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Chemoselective Conjugate Reduction of α,β-Unsaturated Ketones Catalyzed by Rhodium Amido Complexes in Aqueous Media

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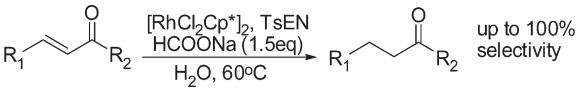

Although a notable feature of Noyori's Ru−TsDPEN complex is that the transfer hydrogenation reaction is highly chemoselective for the C═O functional group and tolerant of alkenes, our early report indicated that the chemoselectivity could be switched from C═O to C═C bonds in the transfer hydrogenation of activated α,β-unsaturated ketones. Now we have found that a variety of α,β-unsaturated ketones, even without other electron-withdrawing functional groups, could be reduced on the alkenic double bonds with high selectivities employing amido-rhodium hydride complex in aqueous media, and up to 100% chemoselectivity has been achieved. It is notable that the chemoselectivity was improved significantly on going from organic solvent to water. Moreover, a 1,4-addition mechanism has been proposed on the basis of the corresponding experimental details and computational analysis.

Introduction

Transfer hydrogenation (TH) is attractive as an alternative to hydrogenation because it requires neither the hazardous hydrogen gas nor pressure vessels and is easy to execute.[1] Noyori and Ikariya have achieved highly enantioselective transfer hydrogenation of ketones and imines by using chiral TsDPEN−Ru(II)[2] (TsDPEN = *N*-(*p*-toluenesulfonyl)-1,2-diphenylethylenediamine) catalysts and proposed a concerted mechanism of hydrogen transfer involving metal-to-ligand "bifunctional" hydrogen activation.[3,4] *Also, another notable feature of these catalysts is that the transfer hydrogenation reaction is highly chemoselective for the C═O functional group and tolerant of alkenes.*[2b,4d] Excellent results have been obtained in the kinetic resolution of allylic alcohols using acetone as hydrogen acceptor.[5] Moreover, α-acetylenic ketones were also selectively reduced to give chiral propargylic alcohols in excellent enantioselectivities.[6] In addition, Xiao[7a] and Li[7b] recently disclosed that α,β-unsaturated aldehydes could be chemoselectively reduced to allylic alcohols in the presence of an Ir−CF_3TsEN catalytic system. On the other hand, in our continuous study on transfer hydrogenation reactions catalyzed by the structure-modified monosulfonylated diamine−Ru(II)

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complexes,[8] we were pleased to find that the chemoselectivity could be completely switched from C=O to C=C bonds through further polarization of the olefins, and high enantioselectivity (up to 89% ee) was obtained in the asymmetric transfer hydrogenation of prochiral α,α-dicyanoolefins.[9]

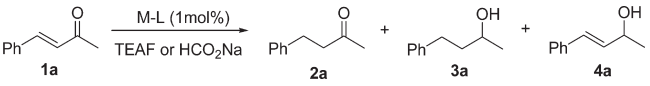
Chemoselective reduction of α,β-unsaturated carbonyl compounds has been widely studied, and the selective reduction of the carbonyl group of α,β-unsaturated ketones to allylic alcohols has been achieved with relative ease.[10] In contrast, the catalytic transfer hydrogenation of the alkenic double bonds of conjugated enones, especially using environmentally benign hydride source and solvent, is limited.[11] The conjugate reduction of enones has been performed by use of ruthenium,[12] rhodium,[13] and iridium[14] complexes as catalyst in transfer hydrogenation manner, and the ligands adopted included phosphine,[12,13a−f,14a,b] carbene,[13h,i] Phebox (Phebox = bis(2-oxazolinyl)phenyl),[13j] and bipyridine.[14c] To the best of our knowledge, the conjugate reduction catalyzed by the corresponding metals containing amine ligands[10b−f] has not been investigated. Herein, we would like to report the highly chemoselective transfer hydrogenation of α,β-unsaturated ketones catalyzed by Rh−diamine complex employing HCO_2Na as hydride source. It was notable that the chemoselectivity could dramatically switch from C=O to C=C bonds when the reaction was conducted in aqueous media.

