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The Asymmetric Kharasch Addition "On Water" Catalyzed by "RhCl[(–)-DIOP]" Species

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Abstract: The asymmetric Kharasch addition reaction was studied by using water as an environmentally friendly solvent. The reaction of styrene with $BrCCl_3$ catalyzed by chiral rhodium species, "RhCl[(–)-DIOP]", gave the corresponding adduct in moderate chemical and asymmetric yields "on water", where all the reactants float on water. By reinvestigation of the literature procedure, the chemical and asymmetric yields "on water" were compared with those obtained in organic solvents. The reaction with $FeCl_2$ / (–)-DIOP catalyst was examined to look at the metal effect. Possible reaction mechanisms were proposed based on these results. (93 words).

Keywords: asymmetric synthesis, Kharasch addition, radical reaction, "on water"

1. Introduction

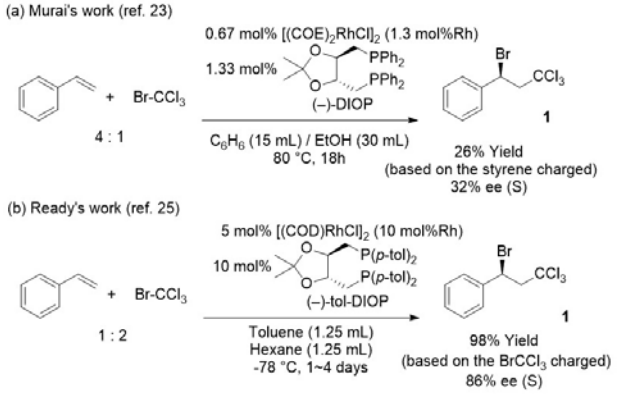
Chemical reactions are often performed in a homogeneous solution, where reactants are well-mixed and allowed to collide each other to carry out the reaction. Solvents are useful to make the solution containing reactive chemical species homogeneous. Water is a solvent having advantages on its cost and easy availability.[1,2)] Moreover, water shows no impact on the environment and to be harmless for life on this planet. It is also important that water is non-flammable and has high heat capacity to avoid the exothermic reaction. When the exothermic reaction is out of control, quick increase of the reaction temperature takes place, leading to ignition and, in extreme case, explosion of the reaction media.

Despite the attractive advantages of water as a solvent, water has not been common as a solvent of organic reactions. Water is a typical polar protic solvent, in which many organic compounds are difficult to dissolve. A mixture of hydrophobic organic reactants and water is often heterogeneous, where collision of the reactive chemical species is inefficient to make the reaction sluggish. In certain reactions, the reactants are decomposed in contact with water before the desired reaction occurs. In this context, studies on the reaction using water as the solvent have been performed by selected reactions which water does not disturb. Addition of surfactants and alcohols has been commonly carried out to make the reaction homogeneous.[3)]

Recent research results broke the mold of water to be inappropriate solvents for organic reactions. In certain reactions, a heterogeneous mixture of water and the organic reactants proceeded smoothly, and in extreme cases, the rate and selectivity of the reaction were improved by using water instead of common organic solvents.[1-4)] A typical example is a famous paper by Rideout and Breslow who reported that Diels-Alder reactions of two non-polar molecules were accelerated when water was used as the solvent in the presence of cyclodextrin. This was explained by "hydrophobic effect", previously proposed for enzymatic reactions. They also discovered significant change of selectivity of the reaction, when the reaction was performed in water instead of in organic solvent.[5)] In 2005, Sharpless found the rate-enhancement in several organic reactions, when the reactions were performed as a heterogeneous mixture of reactants and water. They called the system as "on water", because the reactants float on water, claiming that the system offers ease of product isolation.[6-8)] These two reports have stimulated chemists to explore the unique organic reactions "on water", which are summarized in several books and reviews.[1-4)] Radical reactions and transition metal-catalyzed reactions "on water" have especially received attention from organic chemists: For example, Oshima and coworkers reported

free radical reactions initiated by Et_3B "on water",[9] while our contribution is hydrogenation of ketones catalyzed by Pt nanoparticles supported on hyperbranched polystyrene (HPS) "on water", which did not occur in organic solvents.[10]

It is known that radical reactions were achieved not only by radical initiators but also by catalysis of transition metals.[11,12] Addition of polyhaloalkanes to alkenes known as Kharasch addition[13] was first reported as free radical chain reactions initiated by peroxidic initiators or photolysis,[13-16] which was reinvestigated later by catalysis of copper[17,18] or iron salts[19] and transition metal complexes.[20-22] Although asymmetric radical reactions were generally very difficult, Murai and coworkers discovered successful asymmetric Kharasch addition in 1981,[23] which was accomplished for the addition of $BrCCl_3$ to styrene by a chiral rhodium catalyst species, RhCl[(–)-DIOP], where (–)-DIOP is depicted in Scheme 1(a). This report achieving 32% enantiomeric excess (ee) (Scheme 1a) stimulated organic chemists, but examples to improve the asymmetric yields were rarely published so far.[24] A recent contribution from Ready and coworkers in 2011[25] improved the Murai's work by optimizing the ligand (the phenyl group on (–)-DIOP was modified to a *p*-tolyl group), solvents, and reaction temperature. Chemical and asymmetric yields were increased to 98% and 86% ee, respectively. However, high catalyst loadings (10 mol%) and long reaction time (over 4 days) at very low temperature (–78 °C) were required to achieve them, which have to be improved (Scheme 1b).



