **3**, **7** or **9** dissolved in toluene as one phase and water as the second phase. Following hydrogenation (20 bar H_2), the organic phase was analyzed by gas chromatography. Although complete optimization was not strived for, the results summarized in the Table show some clear trends. In all cases chemoselectivity in favor of halo-amines **4**, **8** or **10** was observed (Scheme 2), but the degree of selectivity varied. The ruthenium and palladium catalysts are least suitable (Table, Entries 9 and 10). In contrast, Rh, Ir, Pt, Ni and Co show better performance, the platinum system appearing to be optimal since it is very active and also highly chemoselective (Table, Entry 5). Upon reusing the aqueous phase in the Pt-catalyzed reduction of substrate **3a**, essentially the same result was obtained (Table, Entry 6).



Reagents and conditions: a) Ligand **1**/metal salt/H_2 (20 bar); see Table

Scheme 2

Thus, this new aqueous catalyst system constitutes an alternative to previous methods for the chemoselective conversion of halo-nitro aromatic substrates.[5–9] In most of the processes problems occur concerning catalyst-product separation, the low activity of the catalyst or its selectivity. This usually leads to incomplete conversion of the starting materials or substantial amounts of dehalogenated by-products or toxic azo compounds. The liberation of undesired halogen acid (HX) causes sever corrosion of equipment, and its neutralization generates undesired amounts of inorganic salts or contaminated wastewaters.[6] In the case of heterogeneous catalysts like Raney nickel or noble metals on inert supports in fluid phases additional problems arise from the separation of the finely dispersed catalyst by filtration and from the removal of the solvent.[7] In addition usually high temperatures and/or hydrogen pressure for fast and complete conversion have to be applied. To overcome the problem of dehalogenation numerous methods have been employed, including modification or deactivation of the catalysts by appropriate additives.[8] Although gas phase reduction of halo-nitro aromatic compounds with modified heterogeneous catalysts is very selective, this cannot be applied to sensitive fine chemicals that are subject to decomposition.[5b]

Chemical reducing agents like Fe/$FeCl_2$ in acidic aqueous solution, (poly)sulfides, sulfites or SO_2 suffer from a lack of chemoselectivity.[5b] Other methods like the reduction under water gas shift conditions (CO/H_2O) by the aid of homogeneous noble metal catalysts[9] or the electrochemical reduction[5b] in general suffer from low activity, although good selectivities (> 99%) towards functional groups have been reported in some cases.

Reduction in an aqueous two-phase system with molecular hydrogen as described in this paper is a desirable goal. It is environmentally benign because water is the solvent and the only by-product. The two-phase system offers simple product-catalyst separation and recycling for batch as well as continuously fed flow processes and in some cases conversion can take place without any organic solvent under very mild reaction conditions (Table, Entries 4 and 16).

Our system also appears to be superior to the use of water-soluble Pt- and Rh-complexes of tris(*m*-sulfonatophenyl)phosphine trisodium salt (tppts),[10] a catalyst system well known in the biphasic hydroformylation of propene.[4e,11] For example, under comparable conditions the reaction of substrate **3c** is catalyzed by (COD)$PtCl_2$/10 tppts to afford 95% of **4c** and 4% of **6**, and Rh$(COD)_2[BF_4]$/10 tppts leads to 89% of **4c** and 10% of **6** which means that selectivity is only 95 and 90%, respectively. The unacceptably low-degree of chemoselectivity in the case of the Rh-tppts-system[10] was reported previously in the patent literature.[7] In contrast, our method based on Pt/**1** is highly chemoselective and also allows for a simple separation and re-use of the catalyst containing aqueous phase without significant loss of activity.

In summary, the water-soluble $PtCl_2$ complex of the β-CD-modified diphosphine **1** is an excellent catalyst in the biphasic hydrogenation of halo-nitro aromatic compounds, the corresponding halo-aniline derivatives being formed chemoselectively. Accordingly, **1**/$PtCl_2$ acts as a

Table Hydrogenation of Compounds **3, 7** and **9** Catalyzed by Transition Metal Salts in the Presence of the Equivalent Amount of Ligand **1** in Aqueous/Organic Two-Phase Systems[a]