Results and Discussion

Table 1 shows the representative results for the transfer hydrogenation of benzylideneacetone **1a** catalyzed by various monosulfonylated diamine complexes in organic solvent and aqueous phase. Initial studies were carried out in DCM at 28 °C using the azeotrope of formic acid and triethylamine (5:2) (TEAF) as hydrogen source. The precatalyst was generated by *in situ* treatment monosulfonylated diamine with metal precursor in degassed MeOH for 1 h in the presence of 2 equiv of Et_3N (triethylamine) when refluxing. Similar to the previous example catalyzed by monosulfonylated diamine−Ru(II) complex,[15] the model substrate **1a** was reduced via 1,4-reduction and 1,2-reduction pathways at the same time and afforded the 1,4-adduct **2a** (4-phenylbutan-2-one), 1,2-adduct **4a** ((*E*)-4-phenylbut-3-en-2-ol), and alcohol **3a** (4-phenylbutan-2-ol) with both C=C and C=O double bonds reduced (Table 1, entries 1−8). The monosulfonylated diamine ligand TsEN (TsEN = *N*-(*p*-toluenesulfonyl)-1,2-ethylenediamine) had an obvious effect on the chemoselectivity, furnishing the desired 1,4-adducts **2a** and **3a** in 56% selectivity and 40% total conversion after 12 h (entry 3). The chemoselectivity could slightly increase after prolonged time, and the ratio of 1,4-reduction reached up to 64% (entry 4). In order to further improve the chemoselectivity, we investigated other metal precursor (Figure 1), $[RhCl_2Cp^*]_2$ ($Cp^* = C_5Me_5$) and $[IrCl_2Cp^*]_2$, and found that better selectivity could be obtained in the presence of $[RhCl_2Cp^*]_2$ with TsEN in DCM (entries 5−8). To our surprise, the conversion could not be improved for a prolonged period of time (85 h) (entries 5 vs 6 and entries 7 vs 8).

Water is a desirable solvent for chemical reactions for reasons of cost, safety, and environmental concerns.[16]

TABLE 1. Catalytic Effect of Metal Precursors and *N*-Sulfonylated Diamine Ligands



entry	metal	ligand	time (h)	conv (%)[b]	selectivity (%)[b] (**2a**:**3a**):**4a**
1[a]	**5a**	**6a**	12	48	19 (16:3):81
2[a]	**5a**	**6b**	12	33	34 (31:3):66
3[a]	**5a**	**6c**	12	40	56 (50:6):44
4[a]	**5a**	**6c**	85	92	64 (40:24):36
5[a]	**5b**	**6c**	12	17	87 (84:3):13
6[a]	**5b**	**6c**	85	21	87 (85:2):13
7[a]	**5c**	**6c**	12	17	73 (71:2):27
8[a]	**5c**	**6c**	85	27	87 (84:3):13
9[c]	**5a**	**6c**	0.5	95	63 (3:60):37
10[c]	**5c**	**6c**	0.5	91	95 (83:12):5
11[c]	**5b**	**6c**	0.5	98	98 (42:56):2
12[c]	**5b**	**6a**	0.5	91	79 (45:34):21
13[c]	**5b**	**6b**	0.5	98	92 (11:81):8
14[c]	**5b**	**6d**	0.5	36	96 (95:1):4
15[c]	**5b**	**6e**	0.5	9	94 (93:1):6

[a]The reaction was performed with 0.5 mmol of **1a** and 0.2 mL of TEAF in 1 mL of DCM under argon atmosphere at 28 °C. [b]Determined by GC. [c]The reaction was performed with 0.5 mmol of **1a** and 7.5 equiv of HCO_2Na in 1 mL of degassed water under argon atmosphere at 60 °C

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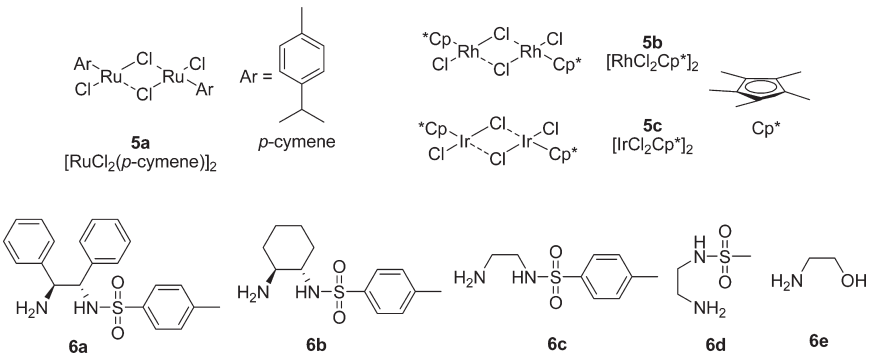


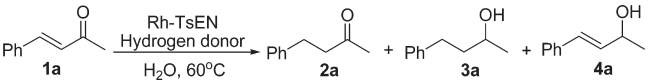
FIGURE 1. Corresponding metal precursors and diamine ligands.

