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Asymmetric Hydrogenation of β-Ketophosphonates and β-Ketothiophosphonates with Chiral Ru (II) Catalysts

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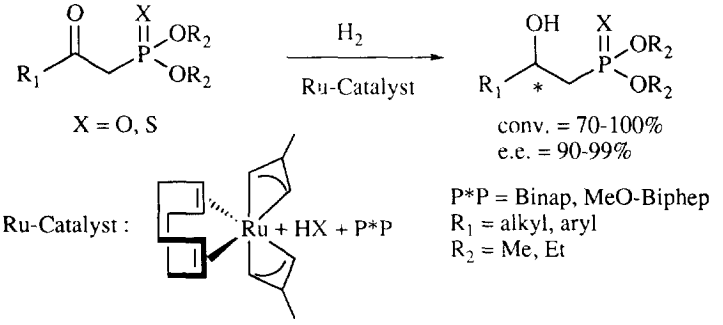
Abstract *: Asymmetric hydrogenation of β-ketophosphonates and β-ketothiophosphonates is described. Enantiomeric excesses up to 99% were obtained.*

Chiral β-hydroxy and α-amino β-hydroxyphosphonic acid analogues of carboxylic acids have stimulated extensive studies in the past decade because they serve as important surrogates for the corresponding carboxylic acids.[1] The enantioselective syntheses of β-hydroxy arylalkylphosphonates were achieved by 1.3.2-oxazaborolidine [2] and baker's yeast [3] catalysis. The asymmetric synthesis of β-hydroxyphosphonic acids via Binap-Ru(II) catalyzed hydrogenation of β-ketophosphonates was recently reported.[4] However, to the best of our knowledge, there is no example of asymmetric hydrogenation of β-ketothiophosphonates via transition-metal catalysis. A general, convenient and practical method of preparation of β-ketophosphonates and thiophosphonates based on the conversion of the organolithium derivative of a dialkylmethylphosphonate into the corresponding organocopper reagent and its reaction with acyl chlorides exists.[5] As we have been interested in asymmetric synthesis and hydrogenation reactions using chiral ruthenium catalysis, we now



Scheme 1

describe in this paper a Ru(II)-catalyzed asymmetric hydrogenation of prochiral β-ketophosphonic and thiophosphonic esters (scheme 1) using our simple *in situ* preparation of Ru(II) catalysts.[6f]

As we have a large variety of β-ketophosphonates and β-ketothiophosphonates available, we first examined different reaction conditions with our chiral Ru(II) catalysts. The influence of solvent, temperature and pressure was observed in order to optimize conditions. The best results were obtained when the hydrogenation was performed in methanol ; when dichloromethane was used as solvent, the reaction proceeded too slowly and the conversions were very moderate even under high hydrogen pressure. A dramatic decrease in enantiomeric excess was generally observed for the β-ketophosphonates and β-ketothiophosphonates when the reaction was heated from room temperature to 50°C, except for diethyl 2-oxopropylphosphonate **1**. In this particular case, the reaction afforded a 99% enantiomeric excess whatever the experimental conditions used. The hydrogen pressure did not modify the enantiomeric excess of the corresponding β-hydroxyphosphonates and β-hydroxythiophosphonates. The best experimental conditions are reported in Table 1.

