Highly Enantioselective Hydrogenation of α-Keto Esters Catalyzed by Ru-Tunephos Complexes

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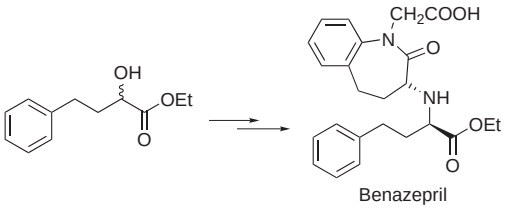
Abstract: Various enantiomerically pure α-hydroxy esters were synthesized by asymmetric hydrogenation of α-keto esters catalyzed by Ru-C_n-Tunephos complex. Up to 97.1% ee has been achieved for both α-aryl and α-alkyl substituted α-keto esters.

Key words: asymmetric catalysis, enantioselectivity, ruthenium, hydrogenation, α-keto esters

Enantiomerically pure α-hydroxy acid derivatives are very important chiral building blocks for the synthesis of a variety of natural products and biologically active molecules,[1] e.g., angiotensin converting enzyme inhibitors: benazepril,[2] delapril hydrochloride,[3] and clopidogrel bisulfate[4] (Scheme 1). An effective method for preparing this class of compounds involves asymmetric hydrogenation of the corresponding α-keto esters.[5] Despite the tremendous progress made on the asymmetric hydrogenation of β-keto esters, highly enantioselective hydrogenation of α-keto esters has not been fully explored.[6]



Scheme 1 Example of an ACE inhibitor

Although axially C_2-symmetric biaryl bisphosphines such as BINAP,[7] BIPHEP[8] and MeO-BIPHEP[8] (Figure 1) are effective chiral ligands for many asymmetric hydrogenation reactions, the current substrate scope of asymmetric hydrogenation is still far from satisfactory. It is well known that subtle changes in conformation, steric and electronic properties of the chiral ligands can often lead to dramatic variation of reactivities and enantioselectivities. Therefore, considerable efforts have been made toward the design and synthesis of a variety of atropisomeric ligands based on the biphenyl, binaphthyl or other biaryl backbones.[9]

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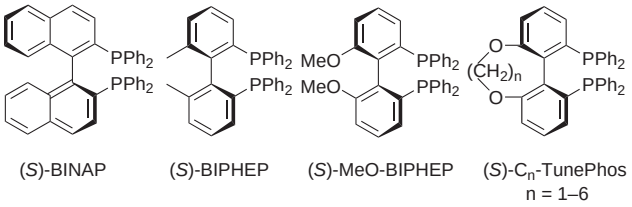
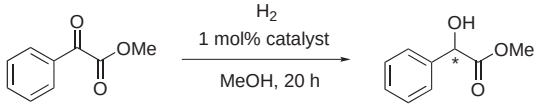


Figure 1

Recently, we have developed a novel class of bisphosphine ligands (C_n-Tunephos, n = 1–6) with tunable dihedral angles.[11] These ligands allow us to systematically study the influence of dihedral angles of atropisomeric biaryl bisphospines on the reactivity and enantioselectivity of asymmetric hydrogenation reactions. For example, in the Ru-catalyzed asymmetric hydrogenation of β-keto esters[10] and α-phthalimide ketones,[11] C_4-Tunephos and C_3-Tunephos have given the best enantioselectivities (up to 99% ee) among the C_n-Tunephos ligands. We envision that a tunable chiral pocket is very important for achieving high enantioselectivity for the hydrogenation of α-keto esters. Herein we report the systematic study of Ru-catalyzed asymmetric hydrogenation of α-keto esters using a series of chiral biaryl bisphosphines (C_n-Tunephos, n = 1–6) with tunable dihedral angles. Up to 97.1% ee has been achieved for both α-aryl and α-alkyl substituted α-keto esters.

We initiated our study by choosing **6a** as the model substrate and screened a number of Ru-C_n-Tunephos complexes to examine both the ligand effects and the influence of different metal complexes. Some representative results are shown in Table 1. Hydrogenation of **6a** catalyzed by Ru[(*S*)-C_3-Tunephos](OAc)$_2$ (**1**)[12] proceeded slowly and resulted in low enantioselectivity (Table 1, entry 1). Similar results have been observed for the hydrogenation of β-keto esters and changing the carboxylate ion to halide can enhance reactivity and enantioselectivity.[13] Therefore, we explored several Ru-halide complexes for the hydrogenation reactions. When [RuCl(benzene)(*S*)-C_3-Tunephos]Cl (**2**)[6b] was employed as catalyst, 94.5% ee was observed at room temperature (Table 1, entry 2). However, under the same reaction conditions hydrogenation of **6a** with [RuCl(cymene)(*S*)-C_3-Tunephos]Cl (**3**)[6b] gave only <10% conversion and 47% ee (Table 1, entry 3). A possible reason is that the dissociation of the η^6-cymene ligand in **3** requires higher energy than that of the η^6-benzene ligand in **2**. As expected, the reaction