However, the disadvantage often associated with catalysis in water is the decrease in catalytic activity and/or selectivity on going from organic solvents to water. The low solubility of organic molecules in water has been harnessed to design hydrophobicity-directed organic synthesis and catalysis, furnishing reaction rates and selectivities superior to those in organic media.[16i] Our group has fortunately found that the asymmetric transfer hydrogenation proceeded even more effectively in terms of selectivity in water than in organic solvent in some cases.[17] Xiao's group has reported that the asymmetric transfer hydrogenation of aromatic ketones could be remarkably accelerated in aqueous media even employing unmodified amine ligand in 2004.[18]

On the basis of these observations, we subsequently conducted the transfer hydrogenation of benzylideneacetone **1a** with sodium formate (HCO_2Na) in neat water and gratifyingly found that the selectivity and reactivity indeed increased remarkably (entries 9−15). The precatalyst was generated by mixing simply the precursor complex with the ligand in water at 40 °C for 1 h. In accordance with the observation made in organic solvent, the Rh and Ir catalyst proved to be much more selective than Ru catalyst in aqueous phase, and the Rh catalyst again displayed the highest selectivity (entries 9−11). The model substrate **1a** was smoothly consumed just in 30 min (98% conversion) and attained the 1,4-adducts **2a** and **3a** in 98% selectivity when employing TsEN **6c** as ligand (entry 11). The diamine ligands, (*S*,*S*)-Ts-DPEN **6a** and (*S*,*S*)-Ts-DACH (DACH = diaminocyclohexane) **6b**, proved to be less effective than **6c** (entry 11 vs entries 12 and 13). However, methylsulfony diamine **6d** exhibited poor catalytic activity (entry 14). Although amino alcohol **6e** was introduced,[19] the reaction was sluggish and only 9% benzylideneacetone **1a** was converted after 0.5 h (entry 15).

Apparently the expected ketone **2a** may undertake a further reduction of the carbonyl group and generate the saturated alcohol **3a** in the presence of a large excess hydrogen source.

TABLE 2. Chemoselective Reduction of α,β-Unsaturated Ketone in Aqueous Media[a]



entry	S/C	hydrogen donor (equiv)	time (min)	conv (%)[b]	selectivity (%)[b] (**2a**:**3a**):**4a**
1	100	HCO_2Na (7.5)	10	99	97 (78:19):3
2	100	HCO_2Na (1.5)	10	95	96 (90:6):4
3	200	HCO_2Na (1.5)	20	98	97 (91:6):3
4	200	HCO_2Na (1.0)	40	92	97 (94:3):3
5	500	HCO_2Na (1.5)	60	98	98 (92:6):2
6[c]	200	HCO_2Na (1.5)	90	99	96 (75:21):4

[a]Unless otherwise noted, the reaction was performed in 1 mL of degassed water under an argon atmosphere at 60 °C. [b]Determined by GC. [c]Performed at 28 °C.

Thus, the transfer hydrogenation of the model substrate **1a** with 1.5 equiv of HCO_2Na was carried out (Table 2). We were pleased to find that the ratio of **2a** to **3a** could remarkably improve and the saturated ketone was obtained in 90% selectivity (entry 2 vs entry 1). An increase of the substrate/catalyst (S/C) ratio to 200 caused a slight decrease in the reactivity and the ratio of **2a** to **3a** almost remained unchanged (entry 3). In addition, using 1 equiv of HCO_2Na at this condition led to poorer conversion (entry 4). Further increase of the S/C ratio to 500 resulted in increase of the ratio of **2a** to 92% in 98% total conversion, and at the same time the transfer hydrogenation remained high reactivity and the model substrate **1a** was consumed within 1 h (entry 5). However, when the S/C ratio was increased to 1000, the reduction proceeded very slowly. The effects of other hydrogen sources were also studied and showed no obvious improvement of the selectivity (see Supporting Information). When the reduction was performed at lower temperature (28 °C), benzylideneacetone **1a** was completely consumed after 90 min and poor chemoselectivity of **2a** was observed (entry 6).

It has been reported that aqueous-phase asymmetric transfer hydrogenation of aromatic ketones by formic acid with the Ru−TsDPEN catalyst was modulated by the pH value of the aqueous phase.[20] By controlling the pH value, much faster rates and higher turnover numbers in conjunction with excellent ee values could be delivered. On the other hand, Frost[12e] and Himeda[14c] have reported that the

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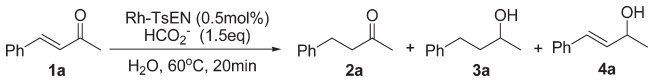
TABLE 3. Catalytic Effect of pH on the Transfer Hydrogenation of Benzylideneacetone 1a[a]



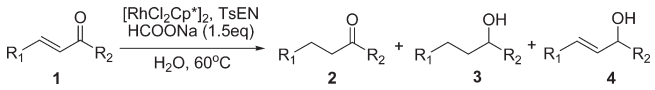
entry	pH (NaOH:HCO_2Na or HCO_2H: HCO_2Na)	conv (%)[b]	selectivity (%)[b] (**2a**:**3a**):**4a**
1	12.71 (1:3)	4	99 (99:0):1
2	11.70 (1:15)	64	97 (96:1):3
3	11.17 (1:30)	99	97 (80:17):3
4	7.86	98	97 (91:6):3
5	4.80 (1:30)	99	97 (88:9):3
6	4.15 (1:6)	94	96 (90:6):4
7	3.41 (2:3)	4	86 (84:2):14
8	3.05 (2:1)	2	86 (84:2):14
9	1.70 (1:0)	<1	ND

