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Convenient General Asymmetric Synthesis of Roche Ester Derivatives through Catalytic Asymmetric Hydrogenation: Steric and Electronic Effects of Ligands

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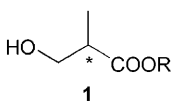
Abstract: An efficient and concise asymmetric hydrogenation of acrylate esters promoted by the cationic ruthenium monohydride complex [Ru(H)(η^6-cot)SYNPHOS]$^+BF_4^-$ is reported. A full investigation of the effects of catalyst precursors, solvents, temperature, hydrogen pressure, substrates as well as steric and electronic properties of ligands was carried out. The corresponding valuable Roche ester derivatives were obtained in good to excellent isolated yields and high enantioselectivities under mild conditions. The robustness and practicability of this highly enantioselective hydrogenation was demonstrated by the synthesis of the 3-hydroxy-2-methylpropanoic acid *tert*-butyl ester on a multigram scale, resulting in excellent yield and *ee* up to 94%.

Keywords: asymmetric catalysis; hydrogenation; Roche ester; ruthenium

Introduction

Transition metal-catalyzed reactions and specifically homogeneous catalysis have had a considerable impact on a wide variety of chemical processes ranging from fine organic synthesis to the large-scale industrial area.[1] Among them, the asymmetric hydrogenation of unsaturated prochiral substrates using inexpensive, clean molecular hydrogen and small amounts of a chiral catalyst is considered as one of the most efficient and atom-economic ways to produce a wide range of enantio-enriched compounds in large quantities without forming any waste.[2]

3-Hydroxy-2-methylpropionic acid methyl ester (**1a**) commonly named as Roche ester is a compound of significant synthetic interest.[3] Besides the currently used industrial enzymatic processes,[4] classical pathways to synthesize synthon **1a** enantioselectively rely on oxidative degradation of a chiral homoallylic acetate,[5] diastereoselective addition of chiral alcohols to arylketenes,[6] or aldol chemistry.[7] However, there are some drawbacks associated with these methods such as the use of stoichiometric amounts of chiral auxiliaries, long reaction sequences and multiple tedious purification steps. As none of these procedures provides an atom-economical route to the Roche ester compound, we envisaged a one-step stereoselective catalytic hydrogenation of the respective unsaturated compounds **2** to be a very attractive and direct method to produce this important building block. Surprisingly, the synthesis of Roche ester derivatives of type **1** (Figure 1) through asymmetric hydrogenation has been scarcely described.[8–11] Saito and co-workers reported enantiomeric excess (*ee*) ranging from 7 to 90% using Rh-DuPHOS or Rh-BeePHOS catalysts[8]



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1a, R = Me, Roche ester
1b, R = Et
1c, R = Bn
1d, R = Cy
1e, R = *t*-Bu
1f, R = C(Me)Et$_2$
1g, R = CH(*i*-Pr)$_2$

Figure 1. Roche ester-type derivatives **1**.

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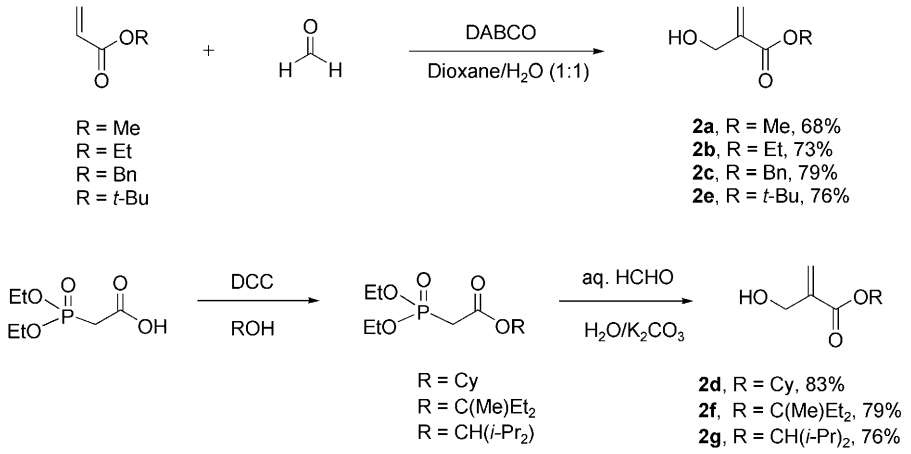

