Selective Reduction of the Carbonyl Group in β,γ-Unsaturated α-Ketoesters by Transfer Hydrogenation with Ru-TsDPEN

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Received 25 November 2003

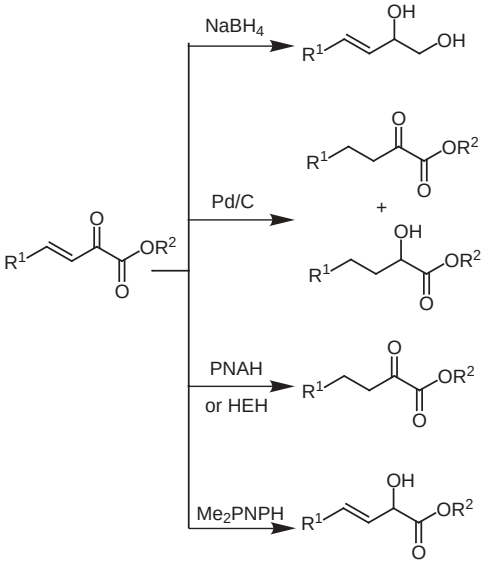
Abstract: A convenient and practical method for the selective reduction of C=O bond of a wide spectrum of α-keto β,γ-unsaturated esters via transfer hydrogenation reaction under the catalysis of Ru(*p*-cymene)(TsDPEN) (TsDPEN: monotosylated 1,2-diphenylethylene-1,2-diamine) was developed.

Key words: ruthenium, transfer hydrogenation, chemoselectivity, carbonyl, reduction

There have been some reports on the synthesis of α-hydroxy β,γ-unsaturated esters or acids,[1,2] however, many of these reports have been focused on the biosynthetic methods.[1] Chemical methods for the selective reduction of such kind of compounds have also been reported with limited success, all of which need stoichiometrically reductive reagents such as sodium amalgam,[2e,f] metal borohydride,[2a,b,g] or dihydropyridine[2c,d] as hydrogen donors.

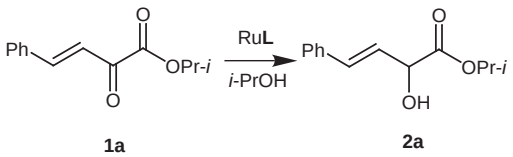
Selective reduction of the carbonyl group in an α-keto β,γ-unsaturated ester is somewhat difficult with the general methods, such as the reduction with sodium borohydride, because both the carbon-carbon double bond and the ester group could be reduced further. Some new reducing reagents and hydrogen donors that have different selectivity have been developed in recent years to realize the regioselective reduction of α-keto β,γ-unsaturated esters (Scheme 1).[1,2] However, regioselective reduction of the carbonyl group in an α-keto β,γ-unsaturated ester still remains a challenging topic. It is important to develop a practical catalytic method to reduce the carbonyl group of α-keto β,γ-unsaturated esters selectively to achieve α-hydroxy β,γ-unsaturated esters, which are important units in many bioactive compounds.[3]

Transition metal-catalyzed reaction has been widely applied in organic synthesis and the corresponding asymmetric hydrogenation or asymmetric transfer hydrogenation has been applied as an important tool for the reduction of unsaturated functionalities.[4] Noyori et al. have reported the Ru-diamine complex; it could be employed as catalyst in reducing the carbonyl group of an α,β-unsaturated ketone selectively,[4f,g] and this is one of the most exciting achievements in asymmetric reduction area. However, the catalytic chemoselective reduction of the carbonyl group of a β,γ-unsaturated α-ketoester has never been reported. Herein, we report our preliminary results with transition metal-catalyzed transfer hydrogenation reaction to solve the hard-bitten selectivity problem in the chemoselective reduction of α-keto β,γ-unsaturated esters.



Scheme 1 Selective reduction of α-keto β,γ-unsaturated esters

In the course of screening the catalysts, we have tried some monotosylated diamines such as monotosylated cyclohexane-1,2-diamine, monotosylated ethylenediamine, and some β-amino alcohols as ligands for the selective reduction of isopropyl 4-phenyl-2-oxo-3-butenoate (**1a**, Scheme 2).

