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# Asymmetric Transfer Hydrogenation of Prochiral Carboxylic Acids Catalyzed by a Five-Coordinate Ru(II)-binap† Complex

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*Key Words*: asymmetric transfer hydrogenation, Ru-binap catalyst, Ru-hydride complex, alcohols, chiral carboxylic acids

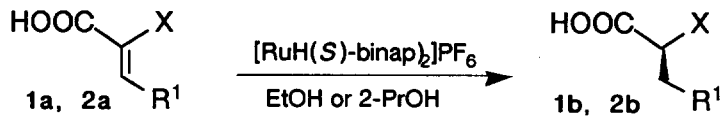
***Abstract*** : Asymmetric transfer hydrogenation of representative prochiral carboxylic acids was performed, using $[RuH((S)\text{-binap})_2]PF_6$ or a related complex as a catalyst and 2-propanol or ethanol as a hydrogen source, to achieve good to excellent enantioselectivities.

It has been recognized that ruthenium(II)-phosphine complexes are effective as catalyst precursors for transfer hydrogenation of unsaturated compounds with an organic hydrogen donor.[1] Although the excellent catalytic activity of Ru-binap complexes for asymmetric hydrogenation of a variety of unsaturated compounds has been established in these years,[2,3,4] the application of Ru-binap catalyst for asymmetric hydrogen transfer reduction of unsaturated compounds has rarely been undertaken. An attempt to utilize Ru-binap complexes as the catalyst for asymmetric transfer hydrogenation of unsaturated carboxylic acids was recently reported.[5] The published reaction system achieved high enantioselectivity in the hydrogenation of methylenesuccinic acid, but it requires a less common hydrogen source, azeotropic mixture of formic acid and triethylamine.[5]

Among several Ru(II)-phosphine complexes, $RuH_2(PPh_3)_4$ has been revealed to be one of the most efficient catalysts for several types of hydrogen transfer reactions.[6,7] It is assumed that, in actual reaction mixtures, $RuH_2(PPh_3)_4$ transforms into a coordinatively unsaturated species, $RuH_2(PPh_3)_3$, which possibly acts as the direct precursor of active species. Our recent success in preparing novel Ru-binap complexes, $[RuH(binap)_2]PF_6$ and $RuH_2(binap)_2$,[8] prompted us to examine their activities for asymmetric transfer hydrogenation. We expected that $[RuH(binap)_2]^+$ cation, which is coordinatively unsaturated and has a hydride ligand, could present a high activity for hydrogen transfer reaction, in a similar manner as $RuH_2(PPh_3)_4$. Here we describe the results of asymmetric transfer hydrogenation of prochiral carboxylic acids, using simple alcohols as the hydrogen source and the above hydride-binap complexes as the catalyst. The results on asymmetric hydrogenations of prochiral carboxylic acids catalyzed by $[RuH(binap)_2]PF_6$ have recently been reported.[9]

The transfer hydrogenation of methylenesuccinic acid (**1a**), a diagnostic substrate for examining the activity of chiral transition metal complexes in hydrogenation[10] and transfer hydrogenation,[5,11] was at first examined, employing 2-propanol (2-PrOH) as a hydrogen source and $[RuH((S)\text{-binap})_2]PF_6$ (**I**) and $RuH_2((S)\text{-binap})_2$ (**II**) as the catalyst. The reactions were carried out in a 1:1 mixture of alcohol and THF at refluxing temperature under a nitrogen atmosphere. The hydrogenation of **1a** was found to complete within 24 h, and the product, (*R*)-methylsuccinic acid (**1b**), was obtained with excellent enantioselectivities (Scheme 1). The results are listed in Table 1, along with detailed reaction conditions.

**Scheme 1**




1; $X = CH_2COOH$, $R^1 = H$  2; $X = NHCOCH_3$, $R^1 = C_6H_5$

† binap = (*R*)- or (*S*)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl

Table 1. Asymmetric transfer hydrogenation of methylenesuccinic acid (**1a**) and 2-acetoaminocinnamic acid (**2a**) catalyzed by Ru-(*S*)-binap complexes[a]

| Entry | Substrate | Catalyst[b] | Alcohol | Conv. / %[c] | e.e. / % | *R* or S[d] |
|---|---|---|---|---|---|---|
| 1 | **1a** | I | 2-PrOH | 100 | 97[e] | *R* |
| 2 | | II | 2-PrOH | 100 | 95 | *R* |
| 3 | | I | EtOH | 100 | 91 | *R* |
| 4 | | II | EtOH | 100 | 92 | *R* |
| 5 | | I | MeOH | 30 | 41 | *R* |
| 6 | | II | MeOH | 15 | 38 | *R* |
| 7 | | I | BnOH | 100 | 95 | *R* |
| 8 | | II | BnOH | 100 | 95 | *R* |
| 9 | **2a** | I | EtOH | 100 | 67[f] | *S* |
| 10 | | I | 2-PrOH | 100 | 67 | *S* |
| 11[g] | | I | EtOH | 84 | 86 | *S* |
| 12[g] | | I | 2-PrOH | 57 | 96 | *S* |