Table 1 Asymmetric Hydrogenantion of Methyl Benzoylformate **6a**



6a **7a**

Entry[a]	Catalyst	θ (o)[c]	Temp	H_2 (atm)	ee (%)[d]
1	**1**	77	r.t.	5	14.0
2	**2**	77	r.t.	5	94.5
3	**3**	77	r.t.	5	47.0
4[b]	**3**	77	50 °C	50	94.0
5	**4a**	60	r.t.	5	90.7
6	**4b**	74	r.t.	5	92.6
7	**4c**	77	r.t.	5	**97.1**
8	**4d**	88	r.t.	5	93.0
9	**4e**	94	r.t.	5	92.9
10	**4f**	106	r.t.	5	91.7
11	**5**	77	r.t.	5	96.7

$Ru[(S)\text{-}C_3\text{-Tunephos}](OAc)_2$ **1** $\{RuCl(benzene)[(S)\text{-}C_3\text{-Tunephos}]\}Cl$ **2**

$\{RuCl(Cymene)[(S)\text{-}C_3\text{-Tunephos}]\}Cl$ **3**

$RuCl_2[(S)\text{-}C_n\text{-Tunephos}](DMF)_m$ (n = 1 **4a**; n = 2 **4b**; n = 3 **4c**; n = 4 **4d**; n = 5 **4e**; n = 6 **4f**)

4a–4f

$[NH_2Me_2]^+[\{RuCl[(S)\text{-}C_3\text{-Tunephos}]\}_2(\mu\text{-}Cl_3)]^-$ **5**

[a] All reactions were completed in 100% conversion except entry 3 (10% conversion).
[b] The reaction was performed at 50 °C and 50 atm for 10 h.
[c] Calculated dihedral angles of Cn-Tunephos from CAChe MM2 program.
[d] Enantiomeric excesses were determined by chiral GC, the configuration of the product is *S*.

proceeded smoothly at 50 °C with **3** and 94% ee and 100% conversion were observed (Table 1, entry 4). We have also explored two other Ru-complexes (**4**, **5**) without the coordination of η^6-arene so that reactions can be carried out under milder conditions. Further experiments showed that up to 97.1% ee was achieved with $RuCl_2[(S)\text{-}C_3\text{-Tunephos}](DMF)_m$ (m can be 2, 3 or 4; **4c**)[10] and $[NH_2Me_2]^+[\{RuCl[(S)\text{-}C_3\text{-Tunephos}]\}_2(\mu\text{-}Cl_3)]$ (**5**)[14] as the catalysts (Table 1, entries 7 and 11).

To test the effect of dihedral angles of chiral biaryl ligands on the enantioselectivity of the reactions, a series of $(S)\text{-}C_n\text{-Tunephos}$[10] was examined (Table 1, entries 5–10). While ligands $(S)\text{-}C_1\text{–}C_6$ Tunephos showed similar reactivity, the enantioselectivity varied dramatically. The optimal ee (97.1%) was achieved with $(S)\text{-}C_3$-Tunephos. To the best of our knowledge, this is the highest ee reported for hydrogenation of this kind of substrate. Hydrogenation of **6a** with Ru-BINAP complex only leads to 79% ee.[6b] Compared with BINAP, tunable C_n-Tunephos provides an opportunity to optimize chiral catalytic pockets for a given substrate.

In the proposed transition state model, hydride transfer to ketones is the stereochemically defining step. The strong interaction between the R group from α-keto esters and the equatorial phenyl group makes **A** a disfavored species compared with **B** (Figure 2). According to this model, *S*-configuration reductive product was obtained due to the addition of H to the *Re* face of the ketone.

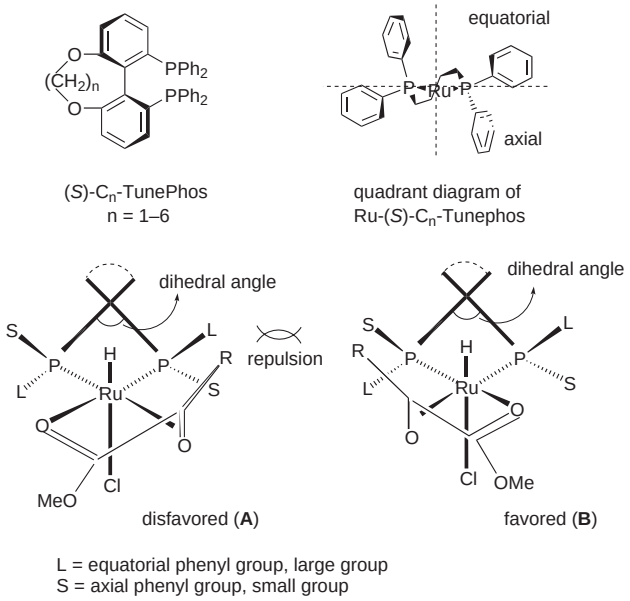
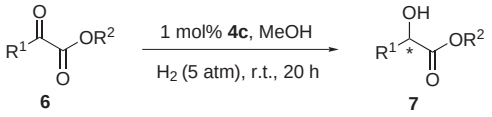


