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Enantioselective Catalytic Transfer Hydrogenation of α,β-Unsaturated Carboxylic Acids with Formates Catalyzed by Novel Ruthenium Phosphine Complexes[1]

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Abstract: Hydrogen transfer from the formic acid/triethylamine (5:2) azeotrope to α,β-unsaturated carboxylic acids is effectively catalyzed by ruthenium complexes of general formula [Ru(acac-F_6)(η^3-C_3H_5)(diphosphine)]. If a chiral diphosphine is employed, the saturated acids are obtained in up to 93% ee, the most active and selective catalyst being formed with BINAP.

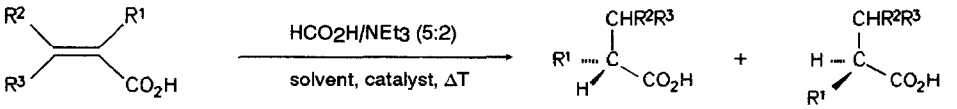
Asymmetric hydrogenation of prochiral olefins catalyzed by chiral transition metal complexes is one of the major applications of enantioselective homogeneous catalysis.[2] Ruthenium catalysts received much attention over the last few years for this type of reaction, as ruthenium complexes of the axially chiral diphosphine BINAP provide high asymmetric inductions for a wide range of olefinic substrates, including unsaturated carboxylic acids.[3,4] High hydrogen pressures are often required in order to obtain these excellent enantioselectivities, however.

We recently reported the use of the azeotrope formed by formic acid and triethylamine in a molar ratio of approximately 5:2 as a hydrogen source in the enantioselective rhodium-catalyzed transfer hydrogenation of α,β-unsaturated carbonyl compounds.[5] Gaseous hydrogen can be avoided by means of this new and simple methodology, the optical purities achieved being comparable in many cases.[5] Here we wish to describe the first highly enantioselective transfer hydrogenation of C-C double bonds catalyzed by optically active complexes of ruthenium (Scheme). Optical purities up to 93% are obtained using the BINAP derived catalyst **8d**.

Initially, we had investigated the transfer hydrogenation of itaconic acid **1a** using the complexes **3** - **6**, which are obtained from the reaction of [{Ru(cod)Cl_2}$_n$] with the ligand in the presence of triethylamine in refluxing toluene or ethanol.[4] They are effective catalysts for the transfer hydrogenation of **1a**, but the ee of product is very low (Table). Complex **3** was reported earlier to catalyze the transfer hydrogenation of **1a** with benzyl alcohol at 180°C.[6] Only 31% (S)-**2a** of 6% ee are obtained under these conditions.

An alternative approach recently became possible with the ready availability of ruthenium compounds **8a-d**.[7] These complexes are only active catalysts for the hydrogenation of (E)-2,3-dimethylacrylic acid (tiglic acid) **1c** with gaseous hydrogen after activation with trimethylsilyltriflate.[7] Complexes **8a-d** are readily soluble in tetrahydrofuran and transfer hydrogenation experiments were carried out in this medium. Although unreactive at

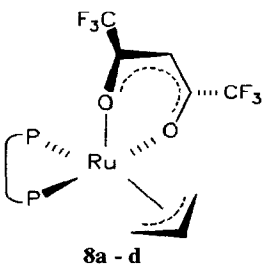
ambient temperature, the ruthenium complexes show catalytic activity at 70°C without any activation. Thus, itaconic acid **1a** is reduced completely to (R)-**2a** of 93% optical purity within ten hours using 0.5 mol% **8d** as a catalyst. The previous highest asymmetric induction reported for ruthenium-catalysed hydrogenation of **1a** with gaseous hydrogen was 88% ee employing complex **4** at 2 atm hydrogen pressure and 35°C.[4]



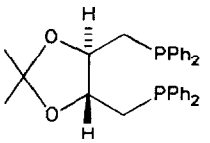
up to 93% ee

1a	itaconic acid	$R^1 = CH_2CO_2H$, $R^2 = R^3 = H$	**2a**	methylsuccinic acid
1b	phenylitaconic acid	$R^1 = CH_2CO_2H$, $R^2 = Ph$, $R^3 = H$,	**2b**	benzylsuccinic acid
1c	(E)-2,3-dimethylacrylic acid	$R^1 = R^2 = Me$, $R^3 = H$	**2c**	2-methylbutyric acid
1d	2-acetamidoacrylic acid	$R^1 = NHC(O)Me$, $R^2 = R^3 = H$,	**2d**	N-acetylalanine
1e	2-acetamidocinnamic acid	$R^1 = NHC(O)Me$, $R^2 = Ph$, $R^3 = H$,	**2e**	N-acetylphenylalanine
1f	atropic acid	$R^1 = Ph$, $R^2 = R^3 = H$,	**2f**	hydratropic acid