Scheme 1. Synthesis of substrates **2a–g**.

whereas Reek and co-workers recently reported *ee*s ranging from 35 to 98% using an Rh catalyst bearing their bidentate phosphine-phosphoramidite INDOL-PHOS ligands.[9] To the best of our knowledge, no report of an efficient Ru-catalyzed hydrogenation reaction has been described except for one example using an Ru-BINAP complex in a patent application.[10] In a previous communication[11] and in connection with our ongoing program on the use of ruthenium-mediated asymmetric hydrogenation,[12] we have reported the Ru-SYNPHOS[13]-catalyzed synthesis of Roche ester derivatives. In this paper, we wish to report the full details of this study regarding both steric and electronic effects of a wide range of chiral ligands and transition metal complexes.

Results and Discussion

Compounds **2a–c** and **2e** required for our study were readily prepared on a large scale by using the Morita–Baylis–Hillman[14] reaction between aqueous formaldehyde and the corresponding commercially available acrylate esters in the presence of DABCO (Scheme 1). Concerning the synthesis of compounds **2d**, **2f** and **2g**, the Morita–Baylis–Hillman[14] reaction failed and only traces of the desired product were detected which was probably due to the very high tendency of these substrates to polymerize during the reaction. Instead, these compounds were finally obtained *via* a two-step reaction sequence involving DCC-mediated esterification of diethylphosphonoacetic acid[15] followed by a Wittig–Horner reaction of the resulting diethylphosphonoester with aqueous formaldehyde[16] (Scheme 1). It should be noted that the entire sequence can be conducted in one-pot, without isolation of the diethylphosphonoester intermediates.

We started our investigation by searching for the most appropriate catalyst system to perform asymmetric hydrogenation of methyl acrylate ester **2a**, which resulted in 3-hydroxy-2-methylpropionic acid methyl ester **1a**. Toward this end, several catalyst systems (**C1–C9**), generally prepared *in situ* by mixing a solution of a metal precursor and (*R*)- or (*S*)-SYNPHOS[13] as ligands were screened. Initial hydrogenation experiments were first performed at 20 bar of hydrogen pressure and 50 °C in methanol for 23 h using 1 mol% of catalyst. As outlined in Table 1, we observed that the stereochemical outcome of the reaction was highly dependent on the nature of the complexes used. Indeed, the neutral dimeric gold(I) complex [$(AuCl)_2$((*R*)-SYNPHOS)] **C1** which was *in situ* generated by reacting our diphosphine with two equivalents of [(AuCl)(tht)] (tht = tetrahydrothiophene) using the procedure recently described by the group of Corma and Echavarren[17] showed no catalytic activity for the hydrogenation of **2a** (Table 1, entry 1). Only 10% conversion was reached when using either the Ir-SYNPHOS complexes **C2** or **C3** (Table 1, entries 2 and 3). The Pd-SYNPHOS complex **C4**[18] and the preformed [Rh(cod)(SYNPHOS)]$^+$ BF_4^- catalyst **C5** possess similar catalytic profiles and gave rise to full conversion with, respectively, 62% and 51% yield but with very disappointing enantiomeric excesses, not exceeding 7% (Table 1, entries 4 and 5). Finally, we found that a dramatic enhancement of the catalytic activity in terms of both yield and enantioselectivity was obtained when chiral Ru-SYNPHOS complexes[19] were used.

For example, compound **1a** was isolated in 71% yield with a promising *ee* of 72% using the cationic [Ru((*R*)-SYNPHOS)(*p*-cymene)Cl]$^+$$Cl^-$ catalyst **C6** (Table 1, entry 6). This result was far superior to those obtained with Rh-, Ir-, Au- and Pd-SYNPHOS complexes (entries 1 to 5). An even better selectivity

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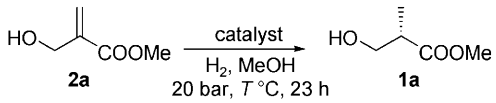
Table 1. Optimization of reaction conditions for asymmetric hydrogenation of methyl acrylate ester **2a** catalyzed by a metal/SYNPHOS (**L1**) complex.[a]