Scheme 1: Asymmetric Kharasch addition reported by Murai and Ready.

We were interested in development of efficient transition metal catalyzed asymmetric Kharasch addition, of which final goal is quick reaction with minimum catalyst loadings at ambient temperature to give the adduct in high chemical and asymmetric yields. In particular, it is desirable from environmentally friendly chemical process, if the addition takes place smoothly "on water". However, this is not easy to be achieved. For example, Oshima and coworkers attempted the Kharasch addition catalyzed by a chiral palladium-phosphine catalyst "on water", which proceeded smoothly to give the product in high chemical yield, but no asymmetric induction was observed.[26] In this context, we decided to perform the addition of $BrCCl_3$ to styrene by the Rh-(–)DIOP catalyst "on water" as a preliminary study to access the final goal described above. The experiments in organic solvents reported by Murai and Ready were reinvestigated, and the data were compared with those obtained on water under similar conditions. The results associated with a related study on the reaction catalyzed by $FeCl_2$[(–)-DIOP] species made clear several aspects, which would help the accomplishment of the final goal.

2. Results and Discussion

2-1. Reinvestigation of the results reported by Murai and Ready.

When we started this study, we were aware that both Murai[23] and Ready[25] studied the reaction of $BrCCl_3$ with styrene catalyzed by "RhCl[(–)-DIOP]" species *in situ* generated from $[RhCl(COE)_2]_2$ (COE: cyclooctene) or $[RhCl(COD)_2]_2$ (COD: 1,5-cyclooctadiene), but the reaction conditions were significantly different. Murai performed the reaction in a 1:2 mixture of benzene and EtOH. Ready examined hexane, THF, dichloromethane, acetonitrile, diethyl ether, acetone, *tert*-butyl methyl ether, benzotrifluoride, ethylbenzene, propionitrile, and a 1:4 mixture of benzotrifluoride and toluene during their screening of the reaction conditions, and a mixture of hexane and toluene for the optimum results shown in Scheme 1(b) using the *p*-tolyl derivative of (–)-DIOP. Both Murai and Ready did not perform the reaction using water as the solvent. As summarized in Table 1, the following six factors are different between the studies by Murai and Ready other than the solvent effects; (1) the molar ratio of $BrCCl_3$ to styrene, (2) concentration of the reactant (*M*) in the solvent, (3) the Rh precursor, (4) the amount of the Rh (mol% to the reactant indicated), (5) the molar ratio of the rhodium atom to (–)-DIOP, and (6) the reaction temperature.

Table 1. Comparison of the reaction conditions reported by Murai and Ready.[a]

	Murai[23]	Ready[25]
(1)	1 : 4	2 : 1
(2)	$[BrCCl_3]$ = 0.5 *M*	[styrene] = 0.1 *M*
(3)	$[RhCl(COE)_2]_2$	$[RhCl(COD)]_2$
(4)	1.3 mol%Rh / $BrCCl_3$	10 mol%Rh / styrene
(5)	1 : 1.1	1 : 1.5
(6)	80 °C	25 ~ –78 °C

[a](1)~(6) are the factors described in the text.

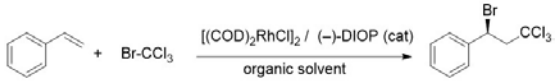
For better understanding of the organic solvent effect on the asymmetric Kharasch addition of $BrCCl_3$ to styrene, we reinvestigated the experiments of Murai and Ready under the two conditions *A* and *B*. For our experiments under *condition A*, we used Murai's factors (1)~(3), and (5). Instead of benzene, we used toluene, because benzene is classified as a carcinogen. Toluene is

widely recommended as the alternative. The rhodium catalyst precursor [the factor (4)] employed was $[RhCl(COD)]_2$, and the temperatures [the factor (6)] applied were 0, 25, 50, and 80 °C. Ready's factors (1)~(6) were used for our experiments under *condition B.* Table 2 shows the solvent and temperature effects under the conditions *A* and *B*. In Entry 1 and entry 7 are described the reported data in Murai's paper[23] and that in the supporting information of the Ready's paper, respectively.[25] We checked the reproducibility of these two experiments, and the results are shown in entry 2 and 8. The result shown in entry 2 exhibit that the product yield was somewhat higher than that of Murai's despite shorter reaction time applied, while the asymmetric yield was lower. The lower asymmetric yield is presumably due to the determination method of asymmetric yields used for entry 1 (derivatization of the product to a known chiral compound), which was less accurate than the chiral HPLC method used the experiment in entry 2. In contrast, the product and asymmetric yields of entry 7 and entry 8 are almost identical, though shorter reaction time was applied for the result shown in entry 8. These results suggest that our experiments are roughly reproduced the experiments reported in the literature.

