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Ru-catalyzed highly chemo- and enantioselective hydrogenation of γ-halo-γ,δ-unsaturated-β-keto esters under neutral conditions†

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Finely-tuned ruthenium-catalyzed highly chemoselective and enantioselective hydrogenation of γ-halo-γ,δ-unsaturated-β-keto esters at the carbonyl group was achieved under neutral reaction conditions (ee up to 97%). Both olefin and alkenyl halogen moieties, which are labile under hydrogenation conditions, remained untouched during the reaction.

The importance of chiral secondary allyl alcohols is not only due to their occurrence as vital building blocks in many natural, pharmaceutical and agrochemical products (Fig. 1), but also lies in that they serve as versatile intermediates for many useful synthetic elaborations, for example the Claisen rearrangement[1] or S_N2' displacement reactions,[2] which enable transfer of chirality by cleavage of C–O bonds and formation of C–C bonds to new chiral centers. Hence various synthetic methods have been developed over the past decades. For instance, kinetic resolution of racemic allyl alcohols by enantioselective acylation,[3] Sharpless epoxidation,[4] asymmetric transfer hydrogenation,[5] enantioselective aldehyde vinylation[6] or asymmetric reduction of α,β-unsaturated ketones by metal hydride reagents,[7] for which stoichiometric reductants are required.

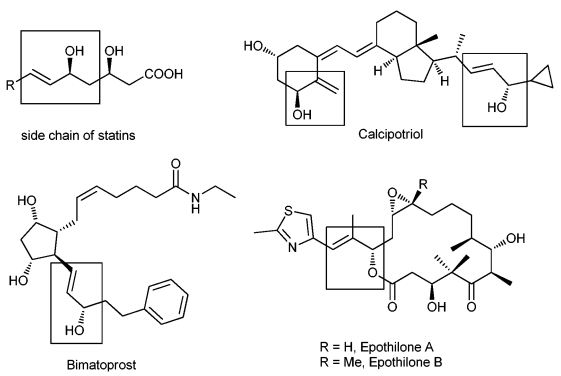

Fig. 1 Examples of chiral allyl alcohols in pharmaceuticals.

Asymmetric hydrogenation has become one of the most efficient and practical strategies for building up chiral centers.[8] Noyori and co-workers accomplished the carbonyl-selective asymmetric hydrogenation of many α,β-unsaturated carbonyls with a Ru/diphosphine/diamine system under basic conditions.[9] However, this efficient catalytic system was totally ineffective for β-keto esters,[10] which served as common touchstones for many newly-designed ligands for asymmetric hydrogenations,[8e,11] in addition, some substrates were not stable in the presence of a base. As a result, carbonyl-selective asymmetric hydrogenation of conjugated unsaturated β-keto esters under neutral conditions was less developed,[12] as the olefin moiety inclined to undergo hydrogenation as well. Only one example was reported up to now by asymmetric transfer hydrogenation.[12b] Consequently, selective hydrogenation of the C=O group of those polyfunctionalized conjugated keto esters is still challenging.

Our group previously designed a family of chiral biaryl diphosphine ligands, SunPhos, and explored their applications in asymmetric hydrogenation of functionalized ketones.[13] Herein we report our recent progress in highly carbonyl-selective asymmetric hydrogenation of γ-halo-γ,δ-unsaturated β-keto esters, giving the corresponding chiral allyl alcohols.

Previous studies showed that achieving highly carbonyl-selective hydrogenation of unsaturated keto esters was rather difficult, especially for those conjugated ones.[12,13d,14] Therefore, we designed a γ-halogen substituted γ,δ-unsaturated β-keto ester, of which the di-substituted olefin was switched to a tri-substituted one, which may reduce the possibility of the olefin reduction thus improving the chemoselectivity. Moreover, the vinyl halide moiety could undergo further transformations by organometallic methods.[15] Considering the probability of debromination during hydrogenation,[13b] the γ-chlorine substituted substrate **1a** was employed for initial trials. The reaction was carried out with 0.5 mol% of [RuCl(benzene)(*S*)-SunPhos]Cl with a substrate concentration of 0.5 M in EtOH at 50 °C under 10 bar of H_2. To our delight, the ketone was fully converted to the reduced alcoholic product in 90.6% ee under this neutral condition, with trace of ketal impurities. Neither C=C bond-saturated nor dechlorinated byproduct was detected by ^{1}H NMR and TLC.[16] Encouraged by this exciting result, we screened a series of