a) Reaction conditions: substrate (0.5 mmol); catalyst (0.01 mmol); solvent, THF-alcohol (1:1, 5 $cm^3$); at refluxing temperature; time, 24 h. b) I; [RuH((*S*)-binap)$_2$]$PF_6$; II, $RuH_2$((*S*)-binap)$_2$. c) Determined by $^1H$ NMR measurement of crude reaction mixtures. d) The configuration of preferentially formed enantiomer. e) The e.e. of **1b** was determined for its dianilide by HPLC with chiral stationary phase column (Daicel Chiralcel OD®). f) The e.e. of **2b** was determined directly for crude products by HPLC with Chiralcel OD. g) Reactions at 50 °C.

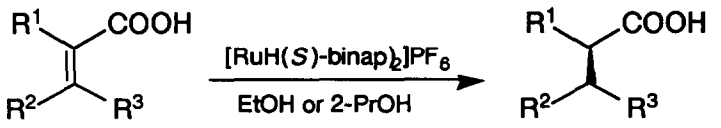
It was found that the hydrogen transfer from ethanol (EtOH) or benzyl alcohol (BnOH) to **1a** catalyzed by I or II proceeded smoothly, while methanol (MeOH) gave insufficient results with regard to both reactivity and stereoselectivity (See Table 1). The enantioselectivities effected with 2-PrOH, EtOH, and BnOH are generally excellent, and (*R*)-**1b** up to 97 % e.e. could be obtained. Brunner and collaborators reported asymmetric transfer hydrogenation of **1a** catalyzed by chiral diphosphine complexes of Rh[11], as well as by those of Ru[5], employing formic acid as a hydrogen source, which also afforded excellent selectivities (up to 94 % e.e.).

The hydrogen transfer reduction of 2-acetoaminocinnamic acid (**2a**), another typical substrate of asymmetric hydrogenation,[10] was carried out, using I as the catalyst and 2-PrOH or EtOH as the hydrogen source. The reactions proceeded smoothly at refluxing temperature to give N-acetyl-(*S*)-phenylalanine (**2b**) quantitatively. The enantioselectivities in this transfer hydrogenation showed a significant temperature effect. Thus, the reactions under refluxing conditions afforded the product **2b** with less than 70 % e.e., while the reactions performed at 50 °C presented much improved selectivities (up to 96 % e.e.), in spite that the conversion of reactions was somewhat lowered (Entries 9-12, Table 1). Complex II affected similar selectivities to those obtained with I at either temperature, but, in II-catalyzed reactions, the activity at 50 °C was significantly reduced (conversion; ca.20 %). Asymmetric transfer hydrogenation of **2a**, using formic acid as a hydrogen source, was also successful,[5,11] but the selectivities, ranging 57-72 % e.e., were lower than those achieved in the present study.

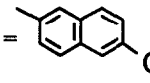
The asymmetric transfer hydrogenation of some substituted acrylic acids with complex I or II was also examined (Scheme 2). Under standard reaction conditions, 2-(6'-methoxy-2'-naphthyl)-propenoic acid (**3a**), a 2-substituted acrylic acid, was readily transfer hydrogenated to give the product **3b** with moderate asymmetric induction (45-55 % e.e.; Table 2). Both I and II effected indistinguishable activities and stereoselectivities for this substrate to give preferentially the (*S*)-**3b** (Scheme 2), that is the same enantiomer obtained by the hydrogenation using a Ru-(*S*)-binap complex as the catalyst.[12] In the present case, however, no appreciable improvement in the asymmetric induction could be obtained by lowering the reaction temperature to 50 °C (Entry 5), contrary to the case of **2a**.

The hydrogen transfer reduction of (*E*)-2-methyl-2-butenoic acid (tiglic acid; **4a**) catalyzed by I or II was also examined. We observed that the transfer hydrogenation of **4a**, using 2-PrOH or EtOH as the hydrogen source, hardly proceeded, especially when II was used as the catalyst. Complex I provided very low

Scheme 2




3a, 4a, 5a 3b, 4b

3, $R^1$ =  $R^2 = H$, $R^3 = H$, 4, $R^1 = CH_3$, $R^2 = CH_3$, $R^3 = H$,

5, $R^1 = CH_3$, $R^2 = H$, $R^3 = CH_3$,

conversions (< 20 %) and moderate asymmetric inductions (< 52 % e.e.), affording preferentially (*R*)-2-methylbutanoic acid (**4b**) (Scheme 2). This is in sharp contrast to that **4a** was readily hydrogenated by Ru-(*S*)-binap catalysts to give (*S*)-**4b** with excellent selectivities (up to 91 % e.e.) under mild reaction conditions.[9,12]