Entries 3~6 and 9~12 are the experiments changing the solvents and the reaction temperature. Under *condition A* at 80 °C, chemical and asymmetric yields of **1** were moderate in a mixed solvent of toluene and EtOH (entry 2). In contrast, **1** was obtained in higher product yield in toluene, but no asymmetric induction was observed (entry 3). It is a general tendency of catalytic asymmetric synthesis, where the reaction proceeds in coordination sphere of chiral metal species that the lower reaction temperature was applied, the lower chemical yield and the higher asymmetric yield were observed. In the experiments changing the reaction temperature under *condition A*, both the chemical and asymmetric yields of **1** were not consistent with this tendency (entries 1~6). This indicates that other reaction pathways than the pathway occurring in the coordination sphere were involved. It should be noted that polystyrene was detected by ^{1}H NMR measurement of the crude product in the experiment shown in entries 2 and 4, suggesting the involvement of free radical chain reactions as discussed later. Of interest is the result shown in entry 5, in which the best chemical and asymmetric yields were attained among the experiments performed under *condition A*, suggesting that the reaction should be performed at 25 °C, much lower temperature than that used by Murai.

The reactions under *condition B* were consistent with the general tendency described above; the reaction became slower and asymmetric yields became higher on lowering the reaction temperature. This indicates that the reaction was governed by the pathway occurring in the coordination sphere of rhodium under *condition B* (*vide infra*). The product yield of 81~94% and the asymmetric yield of 26~34% showing entries 8~10 suggest that they are not dependent on the three solvents applied, toluene, toluene / EtOH, and toluene/hexane at 25 °C. Of interest are the two reactions in toluene / EtOH at 25 °C shown in entries 5 (*condition A*) and 9 (*condition B*), in which the chemical and asymmetric yields were similar. In other words, the high catalyst loading (10 mol%Rh) was not

Table 2. Asymmetric Kharasch reactions of styrene with $BrCCl_3$ catalyzed by Rh / (–)-DIOP system in organic solvent.



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Entry	Condition [a]	Solvent	Temp. [°C]	Time [h]	Yield [%]	%ee	Ref.
1	*A*	Toluene / EtOH (1: 2 v/v)	80	18	26 [b]	32	28
2	*A*	Toluene / EtOH (1: 2 v/v)	80	2	40 [b]	18	
3	*A*	Toluene	80	2	85[b]	0	
4	*A*	Toluene / EtOH (1: 2 v/v)	50	2	51[b]	19	
5	*A*	Toluene / EtOH (1: 2 v/v)	25	2	73 [b]	32	
6	*A*	Toluene / EtOH (1: 2 v/v)	0	2	26 [b]	24	
7	*B*	Toluene	25	12	>95[c]	35	31
8	*B*	Toluene	25	2	94 [c]	33	
9	*B*	Toluene / EtOH (1: 2 v/v)	25	2	81 [c]	34	
10	*B*	Toluene / Hexane (1: 1 v/v)	25	2	90 [c]	26	
11	*B*	Toluene	–20	24	23 [c]	70	
12	*B*	Toluene / Hexane (1: 1 v/v)	–20	24	30[c]	72	
13	*B*	Toluene	–78	48	33[c]	62	
14	*B*	Toluene / Hexane (1: 1 v/v)	–78	48	13[c]	70	

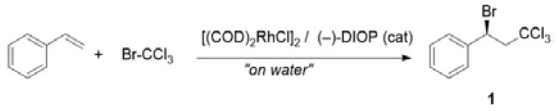
[a] Differences between *condition A* and *condition B*; see, the text and Table 1. [b]Isolated yields based on the charged amount of $BrCCl_3$.
[c] Isolated yields based on the charged amount of styrene.

necessary to achieve the asymmetric Kharasch addition at 25 °C. The asymmetric yields under *condition B* were increased in toluene or toluene/hexane in lowering the temperature to –20 °C, and the maximum %ee reached 70 (entries 11 and 12). Further cooling down to –78 °C did not provide significant improvement of the asymmetric yields (entries 13 and 14). As described above, Ready achieved the maximum asymmetric yields of 86% ee at –78 °C by using the *p*-tolyl derivative of DIOP (Scheme 1b). They also reported the asymmetric yields of 71% ee at –78 °C when DIOP was used instead of its *p*-tolyl derivative.[25)]

2-2. The asymmetric Kharasch addition "on water".

The experiments "on water" were performed under *condition A'* and *condition B'*; these are homologues of *condition A* and *condition B*, respectively. The only difference of the conditions *A'* or *B'* from *A* or *B* is use of water instead of organic solvents. Since the reaction was heterogeneous as expected from the hydrophobic nature of $BrCCl_3$, styrene, and the rhodium catalyst, the reactions were performed with vigorous stirring (1500 rpm). We followed the instruction of Oshima for effective generation of catalytically active species from an organometallic precursor and a ligand on water; $[RhCl(COD)_2]_2$ and (–)-DIOP were first dissolved in styrene, and then, water and $BrCCl_3$ were added.[26)]

Table 3. Asymmetric Kharasch reactions of styrene with $BrCCl_3$ catalyzed by Rh / (–)-DIOP system "on water".