[a]The reaction was performed with 1 mmol of **1a** and 1.5 equiv of hydrogen donor in 1 mL of degassed water under argon atmosphere at 60 °C for 20 min. [b]Determined by GC.

chemoselectivity of transfer hydrogenation of α,β-unsaturated carbonyl compounds is pH-dependent. Inspired by these findings, the effects of pH values on the chemoselective reduction of benzylideneacetone **1a** were investigated. We kept the concentration of $HCOO^-$ constant and varied the pH values by adjusting the ratio of $NaOH/HCO_2Na$ under basic conditions and the ratio of HCO_2H/HCO_2Na under acidic conditions. As described in Table 3, the initial reduction was sluggish at both high pH values (> 11.70) (entry 1) and low pH values (< 4.15) (entries 7−9). The pH window for optimal reactivity was relative broad (entries 2−6), and this was somehow in contrast with the observation made with Rh−TsDPEN in the asymmetric transfer hydrogenation of aromatic ketones.[21] The reduction performed at nearly neutral condition proceeded in the most chemoselective manner (entry 4).

With the optimal reaction conditions in hand, the scope and limitation of the chemoselective conjugate reduction were explored. A range of α,β-unsaturated ketones, which bore various substituents on the terminal double bond and the carbonyl group, were reduced in the presence of Rh−TsEN at 60 °C with 1.5 equiv of HCO_2Na. As summarized in Table 4, α,β-unsaturated enones **1b** and **1c** with bulkier substituents at the α-positions of the C=O proceeded smoothly to afford the 1,4-adducts in excellent selectivities (up to 99%) and high conversions (> 99% and 98%) (Table 4, entries 2 and 3). The enone **1d** with the bulkiest *tert*-butyl group afforded the 1,4-adduct **2d** in 94% isolated yield and no other adducts were detected (entry 4). The steric reason on the aromatic ring had a significant influence on the reactivity. When we introduced a substituent on the *ortho* position of the arene ring, the reduction had to be conducted at a lower S/C ratio (entries 6 and 7 vs entries 5, 8, and 9), and gratifyingly the selectivity just slightly decreased. On the other hand, the reduction occurred smoothly regardless of the electronic properties of the terminal arene ring, and both **1j** and **1k** gave the 1,4-adducts in high selectivities (99%), although **1k** displayed higher reactivity (entry 10 vs 11). It was interesting that the chlorine on the arene ring was tolerated under this catalytic system, which should be reduced in the presence of Pd/C catalytic system under hydrogen gas (entries 7−9). Similarly, the substrates **1l** and **1m** with heteroatoms in the arene rings underwent smooth reaction as well and furnished the 1,4-adducts in 94% and 93% selectivity, respectively (entries 12 and 13). Moreover, **1n**, bearing a bulky naphenthyl group on the β-position

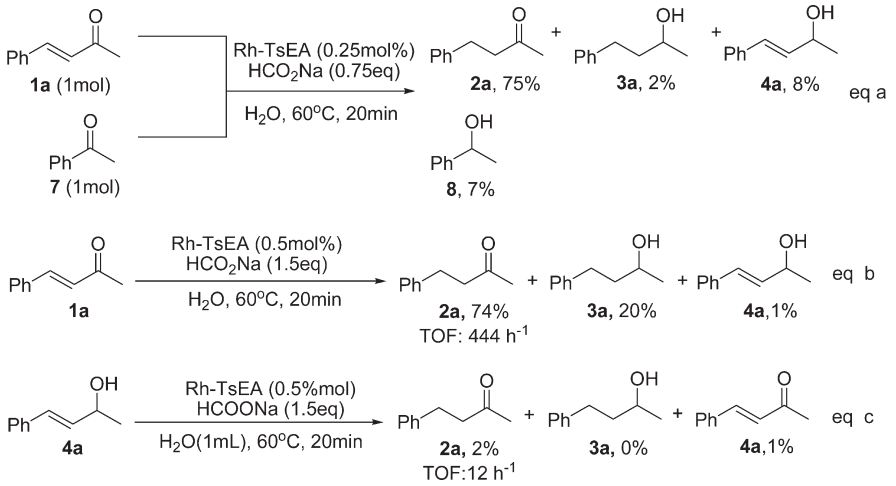
TABLE 4. Chemoselective Conjugate Reduction of α,β-Unsaturated Ketones[a]



