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Highly enantioselective Ru-catalyzed hydrogenation of β-keto esters using electron-donating bis(trialkylphosphine) ligand-TangPhos

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Abstract—Highly electron-donating bis(trialkylphosphine) TangPhos and its corresponding ruthenium complexes provided high enantioselectivities for the hydrogenation of β-keto esters. Up to 99.8% and 99.5% ee have been achieved in hydrogenation of β-alkyl and β-aryl substituted β-keto esters, respectively. Asymmetric hydrogenation of ethyl 4-chloro acetoacetate in 98.2% ee is also reported.

Chiral β-hydroxy esters are important building blocks for the synthesis of biological active compounds and natural products.[1] Catalytic asymmetric hydrogenation is one of the most practical and efficient methods to obtain such compounds.[2] Ru-BINAP [bis(triarylphosphine)] catalyst and many related systems have been demonstrated to be highly enantioselective for the asymmetric hydrogenation of β-alkyl substituted β-keto esters, albeit only moderate ee's for the hydrogenation of β-aryl substituted β-keto esters.[3] Compared with bis(triarylphosphine), electron-rich bis(trialkylphosphine) ligands are rarely used in the Ru-catalyzed systems. To the best of our knowledge, only a couple of chiral bis(trialklyphosphine), such as *i*-Pr-BPE[4] and BisP*,[5] has been utilized for the Ru-catalyzed hydrogenation of β-alkyl substituted β-keto esters with high enantioselectivities (Fig. 1). However, for hydrogenation of β-aryl substituted β-keto ester and methyl 4-chloro acetoacetate, only up to 89% ee and 76% ee were achieved with Ru-BisP* and Ru-*i*-Pr-BPE catalyst systems, respectively.

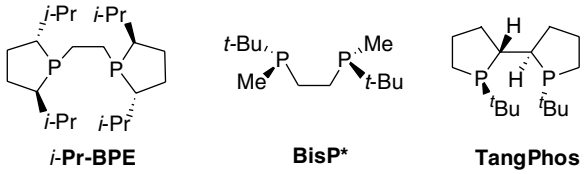

Figure 1. Structures of chiral bis(trialkylphosphine) ligands.

Recently, we have developed a conformational rigid, electron-donating bis(trialkylphosphine) TangPhos, which has been successfully applied in highly active and enantioselective Rh-catalyzed asymmetric hydrogenation of various substrates.[6] To further explore the utility of this highly electronic-rich bisphosphine ligand, we herein report Ru-TangPhos catalyzed asymmetric hydrogenation of β-keto esters. Extremely high enantioselectivities (up to 99.8% ee) have been achieved in hydrogenation of both β-alkyl and β-aryl substituted β-keto esters.

We initiated our studies by choosing methyl acetoacetate **1** as the model substrate of β-alkyl substituted β-keto ester to examine the efficacy of $RuCl_2$(TangPhos)$(DMF)_m$ (**A**)[7] and Ru(TangPhos)Br_2 (**B**).[8] Hydrogenation was conducted at 50 °C and under 5 atm of hydrogen pressure with 0.1 mol % catalyst. The reactions were completed in 10 h, and up to 99.5% and 99.8% ee were obtained with catalysts **A** and **B**, respectively (Table 1, entries 1 and 2). The results indicated that catalysts **A** and **B** have almost the same reactivity and enantioselectivity. We then applied the $RuCl_2$(TangPhos)$(DMF)_m$ (**A**) to hydrogenate a variety of β-alkyl substituted β-keto esters. As shown in Table 1, the steric hindrance of the ester groups has no influence on the enantioselectivities

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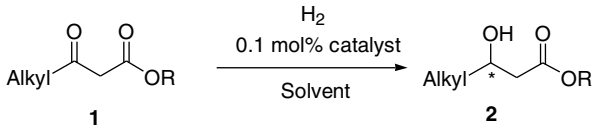
Table 1. Ru-TangPhos catalyzed asymmetric hydrogenation of β-alkyl substituted β-keto ester[a]



1 **2**

1a: Alkyl = Me, R = Me; **1b**: Alkyl = Me, R = Et; **1c**: Alkyl = Me, R = *i*-Pr;
1d: Alkyl = Me, R = *t*-Bu; **1e**: Alkyl = Et, R = Me; **1f**: Alkyl = *i*-Pr, R = Me;
1g: Alkyl = $ClCH_2$, R = Et;

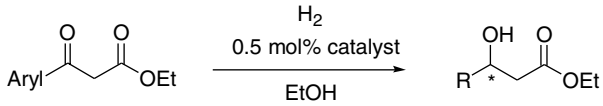
Entry	Catal.	Sub.	*T* (°C)	H_2 (atm)	ee (%)	Config.
1	**B**	**1a**	50	5	99.5	*R*
2	**A**	**1a**	50	5	99.8	*R*
3	**A**	**1b**	50	5	98.9	*R*
4	**A**	**1c**	50	5	98.7	*R*
5	**A**	**1d**	50	5	98.1	*R*
6	**A**	**1e**	50	5	98.8	*R*
7	**A**	**1f**	50	5	99.0	*S*
8[b]	**A**	**1g**	50	5	92.9	*S*
9[b]	**A**	**1g**	50	50	94.2	*S*
10[b]	**A**	**1g**	80	50	**98.1**	*S*
11[b]	**A**	**1g**	100	50	**98.2**	*S*

[a] Reactions were carried out in MeOH/H_2O (10/1) with 0.1 mol % Ru-TangPhos as a catalyst precursor for 10 h. All reactions were completed in full conversion except entry 8 (80% conversion). Enantiomeric excesses were determined by chiral GC.
[b] EtOH was used as the solvent.