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Entry	[a]	Temp. [°C]	Time [h]	Yield [%]	%ee
1	*A'*	80	2	20	10
2	*A'*	50	2	57 [b]	30
3	*A'*	25	2	84 [b]	28
4	*A'*	0	2	58 [b]	46
5 [d]	*A'*	–20	2	23 [d]	52
6 [e]	*A'*	–20	2	60 [b]	26
7	*B'*	80	2	5 [c]	4
8	*B'*	50	2	36 [c]	14
9	*B'*	25	2	27 [c]	16
10	*B'*	0	2	38 [c]	18

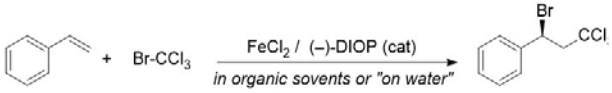
[a]The conditions *A'* and *B'* are similar to the conditions *A* and *B*, respectively, except water was used as the solvent. [b]Isolated yields based on the charged amount of $BrCCl_3$. [c]Isolated yields based on the charged amount of styrene. [d]Brine (21 wt%) was used. [e]A mixture of H_2O / MeOH (1:1 v/v) was used.

As shown in Table 3, the asymmetric Kharasch reaction successfully occurred "on water" at the temperature range from 0~80 °C. At the same temperature, *condition A'* afforded better chemical and asymmetric yields than *condition B'*. Low chemical and asymmetric yields of **1** were seen at 50 or 80 °C (entries 1, 2, 7 and 8), indicating contamination of free radical polymerization of styrene. Of keen interest is the results shown in entries 3; the reaction at 25 °C under *condition A'* "on water" gave 84 % product yield and 28% asymmetric yield, which were comparable to those in toluene / EtOH under *condition A* (Table 2, entry 5; 73% product yield, 32% asymmetric yield). Moreover, in declining the temperature from 25 °C to 0 °C, the product yield was decreased (unreacted styrene remained in the reaction mixture), but the asymmetric yield was increased (46% ee, entry 4). This foresees possible raising the asymmetric yield, if the reaction could carry out at the temperature lower than 0 °C. The reactions can be carried out at –20 °C, when brine or aqueous methanol were used as the solvent. Although the chemical yield was low due to the slow reaction, the highest asymmetric yield (52 % ee) was achieved in brine as shown in entry 5.

2-3. Effect of other metal catalysts having (–)-DIOP as the ligand.

Supplementary results which contribute to mechanistic discussion were obtained when we carried out the reaction of $BrCCl_3$ with styrene using other transition metal species ligated with (–)-DIOP as the catalyst. A catalyst reportedly promoting asymmetric Kharasch addition other than the Rh(I)-DIOP catalyst is $RuCl_2[(–)\text{-DIOP}]_n$ species; Nishiyama and coworkers reported the reaction of $BrCCl_3$ with styrene, which gave **1** in good yield with up to 32% ee.[24)] We examined

Table 4. Kharasch reactions of styrene with $BrCCl_3$ catalyzed by $FeCl_2$ / (–)-DIOP system in organic solvents and water.



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En-try	[a]	Solvent (mL)	Temp. [°C]	Time [h]	Yield [%]	% ee
1	*C*	Toluene (2.5)	25	2	0 [b]	–
2	*C*	CH_2Cl_2 (2.5)	25	2	12 [b]	0
3	*C*	CH_2Cl_2 (2.5)	25	12	18 [b]	0
4	*D*	CH_2Cl_2 (2.5)	25	12	26 [c]	0
5	*D*	CH_2Cl_2 (0.5)	25	12	73 [c]	0
6 [d]	*D*	CH_2Cl_2 (0.5)	25	2	91 [c]	0
7	*C'*	H_2O (2.5)	80	2	0	–
8	*C'*	H_2O (2.5)	50	2	0	–
9	*C'*	H_2O (2.5)	25	2	0	–
10	*C'*	H_2O (2.5)	0	2	0	–
11 [d]	*D'*	H_2O (2.5)	25	2	0	–

[a]The conditions *C* and *D* are homologous to the conditions *A* and *B* in Table 2, whereas the conditions *C'* and *D'* are to the conditions *A'* and *B'* in Table 3. [b]Isolated yields based on the charged amount of $BrCCl_3$. [c]Isolated yields based on the charged amount of styrene. [d]Isolated "$FeCl_2[(–)\text{-DIOP}]$" species was used as the catalyst.