Entry	Substrate	Transition Metal Salt	Temp. (°C)	Time (h)	Main Product[b] (%)	Side Product (%)	Selectivity (%)	TON[c]	TOF[d] (h^{-1})
1	**3a**	$[Rh(COD)_2]BF_4$	100	18	**4a** (87.9)	**6** (11.9)	88.1	10^3	38
2	**3a**	$[Rh(COD)_2]BF_4$	80	18	**4a** (92.4)	**6** (7.2)	92.7	10^3	29
3	**3a**	$[Rh(COD)_2]BF_4$	60	18	**4a** (39.2)	**5** (0.6)/**6** (1.3)	96.8	405	23
4	**3a**[e]	$[Rh(COD)_2]BF_4$	60	18	**4a** (83.7)	**5** (0.1)/**6** (2.3)	97.3	870	48
5	**3a**	(COD)$PtCl_2$	80	15	**4a** (98.7)	**6** (0.5)	99.5	10^3	> 70
6	**3a**[f]	(COD)$PtCl_2$	80	15	**4a** (98.2)	**6** (1.34)	98.7	996	66
7	**3b**	$[Rh(COD)_2]BF_4$	60	18	**4b** (73.7)	**6** (0.4)	99.5	741	42
8	**3c**	$[Rh(COD)_2]BF_4$	60	18	**4c** (88.6)	**5** (0.2)/**6** (0.7)	99.2	888	49
9	**3c**[g]	$[(cymol)RuCl_2]_2$	80	25	**4c** (56.0)	**6** (0.8)	98.6	570	23
10	**3c**	$Pd(OAc)_2$	80	15	**4c** (73.8)	**6** (25.8)	73.9	738	> 70
11	**3c**	$Ir(COD)_2BF_4$	80	15	**4c** (97.0)	**6** (3)	97.3	10^3	> 70
12	**3c**	$Ni(COD)_2$	80	15	**4c** (95.9)	**6** (3.9)	96.0	10^3	> 70
13	**3c**	$[Co(NH_3)_6]Cl_2$	80	15	**4c** (98.1)	**6** (1.1)	98.9	10^3	> 70
14	**3c**	(COD)$PtCl_2$	80	15	**4c** (99.5)	**6** (0.5)	99.5	10^3	> 70
15	**7**	(COD)$PtCl_2$	80	24	**8** (99.8)	**4**/**6** (0.2)	99.8	10^3	> 30
16	**7**[e]	(COD)$PtCl_2$	80	12	**8** (99.5)	**4**/**6** (0.2)	99.5	10^4	840
17	**9**	$[Rh(COD)_2]BF_4$	100	18	**10** (79.0)	**6** (21.0)	79.0	10^3	350
18	**9**	(COD)$PtCl_2$	20	65	**10** (94.8)	**6** (2.8)	97.2	948	–[h]
19	**9**	(COD)$PtCl_2$	20	160	**10** (97.1)	**6** (2.9)	97.1	10^3	–[h]

[a] Toluene and H_2O as solvents/20 bar H_2, except in the case of entries 4 and 16 where the substrate also served as the organic solvent (no toluene).

[b] In those cases in which the sum of the yields of main and side products is less than 100%, the reaction was incomplete, i.e., the difference is the amount of starting material still present.

[c] Turn over number.

[d] Turn over frequency.

[e] No organic solvent used (only substrates and H_2O); product was dissolved in toluene for analysis.

[f] Aqueous phase reused.

[g] Colloidal Rue is formed.

[h] Not determined.

phase transfer catalyst (probably on the basis of host/guest phenomena) and as a transition metal catalyst, therefore constituting an interesting case of supramolecular catalysis.[1b,2]

All reactions were carried out using the standard Schlenk technique. Solvents were dried and distilled under argon, water was degassed in vacuo in an ultrasonic bath. The substrates were obtained from Aldrich or Fluka and were used without further purification. The β-cyclodextrin-phosphine **1** was prepared according to the literature procedure.[1] The products were analyzed with a GC Hewlett Packard 6890 equipped with a H*P*-5 column.

Chemoselective Reduction of Halonitro Compounds 3,7 and 9 Using β-Cyclodextrin-Modified Transition Metal catalysts, General Procedure

A transition metal salt (5 μmol) was added to the solution of **1** (5.5 μmol) in anhyd (free of O_2) MeOH (2 mL). After 15 min the solvent was evaporated in vacuo and the residue was dissolved in H_2O (10 mL) and transferred into an argon flushed steel autoclave (100 or 200 mL) equipped with a magnetic stirring bar. Then $NaHCO_3$ (~ 50 mg) and a solution of the halo-nitrobenzene (5 mmol) in toluene (10 mL) were added. The autoclave was pressurized with H_2 (20 bar) and heated to the temperature indicated in the Table under vigorous stirring. At the end of the reaction samples of the organic phases were collected and analyzed by GC (Table).

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