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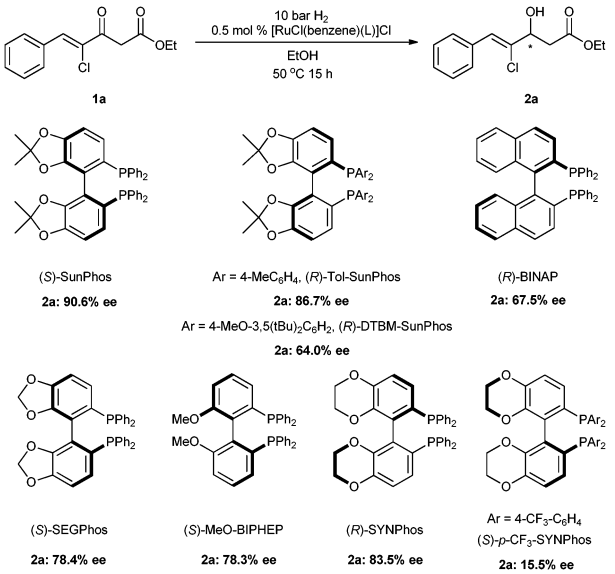
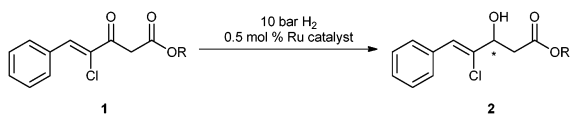


Scheme 1 Screening of ligands.

atropisomeric biaryl diphosphine ligands (Scheme 1). All the tested ligands demonstrated similar C=O/C=C selectivity, giving the sole chlorine substituted allyl alcohol **2a**. The ee's of **2a** were considerably dependent on the ligands employed. Substituents on the phenyl appendages of the ligands were adverse to achieving higher ee's, which might have resulted from the steric effect. (*R*)-BINAP, (*S*)-SEGPhos, (*S*)-MeO-BIPHEP and (*R*)-SYNPhos were inferior to (*S*)-SunPhos. (*S*)-*p*-CF_3-SYNPhos, an electron-deficient ligand, resulted in only a 15.5% ee of **2a**. Based on the above results, (*S*)-SunPhos was the ligand of choice.

Next we investigated the influence of solvent, pressure and temperature on this reaction. Alcoholic solvents were superior to DCM. The pressure exerted little impact on the enantioselectivity, whilst temperature showed significant influence on the results of enantio-discrimination. When **1a** was hydrogenated at 70 °C in EtOH, the ee of **2a** raised to 92.8%, which further upgraded to 93.5% at 90 °C (entries 1–2, Table 1),

Table 1 Optimization of the reaction conditions[a]



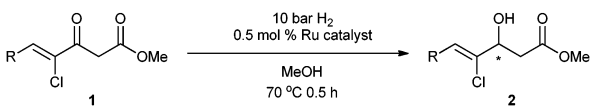
Entry	R	Solvent	Temp. (°C)	ee (%)[b]
1	Et (**1a**)	EtOH	70	92.8
2[c]	Et (**1a**)	EtOH	90	93.5
3[d]	Et (**1a**)	MeOH	70	93.4 (93.2)[e]
4[d]	Et (**1a**)	*n*-PrOH	70	95.5 (95.6)[e]
5	*n*-Pr (**1b**)	*n*-PrOH	70	95.1
6	Me (**1c**)	MeOH	70	94.9
7[f]	Me (**1c**)	MeOH	70	95.7

[a] Unless otherwise specified, all reactions were carried out with a substrate (1.0 mmol) concentration 0.5 M for 15 h under 10 bar of H_2, S/C = 200/1. [b] ee's were determined by HPLC on a Chiralpak IC-3 column. [c] C=C bond-saturated byproduct formed. [d] Transesterification occurred. [e] ee's of the corresponding transesterificated products were stated in parentheses. [f] 0.5 h.