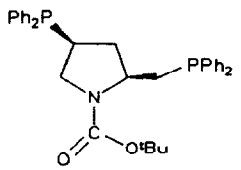
catalysts: [Ru_2Cl_4(-)-DIOP$_3$] **3** [Ru_2(-)-BINAP$_2Cl_4(NEt_3)$] **4** [Ru{(-)-BPPM}Cl_2] **5** [Ru{(-)-BPPM}H_2] **6** [Ru(+)-BINAP$(OAc)_2$] **7**



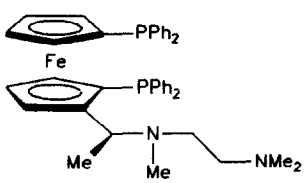
8a - d



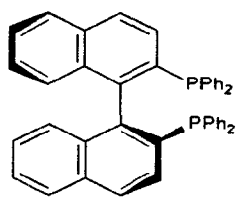
(-)-DIOP, **8a**



(-)-BPPM, **8b**



8c



(-)-BINAP, **8d**

Scheme

Other α,β-unsaturated carboxylic acids can be reduced successfully under similar conditions, although trisubstituted olefinic acids require prolonged reaction times. For most of these reactants the enantiomeric excess in the reduced product is moderate, but detailed optimisation procedures have not been carried out. Interestingly, a sample of the preferred[3] hydrogenation catalyst **7** showed a somewhat lower activity and selectivity than complex

Table : **Enantioselective transfer hydrogenation of α,β-unsaturated carboxylic acids with HCO_2H/NEt_3 (5:2) catalyzed by ruthenium phosphine complexes.**[a]

substrate	catalyst	temp. [°C]	time [h]	hydr. [%]	ee [%][b]	config.[b]
1a	3	70	68	100	14.4	S
1a	4	40	42	100	12.0	S
1a	5	60	42	100	22.8	S
1a	6	60	48	45[c]	16.5	S
1a	8a	70	23	51	42.5	S
1a	8b	70	23	62	5.8	S
1a	8c	70	18	98	21.5	S
1a	8d	70	10	100	93.5	R
1b	8d	70	17	10	—	—
1c	8d	70	46	100	61.0	S
1c	8d	70	47	88	51.7	R
1d	8d	70	36	100	40.0	S
1e	8d	70	34	70	56.8	S
1f	8d	70	24	89	13.4	R

a) For reaction conditions see general procedure in the experimental part.

b) By comparison of its optical rotation with literature value.[5] $[\alpha]_D^{25}$ = +76.3° (c 1.613, $CHCl_3$) was used for (S)-hydratropic acid.[8]

c) 25% Rearrangement to (E)-2-methyl-2-butenedioic acid occurred as a side reaction.

8d in the transfer hydrogenation of **1c** under these conditions.

The transfer hydrogenation of α,β-unsaturated carboxylic acids with the formic acid/triethylamine system catalyzed by the ruthenium complex **8d** is very easy to perform and does not require special equipment for high pressure reactions. The asymmetric inductions are in some cases comparable or even higher than those achieved with gaseous hydrogen under elevated pressure using other ruthenium BINAP catalysts. Further work is necessary, however, before the same level of general utility is afforded by ruthenium transfer hydrogenation.

Experimental:

All manipulations were done under an argon or nitrogen atmosphere using standard vacuum line techniques. Solvents were dried according to standard procedures and distilled under nitrogen prior to use. Formic acid was purified by distillation from anhydrous $Cu[SO_4]$. The ruthenium complexes **3** - **6**,[4] **7**[3] and **8a-d**[7] were prepared according to literature procedures. The hydrogenated products were analyzed by comparing their NMR-spectra

and their optical rotations to those of authentical samples.[5] Reactions using catalysts **3** - **6** were performed as described in previous papers.[5]

*General procedure for the enantioselective catalytic transfer hydrogenation using ruthenium catalysts **8a-d**:* The sample (2.00 mmol) of reactant is dissolved in tetrahydrofuran (3.00 cm^3) and triethylamine (0.60 cm^3, 4.33 mmol) is added, followed by formic acid (0.40 cm^3, 10.53 mmol) upon cooling. The solution is degased thoroughly and 10.0 µmol of the appropriate catalyst is added as a solid in one portion. The resulting red solution is kept at 70°C under argon until the olefinic proton peaks in the ^{1}H-NMR spectrum of aliqouts have disappeared. Over the course of the reaction the colour of the solution changes to a very light yellow. The solvent is removed *in vacuo* and the residue is taken up in 2n NaOH (5 cm^3), filtered and washed with three portions of ether (15 cm^3). After acidification with 10% HCl, the products are extracted with ether (4 x 20 cm^3). The material obtained is usually slightly coloured. After Kugelrohr distillation under reduced pressure (**2c**, **2f**) or filtration of an ethereal solution through a short plug of silica gel (**2a**, **2b**, **2e**) a colourless oil or solid is obtained in 70-90% yield. N-Acetylalanine **2f** is not soluble in ether. Therefore the acidic solution is evaporated to dryness, taken up in EtOH (5 cm^3) and filtered through a short plug of silica gel.

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