entry	R_1	R_2	**1**	S/C	time (h)	conv (%)[b]	selectivity (%)[b] (**2**:**3**):**4**
1	Ph	Me	**1a**	500	1.5	97	98 (95:3):2
2	Ph	Et	**1b**	500	2	> 99	99 (94:5):1
3	Ph	*i*-Pr	**1c**	500	2	98	99 (99:0):1
4	Ph	*t*-Bu	**1d**	500	1.5	94[c]	100 (100:0):0[d]
5	*p*-Me-C_6H_4	Me	**1e**	500	7	97	97 (91:6):3
6	*o*-Me-C_6H_4	Me	**1f**	300	5	97	93 (81:12):7
7	*o*-Cl-C_6H_4	Me	**1g**	300	5	> 99	95 (87:8):5
8	*m*-Cl-C_6H_4	Me	**1h**	500	10	98	97 (93:4):3
9	*p*-Cl-C_6H_4	Me	**1i**	500	7	> 99	98 (92:6):2
10	*p*-MeO-C_6H_4	Me	**1j**	500	7	> 99	99 (79:20):1
11	*p*-F-C_6H_4	Me	**1k**	500	2	> 99	99 (88:11):1
12	thiophenyl	Me	**1l**	300	30	96	94 (84:10):6
13	furanyl	Me	**1m**	200	10	95	93 (84:9):7
14	α-naphenthyl	Me	**1n**	150	5	97	94 (84:10):6
15	-C_3H_6-		**1o**	500	2	94	97 (60:37):3
16	-C_2H_4-		**1p**	500	1	99	99 (86:13):1
17	-C_4H_8-		**1q**	500	5	82	95 (90:5):5
18	*n*-Pr	Me	**1r**	200	1	> 99	98 (93:5):2
19[f]			**1s**	100	10	98[e]	94 (75:19):6[e]
20[g]			**1t**	100	38	89[e]	97 (90:7):3[e]

[a]TsEN and Rh precursor were initially heated in H_2O at 40 °C for 1 h. Unless otherwise noted, the reaction was performed with 1.5 equiv of HCO_2Na in 1 mL of degassed water under an argon atmosphere at 60 °C. [b]Determined by ^1H NMR analysis in the presence of 4-$NO_2C_6H_4CHO$ as internal standard. [c]Isolated yield of the conjugate adduct **2d**. [d]With 30 equiv of HCO_2Na as hydride source. [e]Determined by GC. [f]With 30 equiv of HCO_2Na as hydride source and 1 equiv ofNaOH as additive.

SCHEME 1



of the olefin, was tolerated to exhibit 94% selectivity with a S/C ratio of 150:1 after 5 h (entry 14). Furthermore, the rhodium−diamine complex also displayed high catalytic activity in the reduction of cyclic enones (entries 15−17). Reaction of **1o**−**q** occurred smoothly to furnish the 1,4-adducts with excellent selectivities (95−99%). Moreover, the reduction of alkyl ketone **1r** proceeded smoothly, and only 2% 1,2-adduct was detected by ^{1}H NMR analysis (entry 18). Noticeably, **1s** and **1t** (Figure 2), the α-methyl and the β-methyl analogues of **1a**, were reduced in high chemoselectivities (94% and 97%) and displayed lower reactivity partially owing to the electron-donating effect of methyl group. The α-methyl benzylideneacetone **1s** was reduced by increased S/C ratio (S/C = 100) with excess HCO_2Na, and the β,β-disubstituted enone **1t** was also hydrogenated by prolonged time (38 h) with NaOH as additive in high conversion (entries 19 and 20).

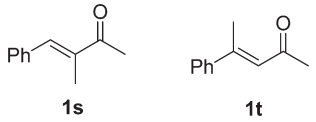


FIGURE 2. Trisubstituted α,β-unsaturated ketones.

All experimental details mentioned above have clearly demonstrated that the reduction of alkenic double bonds proceeded preferentially over reduction of carbonyl groups. Also the competitive experiment that the same equivalents of **1a** and acetophenone (**7**) were added to the solution of precatalyst prepared *in situ* (Scheme 1, eq a) was performed. The ^{1}H NMR analysis clearly demonstrated that **1a** was mainly reduced to saturated ketone **2a** and **7** remained almost untouched. It was reported that the allylic alcohol also could be isomerized to saturated ketone.[22] Thus, the generation pathway of the corresponding adduct **2a** was subsequently studied (Scheme 1). Under the same conditions, the TOF (TOF = turnover frequency) value of transfer hydrogenation of α,β-unsaturated ketone **1a** to 1,4-adduct **2a** (eq b, TOF = 444 h^{-1}) was far higher than isomerization of **4a** to **2a** (eq c, TOF = 12 h^{-1}). It thus indicated that the ketone **2a** was mainly obtained from the direct reduction of enone.