but was accompanied by *ca.* 3% of fully saturated byproduct, as determined by ^{1}H NMR analysis of the crude reaction mixture. Therefore, the optimized temperature was set at 70 °C as a compromise between chemo- and enantioselectivity. When MeOH and *n*-PrOH were used as solvents, the ee's of **2a** were promoted to 93.4% and 95.5% (entries 3–4, Table 1). Partial ethyl ester was converted to methyl and *n*-propyl ester in each case. To avoid transesterification, *n*-propyl (**1b**) and methyl (**1c**) esters were hydrogenated in corresponding alcohols at 70 °C, giving **2b** and **2c** in 95.1% and 94.9% ee, respectively (entries 5–6, Table 1). Obviously, the latter two were superior to ethyl ester (**1a**). Although the *n*-propyl ester (**1b**) presented a better enantioselectivity, methyl ester (**1c**) was chosen for the following investigation, allowing for its convenience of synthesis and purification (see experimental section, ESI†). Furthermore, **1c** could be completely converted to the corresponding chloro-substituted allyl alcohol **2c** within 30 min with slightly higher ee under the standard conditions: 0.5 mol% of [RuCl(benzene)(*S*)-SunPhos]Cl as a catalyst, 0.5 molar concentration of substrate in MeOH, and at 70 °C under 10 bar of H_2 (entry 7 *vs.* 6, Table 1).

A variety of (*Z*)-methyl 4-chloro-3-oxo-5-arylpent-4-enoates (**1**) were submitted to assess the substrate scope, as shown in Table 2. In all cases, the reaction proceeded very well, giving exclusively the carbonyl reduction product with good enantioselectivity and a wide tolerance of functional groups. The electronic nature of the substitution pattern showed insignificant influence on enantio-discrimination. The ee's of **2** fluctuated slightly, from 94.9% (**2m**) to 96.0% (**2d**), when electron neutral (entries 1–2, Table 2), electron rich (entry 3, Table 2) and electron deficient (entries 9, 11, Table 2) substrates were investigated. Substitution at the *meta* position on the phenyl ring led to relatively lower ee, while *ortho* substituted substrates gave the best results, for example, ee's of MeO-substituted **2e–g** were 95.6% (*para*), 94.7% (*meta*) and 97.0% (*ortho*).

Table 2 Asymmetric hydrogenation of **1** by [RuCl(benzene)(*S*)-SunPhos]Cl[a]



	Substrate			
Entry	**1**	R	Yield (%)[b]	ee (%)[c]
1	**1c**	C_6H_5	96	95.7
2	**1d**	4-Me-C_6H_4	98	96.0
3	**1e**	4-MeO-C_6H_4	98	95.6
4	**1f**	3-MeO-C_6H_4	95	94.7
5	**1g**	2-MeO-C_6H_4	98	97.0
6	**1h**	4-Cl-C_6H_4	95	95.3
7	**1i**	3-Cl-C_6H_4	95	94.2
8	**1j**	2-Cl-C_6H_4	98	95.5
9	**1k**	4-F-C_6H_4	97	95.4
10	**1l**	4-Br-C_6H_4	96[d]	95.1
11	**1m**	4-CF_3-C_6H_4	95	94.9
12	**1n**	*E*-PhCH=CH	97	94.1

[a] All reactions were carried out with a substrate (1.0 mmol) concentration of 0.5 M in MeOH at 70 °C for 0.5 h under 10 bar of H_2, S/C = 200/1. [b] Isolated yield. [c] ee's were determined by HPLC on a Chiralpak IC-3 column. [d] Trace of debrominated product (**2c**) formed.

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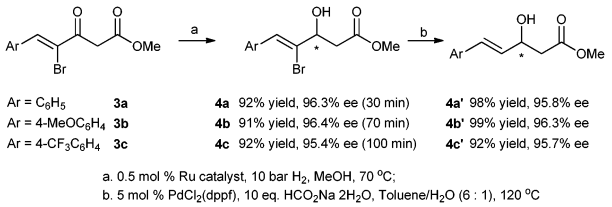

Scheme 2 Asymmetric hydrogenation of the bromo analogues and their debromination.

The same trend was found when Cl was the substituent (entries 3–5 *vs.* 6–8, Table 2). When **1l** was hydrogenated under these reaction conditions, only trace of debrominated product **2c** was detected by HPLC. (4*Z*,6*E*)-Methyl 4-chloro-3-oxo-7-phenylhepta-4,6-dienoate (**1n**), a more functionalized olefinic ketone, was tolerant under these conditions as well, both C=C bonds remained untouched (entry 12, Table 2).

On the basis of the success in asymmetric hydrogenation of **1l**, an aryl bromide, we wondered whether a vinyl bromide moiety would be tolerant under this specified condition. Bromo analogues **3a–c** were synthesized and submitted to hydrogenation. Gratifyingly, they were fully transformed to bromo-substituted allyl alcohols **4a–c** in high yields and enantioselectivities (Scheme 2), ee's were even higher than their chloro analogues. Phenyl ring substituted substrates **3b** and **3c** need longer reaction times to achieve full conversion. No debromination occurred, only trace of fully saturated byproduct was detected by ^{1}H NMR. Compared with vinyl chloride, the remaining vinyl bromide ending could be more easily converted to other structures by transition metal-catalyzed reactions. For example, the C–Br bond could be reduced to a C–H bond by HCO_2Na in high yield without racemisation under the catalysis of $PdCl_2$(dppf) (Scheme 2).