Entry	Catalyst	T [°C]	Conv.[b] (Yield)[c]	*ee*[d]
1	**C1**, $AuCl(tht)_2$ (2 equiv.)+(*R*)-**L1** (1 equiv.)	50	0% (N/D)[e]	N/D[e]
2	**C2**, $[Ir(cod)Cl]_2$+(*R*)-**L1** (1.1 equiv.)+$AgPF_6$ (2.1 equiv.)	50	<10% (N/D)[e]	N/D[e]
3	**C3**, $[Ir(cod)Cl]_2$+(*R*)-**L1** (1.1 equiv.)+I_2 (0.1 equiv.)	50	<10% (N/D)[e]	N/D[e]
4	**C4**, $Pd(CF_3COO)_2$+(*R*)-**L1** (1.1 equiv.)	50	100% (62%)	5% (*S*)
5	**C5**, [Rh(cod)((*R*)-**L1**)]$^+BF_4^-$	50	100% (51%)	7% (*S*)
6	**C6**, $[(RuCl((R)\text{-}\mathbf{L1})_2(\mu\text{-}Cl)_3]^-$ $[NH_2Me_2]^+$	50	100% (71%)	72% (*S*)
7	**C7** $[(RuCl((R)\text{-}\mathbf{L1})_2(\mu\text{-}Cl)_3]^-$ $[NH_2Me_2]^+$	50	100% (74%)	77% (*S*)
8	**C8**, Ru(cod)(η^3-methylallyl)$_2$+(*R*)-**L1**+HBr (2.2 equiv.)	50	100% (76%)	79% (*S*)
9	**C9**, Ru(cod)(η^3-methylallyl)$_2$+(*R*)-**L1**+HBF_4 (1 equiv.)	50	100% (68%)	86% (*S*)
10	**C9**, Ru(cod)(η^3-methylallyl)$_2$+(*S*)-**L1**+HBF_4 (1 equiv.)	30	100% (71%)	86% (*R*)
11	**C9**, Ru(cod)(η^3-methylallyl)$_2$+(*S*)-**L1**+HBF_4 (1 equiv.)	20	100% (69%)	86% (*R*)
12	**C9**, Ru(cod)(η^3-methylallyl)$_2$+(*S*)-**L1**+HBF_4 (2 equiv.)	20	100% (83%)	87% (*R*)
13	**C9**, Ru(cod)(η^3-methylallyl)$_2$+(*S*)-**L1**+HBF_4 (2 equiv.)	15	100% (92%)[f]	86% (*R*)
14	**C9**, Ru(cod)(η^3-methylallyl)$_2$+(*S*)-**L1**+HBF_4 (2 equiv.)	10	100% (82%)	88% (*R*)
15	**C9**, Ru(cod)(η^3-methylallyl)$_2$+(*S*)-**L1**+HBF_4 (2 equiv.)	5	100% (85%)	88% (*R*)

[a] *Conditions:* all reactions were performed using 1 mmol of substrate **2** in methanol for 23 h, catalyst loading, 1 mol%.
[b] Conversion determined by ^1H NMR of crude product.
[c] Isolated yield after flash chromatography.
[d] The *ee* values were measured by HPLC on a Chiralcel OD-H column. The configuration was determined by comparison with commercially available Roche ester **1a**.
[e] Not determined.
[f] 0.5 mol% of benzoquinone was used.

was obtained when the $\{(RuCl[(R)\text{-SYNPHOS}]_2(\mu\text{-}Cl)_3\}^-[NH_2Me_2]^+$ **C7** was used (Table 1, entry 7, 74% yield, 77% *ee*). Further improvement of the enantioselectivity was achieved using the *in situ* generated Ru-SYNPHOS complex **C8** prepared according to our convenient procedure[20] by mixing Ru(cod)(η^3-methylallyl)$_2$ with the diphosphine in the presence of methanolic hydrobromic acid (Table 1, entry 8, 76% yield, 79% *ee*). Finally, the cationic monohydride ruthenium complex $[Ru(H)(\eta^6\text{-cot})SYNPHOS]^+BF_4^-$ **C9**[21], which was successfully used with JOSIPHOS ligand for the synthesis of (+)-*cis*-methyldihydrojasmonate (paradisone®) in an industrial enantioselective hydrogenation process on a multi t/year scale,[22] displayed the best catalytic activity in the hydrogenation of methyl acrylate ester **2a** (Table 1, entry 9, 68% yield, 86% *ee*). Since the $[Ru(H)(\eta^6\text{-cot})SYNPHOS]]^+BF_4^-$ catalytic system prepared by the addition of 1 equiv. of HBF_4 to a mixture of Ru(cod)(η^3-methylallyl)$_2$ and SYNPHOS in dichloromethane proved to be the more efficient catalyst, we further decided to study the effect of the temperature and the catalytic amount of HBF_4 with this system. It was clearly visible from the data presented in Table 1 that lowering the temperature from 50 °C to 5 °C had only minimal effects on the stereoselectivity, independently of the amount of HBF_4 (compare entries 9 *vs.* 10 to 15). By raising the amount of HBF_4 from 1 to 2 mol%, similar enantiomeric excess were still obtained but the yield of the desired hydrogenated compound **1a** was significantly enhanced (Table 1, entries 11 *vs.* 12, 69% and 83% yields, respectively). It was worth noting that the use of 0.5 mol% of benzoquinone as stabilizer to prevent polymerization of the substrate during the course of the reaction further improved the yield to 92% without eroding the asymmetric induction (Table 1, entry 13, 86% *ee*).