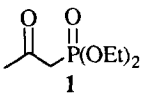
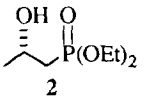
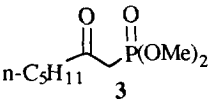
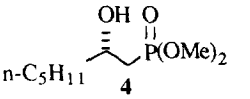
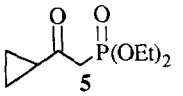
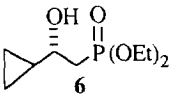
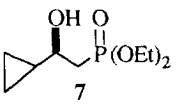
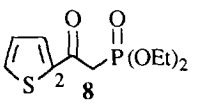
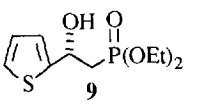
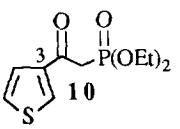
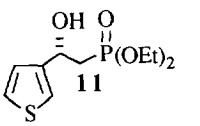
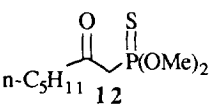
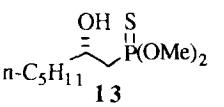
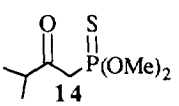
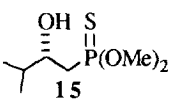
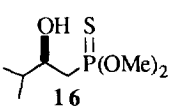
Asymmetric hydrogenation of diethyl 2-oxopropylphosphonate **1** was carried out at atmospheric pressure and 50°C with (S)-Binap leading to the β-hydroxyphosphonate **2** with a complete conversion and a 99% e.e. (entry 1). The reduction of dimethyl 2-oxoheptylphosphonate **3**, having a longer alkyl chain, was conducted with (S)-Binap at higher pressure and at room temperature (entry 2), affording compound **4** with a 98% e.e., slightly better than the e.e. previously described.[4a] Diethyl 2-cyclopropyl-2-oxo-ethylphosphonate **5** was converted to β-hydroxyphosphonates **6** and **7** having (S) and (R) configurations respectively, using (S)-Binap and (R)-MeO-Biphep. Finally, we examined the asymmetric hydrogenation of two aromatic β-ketophosphonates **8** and **10,** substituted by a thienyl ring in positions 2 and 3 (entries 5-8). Interestingly, good conversions were obtained under mild conditions (10 atm, room temperature) in yields from 70% to 100% and e.e. varying from 93% to 97% using (S)-Binap (entries 5 and 7) and (S)-MeO-Biphep (entries 6 and 8).

As mentioned before, the reduction of β-ketothiophosphonates via Ru-catalyzed hydrogenation was not reported ; it was therefore interesting to study the reactivity of these substrates. The hydrogenation of dimethyl 2-oxoheptylthiophosphonate **12** was first studied under the same reaction conditions as described for the reduction of dimethyl 2-oxoheptylphosphonate **3**. Thus, the β-hydroxythiophosphonate **13** was obtained at 100 atm and room temperature with total conversion and a 90% e.e. using (S)-Binap (entry 9).

An increased e.e. was obtained when the reaction was performed with (S)-MeO-Biphep (94% e.e., entry 10). Dimethyl 3-methyl-2-oxobutylthiophosphonate **14** was totally hydrogenated at 10 atm. and room temperature, using respectively (S)-MeO-Biphep and (R)-Binap and yielding **15** and **16** with high enantiofacial discrimination (92% and 94% e.e., entries 11 and 12). The absolute configurations of the β-hydroxyphosphonates and thiophosphonates were determined using Mosher's method.[7-9] The direction of asymmetric induction is consistent with that reported by Noyori and coll.[4]

In conclusion, the asymmetric synthesis of β-hydroxyphosphonates and β-hydroxythiophosphonates by Ru-catalyzed hydrogenation was achieved. Interestingly, β-hydroxyphosphonates substituted with a thienyl ring were obtained with good conversions and enantiomeric excesses. Moreover, the presently reported hydrogenation of β-ketothiophosphonates is compatible with the Ru(II)-catalysts. These results offer interesting perspectives in homogeneous catalysis.

Table 1 : Asymmetric hydrogenation of β–ketophosphonates and β-ketothiophosphonates

Entry	Substrate	Ligand[a]	Conditions[d] P (atm)	Temp. (°C)	Time (h)	Product	Yield[b]	e.e.[c]
1	 **1**	(S)-Binap	1	50	48	 **2**	100	99
2	 **3**	(S)-Binap	100	r.t.	88	 **4**	100	98
3	 **5**	(S)-Binap	75	50	48	 **6**	100	94
4		(R)-MeO-Biphep	75	50	48	 **7**	100	93
5	 **8**	(S)-Binap	10	r.t.	70	 **9**	70	93
6		(S)-MeO-Biphep	10	r.t.	70		77	97
7	 **10**	(S)-Binap	10	r.t.	70	 **11**	100	94
8		(S)-MeO-Biphep	10	r.t.	70		86	96
9	 **12**	(S)-Binap	100	r.t.	88	 **13**	100	90
10		(S)-MeO-Biphep	100	r.t.	88		100	94
11	 **14**	(S)-MeO-Biphep	10	r.t.	70	 **15**	100	93
12		(R)-Binap	10	r.t.	70	 **16**	100	92

(a) Chiral Ru (II) catalyst (1% mol, except entry 1, 2% mol.). (b) Yields are determined by ^1H NMR. (c) e. e. were determined by GC analysis (Megadex 5 column). (d) Reaction times are not optimized.

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