Noyori[3a] and Casey[3f] have noticed that the dehydrogenation of isopropanol to give acetone by metal complex is the rate-determining step for asymmetric transfer hydrogenation when isopropanol is the hydrogen donor. Xiao compared the activation enthalpy for the individual decarboxylation reaction of the formate in [D_8]THF measured by Ikariya[3g] with that of the whole asymmetric transfer hydrogenation of **7** (18.2 vs 12.8 kcal/mol) in DMF/H_2O mixture.[23] The results suggested that the activation barrier of decarboxylation of the ruthenium to form an intermediate is significantly reduced when the reaction is carried out in water. Furthermore, the results of kinetic isotope effects indicated that the hydrogen transfer to **7** was the rate-determining step in the aqueous-phase transfer hydrogenation. Thus, the relative activation barriers of the transition states of the reduction of C=O and the reduction of C=C double bond should suggest the chemoselectivity.

To elucidate the mechanism of the chemoselective reduction of α,β-unsaturated ketone, we did DFT calculations (see Supporting Information for the details). All of the calculations have been carried out using Gaussian03 program packages[24] with B3LYP hybrid density functional.[25] The LANL2DZ basis set[26] was used for Rh atom, and the 6-31 g* basis set was used for other atoms. The Cp* ligand was replaced by Cp (C_5H_5) in the calculation, and the diamine ligand TsEN was simplified to $NH_2CH_2CH_2NH$, which has been proved to be efficient for the mechanism calculations of ATH by diamine−Ru complex.[3d,23]

It has been proved that the transfer hydrogenation for C=O, when the ligand contains at least one metal-coordinated sp^3 NH proton atom, proceeds via a concerted mechanism where a metal-hydride and a NH proton are transferred simultaneously from the catalyst to the C=O

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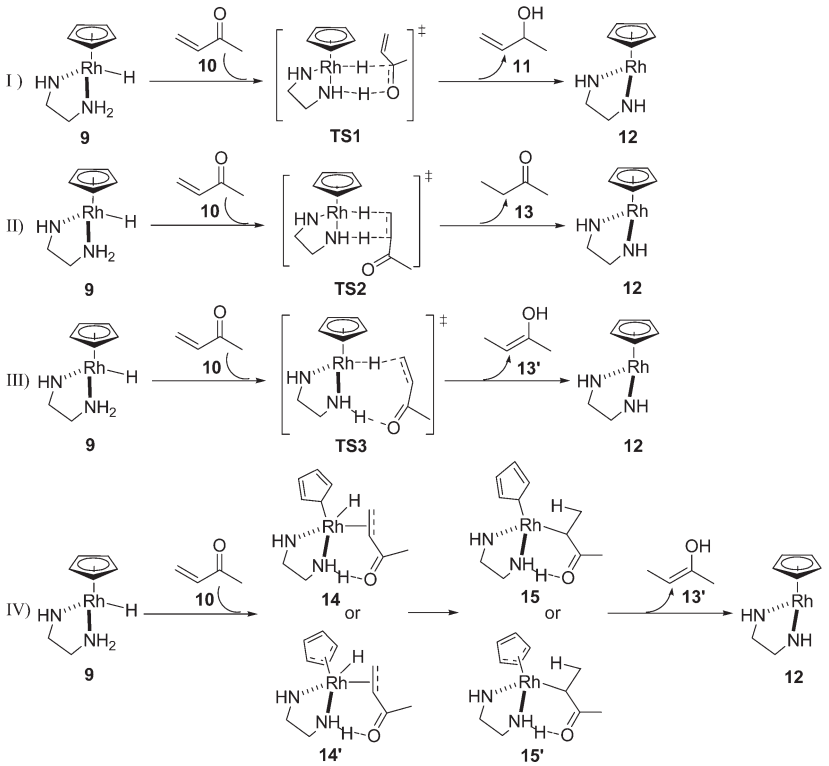
SCHEME 2. Plausible Reaction Pathways



bond.[3] Noyori and co-workers have compared the energies of the transition states (TSs) of the reduction of C=X (X = NH, CH_2, O) via six-membered concerted mechanism by Ru-complex.[3d] It was concluded that the reactivity of the unsaturated substrates reflects the extent of the polarity of double bond. Thus, we initially proposed two mechanisms (Scheme 2): (i) the classic six-membered concerted mechanism for the transfer hydrogenation of the C=O group (via **TS1**) and (ii) the same concerted transfer of the proton of the amine ligand and the metal-coordinated hydride to the C=C double bond (via **TS2**).[3d]

Figure 3 shows the computed energy profiles of the different reaction pathways, and the relative Gibbs free energies (ΔG_{298K}) is also provided for reference. The calculations indicate that the potential energy barrier via **TS2** is 7.3 kcal/mol higher than that of the **TS1** (Figure 3). That means the six-membered concerted mechanism of reduction of C=C double bond is not a favorable pathway, and this is contrary to the experimental results. Thus, there must be another pathway to obtain the saturated ketones by chemoselective reduction of the C=C double bond.

