Regioselective Hydrogenation of Unsymmetrically Substituted Cyclic Anhydrides Catalyzed by Ruthenium Complexes with Phosphine Ligands

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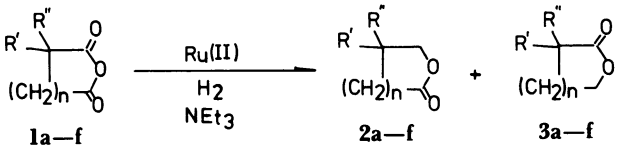
Synopsis. Regioselective hydrogenation of unsymmetrically substituted cyclic anhydrides catalyzed by ruthenium complexes with mono-, di-, or triphosphine ligands produced the corresponding two isomeric lactones, where the regioselectivity was influenced by the bulkiness of the substituent(s) on the anhydrides and of the phosphine ligands of catalyst.

We have previously reported that a ruthenium complex having the diop ((−)-2,3-*O*-isopropylidene-1,4-bis(diphenylphosphino)-2,3-butanediol ligand catalyzed stereoselective hydrogenation of prochiral and *meso*-cyclic anhydrides to the corresponding optically active lactones.[1] Such an enantiotopes differentiating reaction is rarely found in the asymmetric reactions catalyzed by transition metal complexes.[2] However, still ambiguous is how the ruthenium complex distinguishes between pro-*R* and pro-*S* groups in a prochiral molecule. In order to obtain more informations about the steric interaction between the cyclic anhydride and the catalyst, the regioselectivity of the hydrogenation of unsymmetrically substituted cyclic anhydrides, which can potentially produce two isomeric lactones **2** and **3**, (Scheme 1), was examined using ruthenium complexes



Scheme 1.

having mono-, di-, or triphosphine ligands as catlysts. It was briefly reported that $RuCl_2(PPh_3)_3$ catalyzed hydrogenation of 2,2-dimethylsuccinic anhydride gave preferentially 2,2-dimethyl-γ-butyrolactone.[3] More recently we have shown that the stoichiometric reaction of $RuH_2(PPh_3)_4$ with 2-alkylsuccinic anhydrides afforded two isomeric complexes, in which RuH(OCOCHRCH$_2$CHO)$(PPh_3)_3$ is the major product.[4] These results promoted us to reinvestigate the systematic study on the catalytic hydrogenation of cyclic anhydrides to reveal the factors which govern the stereo- and regioselectivities for the transformation of cyclic anhydrides to lactones.

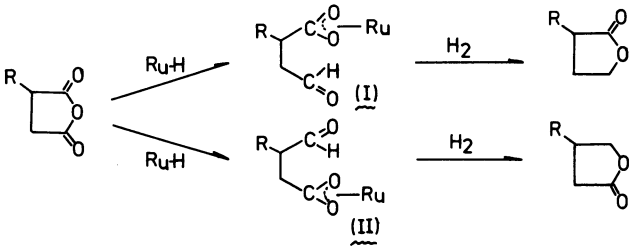
Experimental

Ruthenium complexes, $RuCl_2(PPh_3)_3$, $Ru_2Cl_4(dppb)_3$,[5] $Ru_2Cl_4(diop)_3$,[6] and $RuCl_2(ttp)$,[7] (ttp=bis(3-diphenylphosphino)propyl)phenylphosphine) methods in the literatures.

Hydrogenation of Cyclic Anhydrides. A toluene solution containing cyclic anhydride (5 mmol), $MgSO_4$, and triethylamine (0.1 cm^3) was allowed to react with hydrogen gas (10 atom) in the presence of ruthenium complex (0.1—0.2 mmol) at 120 °C for 10—20 h. After being returned to atmospheric pressure, the insoluble materials were separeted by filtration, and the filtrate was evaporated to remove the solvent. The hydrogenated products were isolated by vaccum distillation and identified by ^{1}H NMR, mass, and IR spectroscopies. The molar ratio of two isomers in each product was determined by GC using acetophenone or propiophenone as an internal standard. Table 1 summerizes the representative results. Hydrogenation of racemic 2-methylsuccinic anhydride using the chiral complex $Ru_2Cl_4(diop)_3$ was carried out in the similar manner to that described above, and the diastereomeric products were isolated by preparative GC (Carbowax 3 m). The optical purities of lactones were determined by measurement of the optical rotation,[8] **2a**; $[\alpha]_D$=+1.3°. 5.9%e.e., **3a**; $[\alpha]_D$=−2.9°, 11.3%e.e.