In conclusion, we have successfully achieved a highly chemoselective and enantioselective asymmetric hydrogenation of a series of γ-halo-γ,δ-unsaturated β-keto esters at the carbonyl group by a Ru/diphosphine catalytic system under neutral conditions. Both the conjugated C=C double bonds and adjacent vinyl halogens remained untouched even at the risk of over-reduction and dehalogenation.[17] This method showed high enantioselectivity (up to 97% ee) with a wide substrate scope. The halogen substituted chiral allyl alcohol may undergo further derivation to access more complex building blocks, especially in the case of the vinyl bromide.

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Notes and references

1 (*a*) *The Claisen Rearrangement: Methods and Applications*, ed. M. Hiersemann and U. Nubbemeyer, Wiley-VCH, Weinheim, 2007; (*b*) P. Wipf, in *Comprehensive Organic Synthesis*, ed. B. M. Trost, I. Fleming and L. A. Paquette, Pergamon, Kidlington, Oxford, 1991, vol. 5, pp. 827–873; (*c*) S. Rhoads and N. Raulins, *Org. React.*, 1975, **22**, 1.

2 For an example see: G. Stork and A. R. Schoofs, *J. Am. Chem. Soc.*, 1979, **101**, 5081.

3 (*a*) For an example see: J. A. MacKay and E. Vedejs, *J. Org. Chem.*, 2004, **69**, 6934. For recent reviews of kinetic resolution see(*b*) H. Pellissier, *Adv. Synth. Catal.*, 2011, **353**, 1613; (*c*) E. Vedejs and M. Jure, *Angew. Chem., Int. Ed.*, 2005, **44**, 3974.

4 (*a*) T. Katsuki and K. B. Sharpless, *J. Am. Chem. Soc.*, 1980, **102**, 5974; (*b*) V. S. Martin, S. S. Woodard, T. Katsuki, Y. Yamada, M. Ikeda and K. B. Sharpless, *J. Am. Chem. Soc.*, 1981, **103**, 6237.

5 For examples see: (*a*) S. Hashiguchi, A. Fujii, K. Haack, K. Matsumara, T. Ikariya and R. Noyori, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 288; (*b*) Y. Iura, S. Tsutomu and K. Ogasawara, *Tetrahedron Lett.*, 1999, **40**, 5735.

6 For an example see: (*a*) W. Oppolzer and R. Radinov, *Helv. Chim. Acta*, 1992, **75**, 170. For reviews see; (*b*) P. Wipf and C. Kendall, *Chem.–Eur. J.*, 2002, **8**, 1778; (*c*) P. Wipf and R. L. Nunes, *Tetrahedron*, 2004, **60**, 1269; (*d*) E. Skucas, M. Ngai, V. Komanduri and M. J. Krische, *Acc. Chem. Res.*, 2007, **40**, 1394.

7 For reviews see: (*a*) H. C. Brown and P. V. Ramachandran, *Acc. Chem. Res.*, 1992, **25**, 16; (*b*) E. J. Corey and C. J. Helal, *Angew. Chem., Int. Ed.*, 1998, **37**, 1986.

8 (*a*) R. Noyori, *Asymmetric Catalysis in Organic Synthesis*, Wiley, New York, 1994, ch. 2; (*b*) G. Shang, W. Li and X. Zhang, in *Catalytic Asymmetric Synthesis*, ed. I. Ojima, John Wiley & Sons, Hoboken, NJ, 3rd edn, 2010, ch. 7, pp. 343–436; (*c*) in *The Handbook of Homogeneous Hydrogenation*, ed. J. G. de Vries and C. J. Elsevier, Wiley-VCH, Weinheim, 2007; (*d*) R. Noyori and T. Ohkuma, *Angew. Chem., Int. Ed.*, 2001, **40**, 40; (*e*) W. Tang and X. Zhang, *Chem. Rev.*, 2003, **103**, 3029; (*f*) W. S. Knowles, *Angew. Chem., Int. Ed.*, 2002, **41**, 1998; (*g*) R. Noyori, *Angew. Chem., Int. Ed.*, 2002, **41**, 2008; (*h*) A. J. Minnaard, B. L. Feringa, L. Lefort and G. J. de Vries, *Acc. Chem. Res.*, 2007, **40**, 1267; (*i*) W. Zhang, Y. Chi and X. Zhang, *Acc. Chem. Res.*, 2007, **40**, 1278; (*j*) N. B. Johnson, I. C. Lennon, P. H. Moran and J. A. Ramsden, *Acc. Chem. Res.*, 2007, **40**, 1291; (*k*) F. D. Klingler, *Acc. Chem. Res.*, 2007, **40**, 1367; (*l*) D. J. Ager, A. H. M. de Vries and J. G. de Vries, *Chem. Soc. Rev.*, 2012, **41**, 3340.