Recently, Ikariya has studied the mechanism of asymmetric Michael addition of malonates to cyclic enones catalyzed by chiral ruthenium amido complex in the details and proposed a "outer-sphere" pathway[27] similar to Noyori's concerted mechanism.[3] Additionally, although the migratory insertion mechanism has been proved unfavorable for the TH of C=O group catalyzed by diamine−Ru[3d] or amino alcohol−Ru complexes,[28] the TH of C=C double bond catalyzed by diamine−Rh complex has not been calculated before. Thus, two further plausible pathways are concluded (Scheme 2): (iii) 1,4-addition mechanism, and (iv) migratory insertion of the C=C double bond into the metal-hydride bond. In the migratory insertion pathway, the transfer hydrogenation reaction includes a slippage of the Cp ligand from η^5 to η^1 or η^3, allowing the formation of an insertion of the C=C double bond into the metal-hydride bond. Similarly, the enol that formed via the both pathways can easily be isomerized to ketone in the solvent.

The calculated results are showed in Figure 3. Actually, the reduction of C=C double bond via 1,4-addition pathway is a stepwise process with the transfer of hydride between Rh and the β-carbon atom initially (the concerted **TS** can not be located in the calculations), and the energy barrier (**TS3**) is 6.6 kcal/mol. After NH proton transfer between N and O atoms (**TS4**, ΔE = 0.2 kcal/mol), the intermediate **18** can easily form the enol complex **19**. Thus, this path can explain the chemoselectivity for the lower energy barrier compared to the pathway of reduction of ketone (ΔE = 21.1 kcal/mol). In the migratory insertion pathway, the energy barrier of slippage of the Cp ligand from η^5 to η^1 (**TS5**)[29] is 11.1 kcal/mol, which is 4.5 kcal/mol higher than the energy barrier via **TS3**. Then the C=C double bond and Rh-cation forms the π complex **14** and after intramolecular hydride transfer reaction via **TS6** (ΔE = 6.2 kcal/mol) gives Rh alkane complex **15**. The intermediate **15** is a formal 14-electron complex, which contains an α-H···Rh agnostic interaction. The transformation of 14-electron complex **15** to 18-electron complex **20** is exothermic, ΔE = −13.0 kcal/mol, and any TS could not be detected by

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(29) The Cp ligand could potentially form a η^3 complex. All attempts to locate such species by using DFT method resulted, however, in the formation of the less strained η^1-coordinated complex.

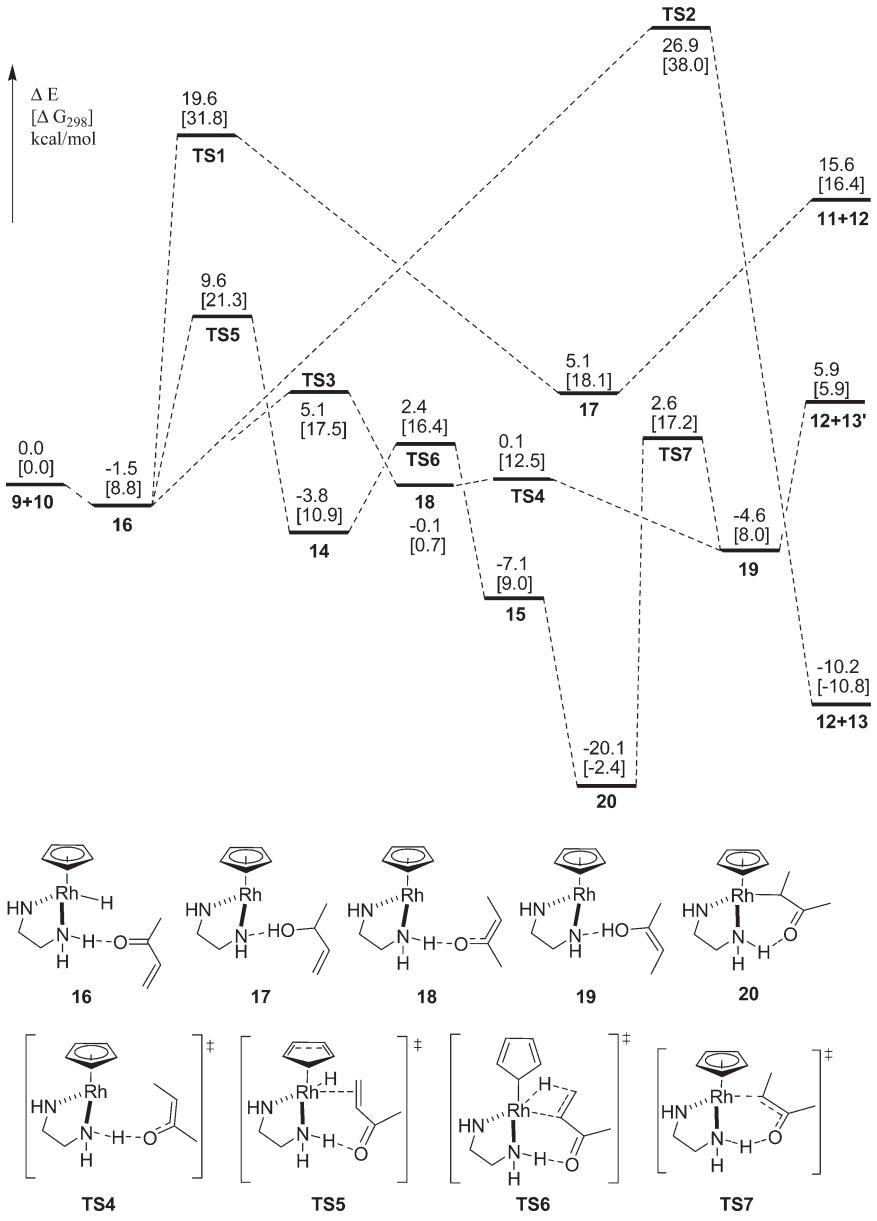
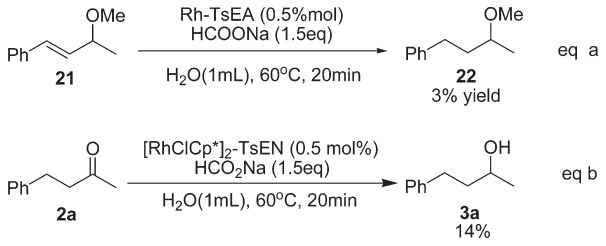