It has been clarified, further, that the hydrogenation of (*Z*)-2-methyl-2-butenoic acid (angelic acid; **5a**) requires severer conditions and produced (*R*)-**4b**, the antipode of hydrogenation product of **4a**, with a lower enantioselectivity.[12] With a view to investigate the influences of substitution pattern in C=C bond of substrates on our reaction system, the transfer hydrogenation of **5a** was carried out. It was found that the reactions of **5a**, especially using **I** as the catalyst, readily proceed, compared with those of the (*E*) isomer, although they were accompanied by a slight isomerization to **4a**. For transfer hydrogenation of **5a**, EtOH is a better hydrogen source than 2-PrOH, and an almost quantitative reduction was accomplished (Entry 11). Interestingly, (*R*)-**4b**, the same enantiomer as that from **4a**, was produced preferentially from **5a**, contrary to that Ru-binap catalyzed hydrogenation of **4a** and **5a** tends to give the antipodal products.[12]

When **I** and **II**, containing (*S*)-binap as the ligand, were employed, the transfer hydrogenated products **1b** and **2b** assumed, respectively, the (*R*) and (*S*) configuration, identical with those obtained by the hydrogenation with $H_2$ gas in the presence of similar Ru-(*S*)-binap catalyst (Scheme 1).[2,3] The transfer hydrogenation of substituted acrylic acids **3a** and **5a** also gave the products **3b** and **4b** having the the same configuration to those obtained by hydrogenation, whereas the transfer hydrogenation product for **4a** adopted the opposite configuration to that of hydrogenation. These observations suggest that there exist intrinsic differences between transfer hydrogenation and hydrogenation with $H_2$ gas. Although the detailed reaction mechanisms of hydrogen transfer

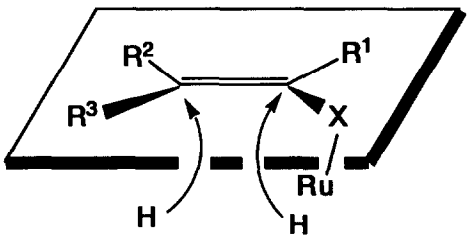
Table 2. Asymmetric transfer hydrogenation of substituted acrylic acids catalyzed by **I** and **II**.[a]

| Entry | Substrate | Catalyst | Alcohol | Conv. / % | e.e. / % | *R* or *S* |
|---|---|---|---|---|---|---|
| 1 | **3a** | **I** | 2-PrOH | 100 | 45[b] | *S* |
| 2 | | **I** | EtOH | 100 | 55 | *S* |
| 3 | | **II** | 2-PrOH | 100 | 52 | *S* |
| 4 | | **II** | EtOH | 100 | 54 | *S* |
| 5[c] | | **I** | EtOH | 42 | 57 | *S* |
| 6 | **4a** | **I** | 2-PrOH | 18 | 52[d] | *R* |
| 7 | | **I** | EtOH | 14 | 44 | *R* |
| 8 | | **II** | 2-PrOH | 0 | - | - |
| 9 | | **II** | EtOH | 6 | - | - |
| 10 | **5a** | **I** | 2-PrOH | 36 (4)[e] | 54[d] | *R* |
| 11 | | **I** | EtOH | 100 (3)[e] | 57 | *R* |
| 12 | | **II** | 2-PrOH | 7 | - | - |
| 13 | | **II** | EtOH | 20 (7)[e] | 42 | *R* |

a) Reaction conditions and designations for catalyst and alcohol are same as those of Table 1. b) The e.e. of **3b** was determined for its methyl ester by HPLC equipped with Chiralcel OD. c) Reaction at 50 °C. d) The e.e. of **4b** was determined for its anilide by HPLC with Chiralcel OD. e) The values in parentheses indicate **4a** formed by the isomerization of **5a**.

from an alcohol to an unsaturated acid catalyzed by I or II are still uncertain, we could recognize a common stereochemistry for these hydrogen additions.

Figure 1




1a, X = $CH_2COOH$
2a, X = $NHCOCH_3$
3a-5a, X = COOH

Thus, in the asymmetric transfer hydrogenation of **1a-5a** by Ru-(*S*)-binap catalyst, the hydrogen addition takes place from the bottom side of the C=C double bond of each substrate placed in a fashion in Figure 1, where the key functional group X, which should interact with the metal center (carboxymethyl group of **1a**, amido carbonyl group of **2a**, and carboxyl group of **3a-5a**),[10,13] occupies the front side of right hand site. As far as these and some other prochiral acids examined to date are concerned, no exceptional case has been found with regard to the stereochemical mode of hydrogen additions in the transfer hydrogenation catalyzed by Ru-(*S*)-binap catalyst.

In conclusion, it was disclosed that simple alcohols, such as 2-PrOH and EtOH, are successfully applied for hydrogen sources of asymmetric transfer hydrogenation of prochiral acids catalyzed by Ru-binap complexes, I and II, to achieve good to excellent asymmetric induction.

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