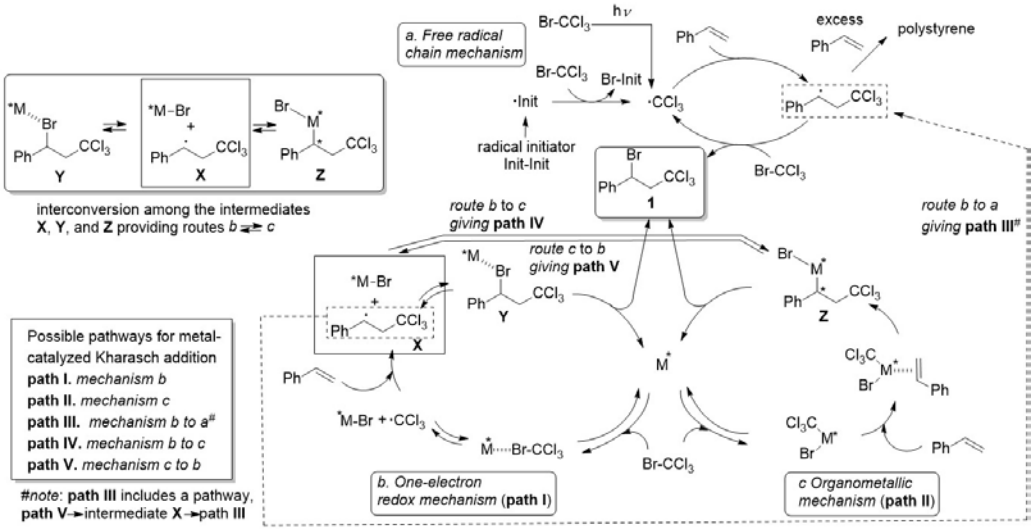
catalysis of "IrCl[(–)-DIOP]" generated from a mixture of $[IrCl(COD)]_2$ and (–)-DIOP, but the results attained were poor chemical yield of **1** and no asymmetric induction.

Since Kharasch addition is known to be promoted by 3d metal catalysts capable of one-electron redox, we examined the reactions catalyzed by Fe(II), Co(II) and Cu(I) species in the presence of (–)-DIOP. Among them, a species generated from a 1: 1 mixture of $FeCl_2$ and (–)-DIOP (1.3 mol%Fe based on $BrCCl_3$) showed unexpectedly high catalytic activity toward the reaction of $BrCCl_3$ with styrene in CH_2Cl_2 to give the product in 91% yield at 25 °C for 2 h, but the product was racemic (Table 6, entries 1~6). Apparently, this is the case the reaction occurs smoothly but does not induce asymmetric induction. We challenged the achievement of asymmetric addition "on water" by using either a species *in situ* generated from $FeCl_2$ and (–)-DIOP or isolated "$FeCl_2$[(–)-DIOP]"; however, no reaction took place (entries 7-11). This is our first experience that water disturbed the Kharasch addition which occurred smoothly in organic solvents. Similar experiments where CuCl or $CoCl_2$ was used instead of $FeCl_2$ resulted in recovery of starting materials. It is worthwhile to refer to a recent paper by Kamigaito and coworkers, who performed addition of CCl_4 to 3-butenyl acetate by catalysis of "RhCl[(–)-DIOP]" and "$FeCl_2$[(–)-DIOP]", and found that the reaction was very slow and no asymmetric induction was observed.[27] They also attempted catalysis of copper species generated from CuCl and sparteine, and obtained similar negative results. Copper salts or complexes are the first reported catalyst for the Kharasch addition,[17,18] and amines and other nitrogen containing ligands are known to accelerate the reaction.[28] Nonetheless, no copper-phosphine complexes were successfully employed as the catalyst as long as we checked the related literature.

2-4. Mechanistic considerations.

As described above, we found that the Kharasch addition catalyzed by RhCl[(–)-DIOP] species proceeded "on water" with asymmetric induction. Several interesting solvent and catalyst effects were also observed. Possible reaction mechanisms are discussed below for understanding these results (Scheme 2).

The original Kharasch addition initiated by radical initiators or photolysis is a typical radical reaction going through the free radical chain mechanism [*a* in Scheme 2].[16] Since styrene is a reactive monomer for free radical polymerization, formation of polystyrene indicates the involvement of the mechanism *a*. In contrast, it is known that transition metal species (M) capable of one electron redox easily reacts with CCl_3-Br to form the CCl_3 radical (CCl_3·) and M-Br. The formed CCl_3· is added to a C=C bond to result in formation of new radical species, CCl_3C-C·, which abstracts Br from M-Br to result in formation of **1** and regeneration of M. This process is known as the one-electron redox mechanism *b* giving **path I**. An alternative metal-catalyzed pathway is the organometallic mechanism *c* affording **path II**, which involves two-electron redox of metal species and proceeds through oxidative addition of CCl_3-Br to the metal to form CCl_3-M-Br, insertion of styrene between the resulting M-C bond, and reductive elimination to form **1** and to regenerate M. There are three other pathways intercrossing the mechanisms. A route from *mechanism b* to *mechanism a* provides **path III**; a part of the free radical intermediate, CCl_3C-C· produced by **path I** does not react with M-Br but does with either CCl_3-Br or styrene to initiate the free radical chain Kharasch addition or styrene polymerization. The other two pathways are provided by equilibrium among the intermediary species **X**, **Y**, and **Z**; the carbon radical in **X** produced by *mechanism b* reacts with M-Br species in **X** the atom transfer radical polymerization.[11] The M-C bond formation is known in the text book of



Scheme 2: Mechanisms for Kharasch addition reaction.

to result in reversible formation of either a C-Br bond or a M-C bond. The C-Br bond formation is proposed in organometallic chemistry as a radical pathway to form the oxidative adduct.[29] The **path I** and **path II** are interconvertible through a route from **Y** to **X** to **Z** (**path I** to **path II**) and a route from **Z** to **X** to **Y** (**path II** to **path I**), providing **path IV** and **path V**, respectively. In the metal-catalyzed Kharasch addition, all **path I~path V** are able to afford **1**. Of importance is that no asymmetric induction is attained by the process involving free radical chain reactions, namely **path III**. In sharp contrast, the intermediate **Z** in the organometallic mechanism *c* has a M-C bond, where (–)-DIOP on M strongly affects the chirality of C. In other words, the product **1** is formed in relatively high asymmetric yields, when **path II** and **path V** are involved. In the cases that **path I** and **path IV** are participated, the key intermediate is the species **Y**, where (–)-DIOP is remote from the carbon. It is not likely that the remote chiral center could provide efficient asymmetric induction.