9 For representative references see: (*a*) T. Ohkuma, H. Ooka, T. Ikariya and R. Noyori, *J. Am. Chem. Soc.*, 1995, **117**, 10417; (*b*) T. Ohkuma, M. Koizumi, H. Doucet, T. Pham, M. Kozawa, K. Murata, E. Katayama, T. Yokozawa, T. Ikariya and R. Noyori, *J. Am. Chem. Soc.*, 1998, **120**, 13529; (*c*) N. Arai, K. Azuma, N. Nii and T. Ohkuma, *Angew. Chem., Int. Ed.*, 2008, **47**, 7457.

10 T. Ohkuma, H. Ooka, S. Hashiguchi, T. Ikariya and R. Noyori, *J. Am. Chem. Soc.*, 1995, **117**, 2675.

11 D. J. Ager and S. A. Laneman, *Tetrahedron: Asymmetry*, 1997, **8**, 3327.

12 For an example of carbonyl-selective asymmetric hydrogenation of tri-substituted γ,δ-unsaturated β-keto ester with partial conversion see: E. A. Reiff, S. K. Nair, B. S. N. Reddy, J. Inagaki, J. T. Henri, J. F. Greiner and G. I. Georg, *Tetrahedron Lett.*, 2004, **45**, 5845. For an example of the asymmetric transfer hydrogenation of a di-substituted γ,δ-unsaturated β-keto ester see: D. Cartigny, K. Puntener, T. Ayad, M. Scalone and V. Ratovelomanana-Vidal, *Org. Lett.*, 2010, **12**, 3788.

13 For recent results see: (*a*) W. Li, X. Ma, W. Fan, X. Tao, X. Li, X. Xie and Z. Zhang, *Org. Lett.*, 2011, **13**, 3876; (*b*) W. Fan, W. Li, X. Ma, X. Tao, X. Li, Y. Yao, X. Xie and Z. Zhang, *J. Org. Chem.*, 2011, **76**, 9444; (*c*) X. Tao, W. Li, X. Ma, X. Li, W. Fan, X. Xie and Z. Zhang, *J. Org. Chem.*, 2012, **77**, 612; (*d*) Q. Meng, L. Zhu and Z. Zhang, *J. Org. Chem.*, 2008, **73**, 7209.

14 For examples of asymmetric hydrogenation of unconjugated olefinic β-keto esters see: (*a*) D. F. Taber and L. J. Silverberg, *Tetrahedron Lett.*, 1991, **32**, 4227; (*b*) J. P. Genêt, C. Pinel, V. Ratovelomanana-Vidal, S. Mallart, M. X. Pfister, L. Bischoff, M. C. Cano De Andrade, S. Darses, C. Galopin and J. A. Laffitte, *Tetrahedron: Asymmetry*, 1994, **5**, 675.

15 (*a*) in *Handbook of Organopalladium Chemistry for Organic Synthesis*, ed. E. Negishi, John Wiley & Sons, New York, 2002; (*b*) R. H. Crabtree, *The Organometallic Chemistry of the Transition Metals*, John Wiley & Sons, Hoboken, NJ, 4th edn, 2005.

16 For an example of asymmetric hydrogantion of vinyl chloride see: I. G. Smilovic, E. Casas-Arce, S. J. Roseblade, U. Nettekoven, A. Zanotti-Gerosa, M. Kovacevic and Z. Casar, *Angew. Chem., Int. Ed.*, 2012, **51**, 1014.

17 The introduction of halogen was crucial for the selectivity of the C=O/C=C bond. When (*E*)-methyl 3-oxo-5-phenylpent-4-enoate was hydrogenated under standard conditions for 1 h, *ca.* 15% fully saturated byproduct was detected by ^{1}H NMR at *ca.* 85% conversion.

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