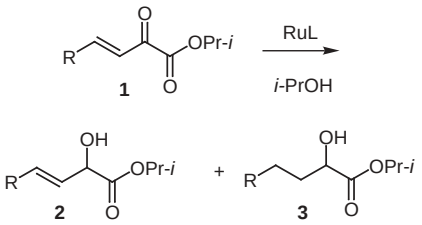


L: monotosylated 1,2-diamines or β-amino alcohols

Scheme 2 Ruthenium-catalyzed selective transfer hydrogenation reaction of α-keto β,γ-unsaturated esters

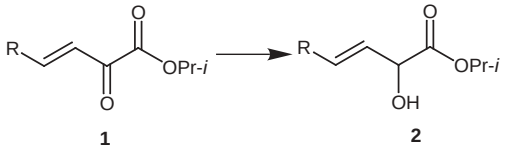
SYNLETT 2004, No. 4, pp 0741–0743
Advanced online publication: 10.02.2004
DOI: 10.1055/s-2004-817765; Art ID: U25603ST

A mixture of ketoester 0.5 mmol, $[RuCl_2(p\text{-cymene})]_2$ (2.1 mg, 0.005 mmol) and monotosylated 1,2-diamines or amino alcohols (0.01 mmol) as ligands in *i*-PrOH at 60 °C (5 mL) under argon atmosphere was monitored by TLC. After the starting material was consumed, the solvent was removed under reduced pressure and the residue was purified by flash chromatography to give the products.



Scheme 3 Ru-catalyzed transfer hydrogenation reaction of β,γ-unsaturated α-ketoesters with 1,2-diamines or amino alcohols as ligands

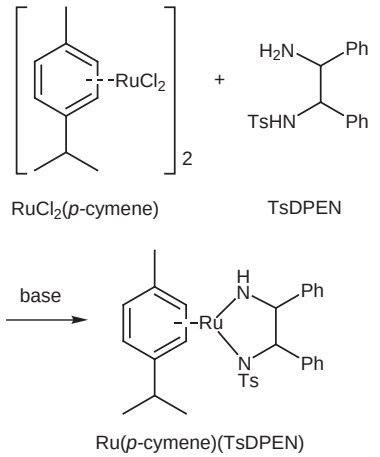
Table 1 Ru-TsDPEN Catalyzed Transfer Hydrogenation Reaction of β,γ-Unsaturated α-Ketoesters[a]



Entry	**1**, R	**2**, Yield (%)[b] [ee (%)][c]
1	Phenyl (**1a**)	**2a**, 94 (8)
2	*p*-$CF_3C_6H_4$ (**1b**)	**2b**, 95
3	*p*-$MeOC_6H_4$ (**1c**)	**2c**, 93
4	*p*-BrC_6H_4 (**1d**)	**2d**, 92 (6)
5	2, 4-Dichlorophenyl (**1e**)	**2e**, 91
6	(*E*)-PhCH=CH (**1f**)	**2f**, 99 (7)
7	2-Furanyl (**1g**)	**2g**, 99 (59)
8	2-Thiophenyl (**1h**)	**2h**, 95 (65)
9	Et_2CH (**1i**)	**2i** + **3i**, 99 (**2i**:**3i** = 4:1)

[a] All reactions were run with ketoester (0.5 mmol), Ru (*p*-cymene) (TsDPEN) (3 mg, 0.005 mmol) in *i*-PrOH (5 mL) at r.t. for 1 h under argon atmosphere.
[b] Isolated yields.
[c] Ee obtained when enatiopure (1*S*, 2*S*)-TsDPEN was employed as ligand.

In all these reactions, the catalysts for transfer hydrogenation were formed in situ with $[RuCl_2(p\text{-cymene})]_2$ and the ligands in the presence of at least 2 equivalents of base. However, under all these conditions, the reaction was very slow and we had to raise the temperature to 60 °C for the complete conversion of the starting materials. And the reaction usually resulted in the mixture of α-hydroxy β,γ-unsaturated esters **2** and undesired β,γ-saturated α-hydroxy esters **3** (Scheme 3). The undesired compound **3** could not be easily separated from the desired compound **2**; the low regioselectivity toward carbonyl group made this method impractical. Gratifyingly, when we employed TsDPEN (monotosylate of 1,2-diphenylethylene diamine) as ligand, we achieved very good reactivity and regioselectivity under room temperature, compound **3** is not detectable if the reaction time is well controlled.[6] In order to obtain repeatable results, we prepared the catalyst Ru(*p*-cymene)(TsDPEN) from $[RuCl_2(p\text{-cymene})]_2$ and TsDPEN and run the reaction in *i*-PrOH without extra base (Scheme 4).