The results obtained in toluene / EtOH under *condition A* above 25 °C did not follow the general trend that the lower chemical yields and higher asymmetric induction attained in decreasing the temperature (Table 2). Polystyrene was detected. This suggests dual reaction pathways to be involved, in which **path III** plays an important role. In contrast, the experiments at lower than 25 °C under the conditions *A* and *B* followed the general trend, and no significant solvent effect was observed among the reactions in toluene, toluene / EtOH, and toluene / hexane. These suggest the involvement of more simple mechanisms, which may be one or some of **path I**, **II**, **IV** and **V**. The Rh-catalyzed reaction in toluene at 80 °C (Table 2, entry 3) differs from that in toluene / EtOH, giving good chemical yields with 0% ee. This is due to **path I**, where asymmetric induction by the remote (–)-DIOP was totally ineffective under the conditions.

In the reactions catalyzed by "RhCl[(–)-DIOP]", the the results "on water" were almost similar to those in organic solvents, though the reaction medium was heterogeneous. At higher temperatures, the results were inconsistent with the general trend, suggesting the involvement of the dual pathways including **path III**. The product was obtained in good chemical yields and moderate asymmetric yields below 25 °C. It is clear that water provides a good circumstance to let the reaction proceed through simple mechanisms involving one or some of **path I**, **II**, **IV** and **V**.

Finally, the result of $FeCl_2$-DIOP catalyst is worth mentioning, which promoted the Kharasch addition efficiently in CH_2Cl_2 but gave no asymmetric induction. No Kharasch addition took place "on water". The asymmetric yield of 0% ee is ascribed to the one-electron redox mechanism *b*, where the (–)-DIOP remote from the carbon does not provide good circumstances for asymmetric induction. No reaction when water was used as the solvent is explainable by amphiphilic nature of $FeCl_2$-DIOP. In fact, the $FeCl_2$[(–)-DIOP] complex showed high solubility in water. During the reaction, styrene and $BrCCl_3$ exist on water, but $FeCl_2$-DIOP species was diffused in the aqueous phase and did not work as the catalyst.

3. Conclusion

We demonstrate the asymmetric Kharasch addition exemplified by the reaction of $BrCCl_3$ with styrene to be achieved by RhCl[(–)-DIOP] catalyst "on water". Water did not disturb the reaction, and asymmetric induction was accomplished "on water". As shown in Table 3, entries 4 and 5, the asymmetric yield of 46 and 52%, respectively. These achieved "on water" at 0 °C or on brine at -20 °C were not bad compared with the results in organic solvents at this temperature range. The results were achieved by a catalyst loading of 1.3 mol%Rh (Murai's catalyst concentration), which is much lower than Ready's catalyst concentration (10 mol%Rh).

As described in the introduction, the final goal of the asymmetric Kharasch addition is achievement of high chemical and asymmetric yields available by the reaction proceeding at ambient temperature in short reaction time. The catalyst loadings should be as low as possible. The present study suggests that water is a candidate solvent to reach the goal. It is important that water is an environmentally benign solvent, and the reaction "on water" offers easy separation of the product from the solvent, and promises the safe chemical process, even if the reaction is performed in large scales. A problem which should be solved in a future study is development of new efficient catalysts to afford high chemical and asymmetric yields under the conditions suitable for the final goal. It is known in the numerous research papers of catalytic asymmetric synthesis that discovery of appropriate chiral ligands, e.g. (–)-DIOP and other bidentate phosphorous ligands, led to efficient asymmetric induction even at ambient temperature.[30] Under the circumstances, discovery of the new catalyst is awaited, which is usable on water, e.g. catalysts hydrophobic enough to keep them on water.

Finally, it is worthwhile to refer to the following three discussions. The first is the net catalytic species. Although the formal active species assumed in the catalytic cycle is RhCl[(–)-DIOP] with 14 electron configuration,[25] this is unstable and actually exist as 16 electron species RhCl[(–)-DIOP](solvent) in the solution state. The solvent is weakly coordinated and easily replaced by $BrCCl_3$ to initiate the catalytic cycle. We denoted the RhCl[(–)-DIOP] species stabilized by weekly coordinated ligands such as solvents and $BrCCl_3$ to be "RhCl[(–)-DIOP]". The reaction of $[(COD)RhCl]_2$ with (–)-DIOP has recently been studied in detail,[31] and three rhodium complexes bound to (–)-DIOP were characterized by NMR. All of them are able to act as the catalyst precursor of "RhCl[(–)-DIOP]" for the Kharasch addition in solution. In similar fashion, we denoted the