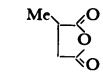
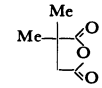
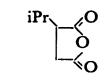
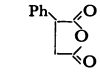
Results and Discussion

The hydrogenation of cyclic anhydrides **1a—f** catalyzed by ruthenium complexes produces the corresponding isomeric lactones **2a—f** and **3a—f**, where the reaction preferentially occured at the less hindered carbonyl group to give **2a—f** selectively except phenylsuccinic anhydride (**1d**). This is a marked contrast to that the reduction of cyclic anhydrides with $LiAlH_4$ or $NaBH_4$ tends to take place selectively at the more hindered carbonyl group.[9] The regioselectivity increased in the order of 2-methyl<2-isopropyl<2,2-dimethyl-substituted cyclic anhydride, which is the order of the steric bulkiness of the substituent(s). It is possible that the hydrogenation of cyclic anhydrides proceeded *via* an intermediacy ruthenium formyl carboxylate complex formed by the cleavage of one of two C-O bonds on the anhydride.[4] The initial attack of ruthenium to the carbonyl group and succesive C-O fission of one of the C-O bonds should be controlled by the steric hindrance of substituent to give preferentially the formyl carboxylate complex (**II**) as shown in Scheme 2. Thus the carbonyl group adjacent to substituent(s) becomes less reactive. In the case of phenylsuccinic anhydride (**1d**) the more hindered carbonyl group was reduced selectively to some extent. It is obvious that the electron-withdrawing phenyl group weakens the neighboring C-O bond, resulting in the preferable formation of the intermediate complex (**II**) as shown in Scheme 2.



Scheme 2.

Table 1. Regioselective hydrogenation of cyclic anhydrides

Run	Cyclic anhydride		Catalyst[a]	Temp/°C	Time/h	Yield/%	2/3
1			(A)	120	10	48	46/54
2			(B)	120	10	31	35/65
3			(D)	120	20	54	36/64
4		(*RS*)	(C)	120	10	40	30/70
5	(**1a**)	(*R*)	(C)	120	10	34	27/73
6		(*S*)	(C)	120	10	53	32/68
7			(A)	120	10	52	8/92
8			(B)	120	10	39	2/98
9	(**1b**)		(D)	120	20	13	1/99
10			(A)	120	10	51	23/77
11			(B)	120	10	33	20/80
12		(*RS*)	(C)	120	10	40	27/73
13	(**1c**)	(*R*)	(C)	120	10	49	19/81
14		(*S*)	(C)	120	10	46	31/69
15			(A)	140	20	31	42/58
16			(B)	140	20	30	44/56
17	(**1d**)		(D)	140	20	62	52/48
18			(A)	120	20	15	28/72
19			(B)	120	20	30	25/75
20	(**1e**)		(D)	120	20	10	23/77
21			(A)	120	20	11	3/97
22			(B)	120	20	20	2/98
23			(D)	120	20	17	0/100
24	(**1f**)		(D)	140	20	29	1/99

a) (A) = $RuCl_2(PPh_3)_3$; (B) = $Ru_2Cl_4(dppb)_3$; (C) = $Ru_2Cl_4(diop)_3$; (D) = $RuCl_3(ttp)$.

To clarify further that the steric interaction between the substituent and ligand controls the selectivity, the hydrogenation of racemic 2-methylsuccinic anhydride (**1a**) with the chiral ruthenium complex $Ru_2Cl_4(diop)_3$ was examined. Of interest is that 2-methyl-γ-butyrolactone (**2a**) obtained from the hydrogenation of racemic **1a** using $Ru_2Cl_4(diop)_3$ was found to contain *R*-isomer in excess (5.9%e.e.), while 3-methyl-γ-butyrolactone (**3a**) obtained as the minor component contained the *S*-isomer in excess (11.3%e.e.).[8] The 2-methylsuccinic anhydride recovered from the reaction mixture exhibited negligible optical activity. These results obviously indicate that the optical activity of the above mentioned lactones could be explained in term of difference in the reactivities between *R*- and *S*-enantiomers toward the chiral complex $Ru_2Cl_4(diop)_3$ caused by the distinctive steric interaction of the chiral phosphine ligand with the substituent on *R*- and *S*-enantiomers. This is supported by the fact that the hydrogenation of (*R*)-2-methylsuccinic anhydride[11] catalyzed by $Ru_2Cl_4(diop)_3$ exhibited the apparently higher regioselectivity than that with *S*-enantiomer as shown in Table 1. The similar difference in the reactivity was observed in the hydrogenation of 2-isopropylsuccinic anhydride (**1c**) catalyzed by $Ru_2Cl_4(diop)_3$.

In conclusion the factor which governs primarily the regio- and stereoselectivities of the ruthenium complex-catalyzed hydrogenation of cyclic anhydrides is the steric interaction between substituent(s) on the substrate and the phosphine ligand. In the case of phenylsuccinic anhydride the electronic effect becomes superior to the effect of the steric demand. With the combination of this hydrogenation of cyclic anhydrides and the dehydrogenation of diols catalyzed by the same complex,[10] the selectivity of the latter being in the opposite direction to the former, the synthetic control of lactone formation can be performed employing the dicarboxylic acids as the starting materials.

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