Scheme 4 Preparation of the 16e catalyst Ru(*p*-cymene)(TsDPEN)

To expand the scope of the reaction substrates and study the effect of substituents on the reactions, we have synthesized different substrates[1a,5] with electron-withdrawing or electron-donating groups (**1a**–**e**) and substrates bearing a heterocycle or conjugated diene substituents (**1f**–**h**). All of these substrates could be transferred to the desired products under the catalysis of Ru(*p*-cymene)(TsDPEN) within one hour with high yields (Table 1). It is worthy of noting that, not only the substrates with electron-donating or electron-withdrawing groups could be efficiently reduced, the substrates with a coordinating heteroatom (**1g**,**h**) could also be selectively reduced with no detectable reactivity decrease. This provides a convenient and much mild method for the synthesis of α-hydroxy β,γ-unsaturated esters and the reaction yield is nearly quantitative. When we employed enantiopure (1*S*,2*S*)-TsDPEN as the ligand, the product was obtained with poor to moderate enantioselectivity (Table 1, entries, 1, 4, 6–8). However, if the substrate bears an alkyl substituent at γ-position, the selectivity decreases, over-reduction product **3i** reaches up to 25% (Table 1, entry 9) even if the reaction was well controlled (once the starting material consumed, the reaction was quedched with 1 N HCl).

In conclusion, we have found a convenient and practical method for the selective reduction of C=O bond of a wide spectrum of α-keto β,γ-unsaturated esters with Ru(*p*-cymene)(TsDPEN) as catalyst. The transition metal catalyzed transfer hydrogenation reaction with good

selectivity and high efficiency provides the possibilities to provide the optically active α-hydroxy β,γ-unsaturated esters with chiral catalysts.

A general procedure was as follows: A degassed Schlenk reaction tube was charged successively with the ketoester (0.5 mmol), *i*-PrOH (5 mL) under argon atmosphere. The reaction mixture was degassed for three times by the circulation of freeze-pump-thaw, then Ru(*p*-cymene)(TsDPEN) (3 mg, 0.005 mmol) was added under argon atmosphere. The reaction mixture was then stirred at argon atmosphere for about 1 h to effect a complete conversion of the substrate. The solvent was removed under reduced pressure and the residue was purified by flash chromatography to give the product.

Representative analytical data: Compound **2a:** ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.41–7.26 (m, 5 H), 6.82 (dd, *J* = 15.9, 1.5 Hz, 1 H), 6.24 (dd, *J* = 15.9, 5.7 Hz, 1 H), 5.13 (hept, *J* = 6.0 Hz, 1 H), 4.81–4.76 (m, 1 H), 3.13 (d, *J* = 5.7 Hz, 1 H), 1.32 (d, *J* = 6.0 Hz, 3 H), 1.28 (d, *J* = 6.0 Hz, 3 H). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 172.95, 136.30, 131.88, 128.55, 127.91, 126.63, 125.57, 71.25, 70.21, 21.73, 21.70. IR (KBr): 3451, 1729, 1201, 1106 cm^{-1}. MS: *m*/*z* (%) = 220 (2.88) [M^+]. HRMS: calcd for $C_{13}H_{16}O_3$: 220.1100; found: 220.1099. Compound **2h:** ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.16–7.15 (m, 1 H), 6.98–6.89 (m, 3 H), 6.08 (dd, *J* = 15.9, 5.4 Hz, 1 H), 5.17–5.04 (m, 1 H), 4.74–4.73 (m, 1 H), 3.34 (broad, 1 H), 1.29 (d, *J* = 6.0 Hz, 3 H), 1.26 (m, *J* = 6.3 Hz, 3 H). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 172.57, 141.18, 127.32, 126.31, 124.92, 124.90, 124.64, 70.87, 70.16, 21.63, 21.60. IR (KBr): 3465, 1731, 1271, 1105 cm^{-1}. MS: *m*/*z* (%) = 226 (17.91) [M^+]. HRMS: calcd for $C_{11}H_{14}O_3S$: 226.0664; found: 226.0667.

Acknowledgment

We thank the National Natural Science Foundation of China, Chinese Academy of Sciences and the Science and Technology Commission of Shanghai Municipality for financial support.

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(6) The reaction process can be monitored by TLC, GC or HPLC. The unsaturated ketoester are generally consumed within 1 h. Once the starting material was consumed, the reaction can be quenched with 1 N HCl. The double bond in the product will be slowly reduced at elevated temperature (80 °C) and prolonged reaction time (10–120 h). However, it is relatively stable at r.t. under the catalysis of Ru(*p*-cymene)(TsDPEN), no significant amount (<1%) of **3** was detected 5 h after the consumption of the starting material.