active species for the iron-catalyzed reaction to be "$FeCl_2$[(–)-DIOP]", which is also equivalent to 14 electron $FeCl_2$[(–)-DIOP] species stabilized by solvents or other weakly coordinated ligands. The results shown in Table 4, entries 2~6 suggest that $FeCl_2$[(–)-DIOP] stabilized by CH_2Cl_2 is catalytically active in CH_2Cl_2. Unfortunately, most of iron-phosphine complexes so far reported are paramagnetic and difficult to be characterized by NMR.[32] In fact, attempted NMR analysis of "$FeCl_2$[(–)-DIOP]" generated in CD_2Cl_2 afforded several bumps due to its paramagnetic nature, which were hardly assignable. The "$FeCl_2$[(–)DIOP]" formed from a mixture of $FeCl_2$ and (–)-DIOP in CH_2Cl_2 could be isolated as a white solid by concentration of the CH_2Cl_2 solution. This white solid soluble in both CH_2Cl_2 and water showed good catalytic activity in CH_2Cl_2 and no catalytic activity in water as shown in entry 6 and 11, Table 4.

The second is the reaction mechanisms. As described above, Ready and coworkers achieved high asymmetric yields by using a modified DIOP with high catalyst loadings (extremely low TOF) at low temperatures.[25] They examined DFT calculations of **path I** and **path II**, suggesting **path I** is more probable. The third is the hydrophobic effects observed for the organic reactions "on water" described in the introduction.[1,2,7,8] For example, it was proposed for "on water" conditions that the reaction occurs in a small hydrophobic cavity surrounding by water. Outside water gives pressure to the cavity, realizing the organic reaction under pressure. For the foregoing experimental and theoretical studies, it is of interest to examine whether the Ready's mechanistic suggestion can also be adopted to the reaction mechanisms "on water" occurring with lower catalyst loadings with higher TOF at ambient temperatures, where the hydrophobic effects of water may be involved in the reaction mechanisms.

4. Experimental

General All manipulations were carried out under an argon atmosphere. Reagents were purchased from Tokyo Chemical Industry Co., Ltd. (styrene and $BrCCl_3$), Wako Pure Chemical Industries Ltd. [$FeCl_2$, $CDCl_3$, CD_2Cl_2 and (–)-DIOP], and Kanto Chemical Co., Inc. (anhydrous solvents). All reagents were used as received except styrene, which was purified by distillation prior to use. $[(COD)RhCl]_2$ (COD; 1,4-cyclooctadiene) was prepared according to the reported procedure.[33]

Product analysis ^1H and ^{13}C NMR spectra were measured on a JEOL ECA 400 (396 MHz) or ECA 600 (600 MHz) spectrometer. Chemical shifts are reported in parts per million relative to the solvent signal (^1H and ^{13}C NMR). The enantiomeric excess (%ee) of **1** was determined by chiral HPLC analysis (SHIMADZU Prominence LC-20AD; detector, SPD-M20A; column, Daicel Chiralpak OJ-H column (250 mm x 46 mm). **1:** ^1H NMR of ($CDCl_3$, rt, 400 MHz); δ3.75 (d, $J_{H\text{-}H}$ = 9.0 Hz, 2H, -C*H*$_2$CCl$_3$), 5.37 (t, $J_{H\text{-}H}$ = 9.0 Hz, 1H, -C*H*Br-), 7.30 (t, $J_{H\text{-}H}$ = 7.6 Hz, 1H, *p-Ph*), 7.34 (dd, $J_{H\text{-}H}$ = 7.6 Hz, 2H, *m-Ph*), 7.46 (d, $J_{H\text{-}H}$ = 7.6 Hz, 2H, *o-Ph*). ^{13}C NMR of **1** ($CDCl_3$, rt, 151 MHz); δ 47.7, 62.7, 96.6, 127.9, 129.0, 129.1, 140.9. The HPLC conditions for (*R*)-**1** and (*S*)-**1**: hexanes, flow rate = 0.2 mL/min., wavelength = 254 nm, t_R[(*R*)-**1**] = 11.0 min. and t_R[(*S*)-**1**] = 14.7 min.

The reactions of styrene with $BrCCl_3$ catalyzed by RhCl [(–)-DIOP] species in organic solvents.

Condition A (Table 2, entry 1-5): In a 20 mL Schlenk tube, $[(COD)RhCl]_2$ (4.1 mg, 8.3 x10^{-3} mmol) and (–)-DIOP (9.1 mg, 1.9 ×10^{-2} mmol) were dissolved in toluene (0.83 mL), and the solution was stirred at room temperature for 20 min. To the solution, styrene (0.57 mL, 5.0 mmol) and $BrCCl_3$, (0.12 mL, 1.3 mmol) dissolved in EtOH (in the case of entries 1, 3-5; 1.7 mL) or toluene (entry 2, 1.7 mL) were added, and the mixture was stirred for 2 h at the temperature indicated in Table 2. After removal of the solvent *in vacuo*, chromatographic purification (silica gel, eluted by hexane) gave **1**.