(Table 1, entries 1–5), and excellent ee ranging from 98% to 99% were observed for all the selected substrates (Table 1, entries 1–7). It is noteworthy that these results are comparable to those obtained with the Ru-BINAP system.

To make the key intermediate for the synthesis of pharmaceutical products such as Lipitor, we have carried out the hydrogenation of ethyl 4-chloro acetoacetate (**1g**), containing a heteroatom at the γ-position of the β-keto ester (Table 1, entries 8–11). The ee values of the product were highly dependent on the reaction temperature: the enantioselectivity was increased remarkably from 92.9% to 98.1%, when the reaction temperature was elevated from 50 to 80 °C. Similar results have been observed when Ru-BINAP was used as a catalyst.[9] To the best of our knowledge, enantioselectivity achieved with the Ru-TangPhos catalyst for the hydrogenation

Table 2. Ru-TangPhos catalyzed asymmetric hydrogenation of β-aryl substituted β-keto ester[a]



3 **4**

3a: Aryl = Ph; **3b**: Aryl = *p*-Cl-Ph; **3c**: Aryl = *p*-Br-Phr;
3d: Aryl = *p*-Me-Ph; **3e**: Aryl = *o*-Me-Ph; **3f**: Aryl = *p*-MeO-Ph;
3g: Aryl = *o*-MeO-Ph.

Entry	Catal.	Sub.	*T* (°C)	H_2 (atm)	ee (%)	Config.
1	**A**	**3a**	50	5	90.1	*S*
2	**A**	**3a**	50	50	92.8	*S*
3	**A**	**3a**	80	5	92.6	*S*
4	**A**	**3a**	80	50	96.2	*S*
5	**A**	**3a**	100	50	93.2	*S*
6	**A**	**3b**	80	50	**99.5**	*S*
7	**B**	**3b**	80	50	**99.3**	*S*
8[b]	**A**	**3b**	80	50	**99.0**	*S*
9	**A**	**3c**	80	50	**99.5**	*S*
10	**A**	**3d**	80	50	94.2	*S*
11	**A**	**3e**	80	50	94.5	*S*
12	**A**	**3f**	80	50	97.5	*S*
13	**A**	**3g**	80	50	94.9	*S*

[a] Reactions were carried out in EtOH with 0.5 mol % Ru-TangPhos as catalyst precursor for 20 h with full conversion. Enantiomeric excesses were determined by chiral GC or HPLC.
[b] 0.1 mol % Ru-TangPhos was used as a catalyst precursor.

of this challenging substrate is one of the best results reported to date.

Although the Ru-BINAP system has been recognized as an efficient and general catalyst for hydrogenation of β-alkyl substituted β-keto esters, only inferior ee values were obtained for analogous β-aryl substituted β-keto esters.[3] Asymmetric hydrogenation of β-aryl substituted β-keto esters remains a challenging task. Only limited C_2-symmetric bisphosphine ligands have been reported to show good to excellent ee in the Ru-catalyzed hydrogenation of β-aryl substituted β-keto esters recently.[10] For example, up to 99% ee has been reported with bisphosphinites ligands[10f] and 4,4′-substituted BINAP ligands.[10g]

To our delight, Ru-TangPhos complexes have also shown excellent enantioselectivities for β-aryl substituted β-keto esters. The results are summarized in Table 2. Compared with the hydrogenation of β-alkyl substituted β-keto esters, high temperature and high pressure are the key factors for achieving higher ees for β-aryl substituted β-keto ester (Table 2, entries 1–5). Under the optimized reaction condition, a series of β-aryl substituted β-keto esters proceeded smoothly to give the desired hydrogenation products. For β-aryl substituted β-keto esters with electron-donating group on the phenyl ring, 94.2–97.5% ee were observed (Table 2, entries 4 and 10–13). The best results were obtained in the hydrogenation of substrates with electron-withdrawing group on the phenyl ring, and up to 99.5% ee was achieved for 3-(4-chloro-phenyl)-3-oxo-propionic acid ethyl ester (**3b**) and 3-(4-Bromo-phenyl)-3-oxo-propionic acid ethyl ester (**3c**) (Table 2, entries 6–9). Complete conversion and very high ee value (99.0%) were still observed even when the hydrogenation of **3b** was carried out with 0.1 mol % catalyst loading. To the best of our knowledge, this is the first report that electron-donating chiral bis(trialkylphosphine) ligand can achieve very high enantioselectivities in the hydrogenation of both β-alkyl and β-aryl substituted β-keto esters.

In conclusion, we have applied the Ru-TangPhos catalyst for the asymmetric hydrogenation of β-keto esters, and up to 99.8% ee has been observed for both β-alkyl substituted and β-aryl substituted β-keto esters. These results demonstrate that the Ru-Tangphos catalyst has a potential for practical synthesis of a variety of chiral β-hydroxy esters. Further applications of the Ru-TangPhos catalyst are underway and progress will be disclosed in the future.

Acknowledgement

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