FIGURE 3. Energy profile of the transfer hydrogenation of α,β-unsaturated ketone by DFT.

the calculation. Finally, the NH proton transfer forms enol complex **19** via **TS7** (the energy barrier is 22.7 kcal/mol), which is also kinetically unfavorable compared to the 1,4-addition pathway. Hence, the calculations suggest that the 1,4-addition mechanism is preferred, while the migratory insertion pathway involves many discrete intermediates or unfavorable transitional state (TS). Furthermore, the activation barriers of one water hydrogen-bonding to the carbonyl oxygen of α,β-unsaturated ketones at the main TSs of the four pathways were also calculated because the reaction environment was in water,[23,30] and the results also showed that the 1,4-addition mechanism is preferred (see Figure S2 in Supporting Information).

On the basis of this consideration, we conducted the transfer hydrogenation of **21** under the same conditions. If the transfer hydrogenation proceeded mainly via migratory insertion pathway, it is reasonable to assume that **21** should be reduced to **22** smoothly. However, only a trace of **21** was converted into **22** after 20 min (Scheme 3, eq a). The result confirmed that the electron-withdrawing carbonyl group was crucial for this transformation and the 1,4-addition pathway is more favorable. Furthermore, it is also clarified that the saturated alcohol **3a** was mainly obtained by reduction of ketone **2a** (Scheme 3, eq b) and that both **2a** and **3a** are 1,4-reduction products.

SCHEME 3



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Conclusions

In conclusion, we have demonstrated that the chemoselectivity can be switched from C=O to C=C bonds in the transfer hydrogenation of α,β-unsaturated ketones, even without other electron-withdrawing functional groups,[9a] catalyzed by the amido-rhodium complex with sodium formate as hydride source in aqueous media. This methodology has been applied to a variety of α,β-unsaturated ketones, and 93−100% chemoselectivity has been achieved. It is notable that the chemoselectivity improved significantly on going from organic solvents to water for the reaction media. Moreover, a 1,4-addition mechanism has been proposed on the basis of the corresponding experimental details and computational analysis. Further research on fine-tuning the structure of the ligand and realizing the asymmetric conjugate reduction of branch α,β-unsaturated ketones is now well under way in our laboratory.

Experimental Section

General Procedure for Transfer Hydrogenation of α,β-Unsaturated Ketones. Diamine ligand TsEN (**6c**) (1.2 mg, 0.0055 mmol) and $[RhClCp^*]_2$ (1.6 mg, 0.0025 mmol) were stirred in degassed water (1 mL) at 40 °C for 1 h. Then the corresponding α,β-unsaturated ketone and 1.5 equiv of HCO_2Na were added in turn. The mixture was stirred at 60 °C for the corresponding time under argon. Then the solution was extracted with dichloromethane and dried over anhydrous Na_2SO_4, and the solvent was removed under vacuum. The conversion and ratio of the products were determined by ^1H NMR analysis adopting 4-nitrobenzaldehyde as internal standard or by GC analysis after removing the metal complex by flash chromatography.

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Supporting Information Available: Experimental procedures of synthesis of the ligands, α,β-unsaturated ketones and their derivatives; the coordinates and energies of the *ab initio* structures; complete ref 24. This material is available free of charge via the Internet at http://pubs.acs.org.