Condition B (Table 2, entry 6-12): The catalyst solution was prepared from a mixture of $[(COD)RhCl]_2$ (6.2 mg, 1.3 ×10^{-2} mmol) and (–)-DIOP (20.8 mg, 3.8 ×10^{-2} mmol) and the solvent indicated in the table (2.0 mL). After the solution was stirred at room temperature for 20 min, a mixture of styrene (29 μL, 0.25 mmol)) and $BrCCl_3$ (49 μL, 0.50 mmol) dissolved in the same solvent as that used for the catalyst solution was added. The mixture was stirred for the reaction time at the temperature indicated in the table. After removal of the solvent *in vacuo*, chromatographic purification (silica gel, eluted by hexane) gave **1**.

The experiment shown in entry 9 in the table was aimed at comparing the result of *condition A* with that of *condition B*. Thus, amounts of the catalyst and the reactants were the same as those of *condition B*, whereas the catalyst solution was prepared in toluene (0.83 mL), to which the reactants dissolved in EtOH (1.67 mL) were added.

The reactions of styrene with $BrCCl_3$ catalyzed by RhCl [(–)-DIOP] species on water (Table 3).

In general, a mixture of $[(COD)RhCl]_2$, (–)-DIOP, and styrene was stirred in a 20 mL Schlenk tube until the solid was fully dissolved and color of the solution changed from pale yellow to orange. Water was degassed by argon bubbling just prior to use. To the resulting organic solution was added the degassed water (2.5 mL), and the two layered mixture was vigorously stirred (1,500 ppm) at the temperature described in the table. $BrCCl_3$ was added dropwise. The solution was stirred at the temperature and time described in Table 3. After the reaction, the organic layer was extracted with hexane (10 mL ×3) and concentrated under a reduced pressure. Chromatographic purification (silica gel, eluted by hexane) gave **1**. The following two conditions were examined.

Condition A': The catalyst solution was prepared from $[(COD)RhCl]_2$ (4.1 mg, 8.3×10^{-3} mmol) and (–)-DIOP (9.1 mg, 1.8×10^{-2} mmol), to which styrene (0.57 mL, 5.0 mmol) and $BrCCl_3$ (123 μL, 1.25 mmol) were added.

Condition B': The catalyst solution was prepared from $[(COD)RhCl]_2$ (6.2 mg, 1.3×10^{-2} mmol) and (–)-DIOP (20.8 mg, 3.8×10^{-2} mmol), to which styrene (29 μL) and $BrCCl_3$ (49 μL, 0.5 mmol) was added.

Instead of water, brine (21 wt% of NaCl) was used, for the experiment shown in entry 7, whereas a 1:2 mixture of MeOH and water was used for that shown in entry 6.

The reactions of styrene with $BrCCl_3$ catalyzed by $FeCl_2$[(–)-DIOP] species in organic solvents (Table 4, entries 1-6). In general, $FeCl_2$ (2.1 mg, 1.7×10^{-2} mmol) and (–)-DIOP (9.1 mg, 1.9×10^{-2} mmol) were dissolved in a solvent (toluene for entry 1, CH_2Cl_2 for entry 2-6; 0.5 mL). After stirring for 1 h, a solution of styrene and $BrCCl_3$ in CH_2Cl_2 (0.5 or 0.25 mL) was added dropwise. The solution was stirred at the temperature and time described in the table. After the reaction, the solution was concentrated under a reduced pressure. Chromatographic purification (silica gel, eluted by hexane) gave **1**. The amounts of styrene and $BrCCl_3$ were 0.57 mL (5 mmol) and 0.12 mL (1.25 mmol) (*condition C*), whereas 28.6 μL (0.25 mmol) and 49.1 μL (0.5 mL) (*condition D*), respectively. In the experiment shown in entry 6, isolated $FeCl_2$[(–)-DIOP] (10.1 mg, 1.7×10^{-2} mmol) was used. This was independently prepared from a 1:1 mixture of $FeCl_2$ (2.1 mg, 1.7×10^{-2} mmol) and (–)-DIOP in CH_2Cl_2, isolated as a white solid after removal of the solvent *in vacuo*, and used for the Kharasch addition without further purification.

The reactions of styrene with $BrCCl_3$ catalyzed by $FeCl_2$[(–)-DIOP] species on water (Table 4, entries 7-11).

A mixture of $FeCl_2$ (2.1 mg, 1.7×10^{-2} mmol), (–)-DIOP (9.1 mg, 1.9×10^{-2} mmol), and styrene was stirred at room temperature for 1 h. Water degassed by argon bubbling (2.5 mL) was added, and the mixture was stirred vigorously (1,500 rpm). $BrCCl_3$ was added, and the mixture was stirred for the reaction time at the temperature described in the table. After the reaction, the reaction mixture was extracted with hexane (10 mL ×3), and the organic layer separated was concentrated under a reduced pressure. Chromatographic purification (silica gel, eluted by hexane) gave **1**. Two conditions were examined: *Condition C'*: styrene (5.0 mmol) and $BrCCl_3$(1.25 mmol). *Condition D'*; styrene (1.25mmol) and $BrCCl_3$(2.5 mmol). The isolated $FeCl_2$[(–)-DIOP] (10.1 mg, 1.7×10^{-2} mmol) was used as the catalyst for the experiment shown in entry 11.

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