Figure 2

Under optimized reaction conditions (Table 1, entry 7), a variety of α-aryl substituted α-keto esters **6a–i** were examined for the hydrogenation reaction with $RuCl_2[(S)\text{-}C_3\text{-Tunephos}](DMF)_m$ (**4c**, Table 2, entries 1–9). High enantioselectivities have been achieved with the exception of *o*-fluoro-substituted α-keto ester **6d** (Table 2, entry 4). There is no major electronic effect on the substitution pattern of the substrates (92.4–96.9% ee). A proposed explanation of the low ee (84.6%) with the *o*-fluoro-substituted α-keto ester **6d** is that competing coordination of the *o*-fluoro group exists in the Ru system. For α-alkyl-substituted α-keto esters **6j–l**, high enantioselectivities (95–96% ee) have also been observed regardless of the steric hindrance (Table 2, entries 10–12). To provide a key intermediate for the synthesis of ACE inhibitors benazepril (Figure 2), we have carried out the hydrogenation of **6m** and up to 95.8% ee has been achieved, which represents the highest ee ever reported for the hydrogenation of this challenging substrate (Table 2, entry 13). Therefore, our hydrogenation of α-keto esters with **4c** provides a broad substrate scope.[15]

In conclusion, a family of chiral bisphosphines with tunable dihedral angles has been employed in the asymmetric Ru-catalyzed hydrogenation of α-keto esters, and up to 97.1% ee has been achieved with $RuCl_2[(S)\text{-}C_3\text{-Tunephos}](DMF)_m$ (**4c**) as the catalyst. The highly enantioselective hydrogenation provides a powerful way to prepare chiral α-hydroxy esters, which are important

Table 2 Asymmetric Hydrogenantion of α-Keto Esters **6**



Entry[a]	Substrate	R^1	R^2	Yield (%)[e]	ee (%)[f]
1	**6a**	Ph	Me	92	97.1
2	**6b**	*p*-F-C_6H_4	Me	94	94.5
3	**6c**	*m*-F-C_6H_4	Me	91	94.1
4	**6d**	*o*-F-C_6H_4	Me	90	84.6
5[b]	**6e**	*p*-Cl-C_6H_4	Me	95	93.2
6[b]	**6f**	*p*-Br-C_6H_4	Me	92	92.4
7	**6g**	*p*-Me-C_6H_4	Me	89	96.4
8	**6h**	*p*-MeO-C_6H_4	Me	90	95.5
9	**6i**	*m*-$MeOC_6H_4$	Me	91	95.0
10	**6j**	Me	Me	70	95.5
11[c]	**6k**	*i*-Pr	Et	75	96.0
12[c]	**6l**	*t*-Bu	Et	90	95.3
13[c]	**6m**	$Ph(CH_2)_2$	Et	94	95.8
14[d]	**6m**	$Ph(CH_2)_2$	Et	93	94.1

[a] All reactions went to 100% conversion.
[b] The reaction was performed at 50 °C and 50 atm for 15 h. 91.0% ee and 90.5% ee were obtained for **6e** and **6f**, respectively, at r.t. and 5 atm for 20 h.
[c] EtOH was used as solvent.
[d] The reaction was carried out by using 0.1 mol% of the catalyst **5** at 50 °C and 50 atm for 48 h.
[e] Isolated yields. For **6j** and **6k** lower yields were due to the volatility of the reductive product.
[f] Enantiomeric excesses were determined by chiral GC; the configuration of the products is *S*.

chiral building blocks for organic synthesis. Further studies of other transition metal complexes of these ligands and their applications are in progress.

Acknowledgment

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(15) **General Procedure for the Asymmetric Hydrogenation of α-Keto Esters.**
$[Ru(cymene)Cl_2]_2$ (6.2 mg, 0.01 mmol) and (*S*)-C_3-Tunephos (12.5 mg, 0.021 mmol) were dissolved in degassed DMF (3 mL) in a Schlenk tube under N_2. The solution was heated at 100 °C for 3.5 h. After the mixture was cooled to 50 °C, the solvent was removed under vacuum to give the catalysts as an orange-red solid. The catalyst was dissolved in degassed MeOH (8 mL) in a glovebox and distributed equally between four vials. Substrate **6a** (82 mg, 0.5 mmol) was then added to the catalyst solution. The resulting mixture was transferred into an autoclave and charged with 5 atm pressure of H_2. The autoclave was stirred at r.t. for 20 h. The autoclave was then cooled to r.t. and the H_2 was carefully released. The reaction solution was then evaporated and the residue was purified by column chromatography to give the corresponding hydrogenation product (76 mg, 92% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.34–7.44 (m, 5 H), 5.18 (d, *J* = 3.5 Hz, 1 H), 3.76 (s, 3 H), 3.59 (d, *J* = 3.5 Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.5, 138.7, 129.0, 128.9, 127.0, 73.3, 53.4. $[\alpha]_D^{20}$ +180.5 (*c* 1.3, $CHCl_3$) for 97.1% ee; Gamma Dex 225, 30 m × 0.25 mm, column temperature: 130 °C, carrier gas: He, 1 mL/min, t_1 = 19.000 min, t_2 = 21.593 min.