The absolute configuration of the hydrogenated product was determined by comparison with commercially available 3-hydroxy-2-methylpropionic acid methyl ester **1a** also known as the Roche ester. In all cases, the Ru catalyst containing the ligand with the (*S*)-configuration gave rise to the corresponding (*R*)-**1a** compound whereas the ligand with the (*R*)-configuration produced the (*S*)-enantiomer.

The selectivity observed for the asymmetric hydrogenation of methyl ester **2a** could be explained through the use of quadrant rules[23] as shown in Figure 2. We postulated that the prochiral allylic alcohol coordinates to the Ru catalyst in a bidentate manner by the alkene and the alcohol functions, providing two diastereomeric complexes (*re*- or *si*-face). Due to steric hindrance of the ligand towards the substrate, one of the diastereomeric complexes was ener-

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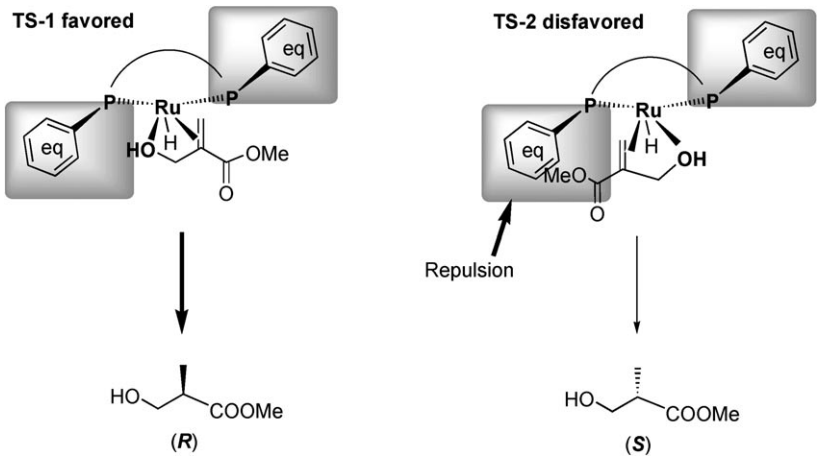
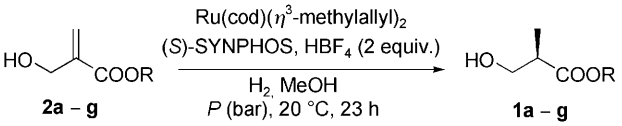


Figure 2. Transition state model to rationalize the enantioselectivity for Ru-(*S*)-SYNPHOS-catalyzed asymmetric hydrogenation of methyl ester **2a**.

getically favored. The transition state (TS-2) suffers from steric repulsion between the ester group of the substrate and the phenyl group of the considered ligands in a pseudo equatorial position whereas the transition state 1 (TS-1) avoids this steric repulsion, allowing the reaction to proceed, yielding the (*R*)-isomer as the major product. From a theoretical point of view, the allylic alcohol **2a** can also coordinate to the metal center through another bidentate coordination mode which involves the alkene and the carbonyl functions, affording also the (*R*)-isomer as the major product. However, this possibility was ruled out by the result obtained for the asymmetric hydrogenation of the silylated derivative of allylic alcohol **2a** (TBS protection). Indeed, only 10% conversion was reached when the reaction was carried out at 20 bar of hydrogen pressure and 50 °C in methanol for 23 h using 1 mol% of [Ru(H)(η^6-cot)SYNPHOS]$^+BF_4^-$ catalyst **C9**.}

Based on the previous model depicted in Figure 2, we anticipated that the enantioselectivity of the reaction should increase if the steric interactions between the bottom left quadrant of the ligand and the substrate increase. Several substrates bearing more sterically demanding ester groups were then prepared. Ethyl ester **2b** led to a slight drop in enantioselectivity compared to the methyl ester **2a** (Table 2, entries 1 and 2, 87% and 83% *ee*), while substrate **2c** with a benzyl substituent, gave similar results to the methyl ester **2a** (Table 2, entry 3, 87% *ee*). The cyclohexyl-substituted derivative **2d** resulted in an enantiomeric excess of 90%, which was a slightly better value than for the methyl-substituted substrate **2a** (Table 2, entry 4). As expected, an increase of the steric demand of the ester moiety by using the bulky *tert*-butyl group **2e** led to a drastic increase of the enantioselectivity. Thus the corresponding adduct **1e** was obtained in high isolated yield (91 to 98%) with up to 94% *ee* (Table 2, entries 5 to 10). We next turned our attention to the hydrogenation of the even more hindered substrates such as 3-methyldiisopropyl ester **2f**[24] and 3-methylpentyl ester (Mpe) **2g**[25] hoping to further increase the selectivity of the reaction. However, comparable results to the *tert*-butyl ester **2e** in terms of both yield and enantioselectivity were obtained (Table 2, entries 12 and 13). The data in

Table 2. Ru-(*S*)-SYNPHOS-catalyzed asymmetric hydrogenation of substrates **2a–g**.[a]



Entry	R	*P* [bar]	Yield [%][b]	*ee*[c]
1	**2a**: R = Me	20	83	87 (*R*)-**1a**
2	**2b**: R = Et	20	82	83 (*R*)-**1b**
3	**2c**: R = Bn	20	91	87 (*R*)-**1c**
4	**2d**: R = *c*-Hex	20	96	90 (*R*)-**1d**
5	**2e**: R = *t*-Bu	20	94	94 (*R*)-**1e**
6		80	93[d]	94 (*R*)-**1e**
7		50	95[d]	94 (*R*)-**1e**
8		5	94[e,d]	94 (*R*)-**1e**
9		5	98[e]	94 (*R*)-**1e**
10		5	95[e,f]	94 (*S*)-**1e**
11		5	91[g]	86 (*R*)-**1e**
12	**2f**: R = CH(*i*-Pr)$_2$	5	96	93 (*R*)-**1f**
13	**2g**: R = C(Me)Et$_2$	5	95	94 (*R*)-**1g**

[a] *Conditions:* all reactions were performed using 1 mmol of substrate **2** in methanol for 23 h, catalyst loading, 1 mol%. In all cases, complete conversions were achieved.
[b] Isolated yield after flash chromatography.
[c] Measured by HPLC analysis (see Supporting Information).
[d] 0.5 mol% of benzoquinone was used.
[e] Hydrogenation carried out on a 5-gram scale.
[f] (*R*)-SYNPHOS was used instead of (*S*)-SYNPHOS.
[g] 0.5 mol% of catalyst was used.

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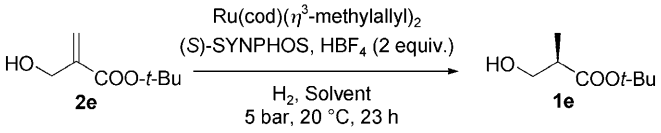
Table 3. Solvent screening for asymmetric hydrogenation of *tert*-butyl acrylate ester **2e**.[a]



Entry	Solvent	Conv. [%][b]	Yield [%][c]	*ee*[d]
1	MeTHF	100	97	66 (*R*)
2	Et_2O	100	88	70 (*R*)
3	Toluene	55	N/D[e]	N/D[e]
4	CH_2Cl_2	100	98	85 (*R*)
5	*t*-BuOH	100	96	82 (*R*)
6	*i*-PrOH	100	96	78 (*R*)
7	EtOH	100	95	89 (*R*)
8	MeOH	100	98	94 (*R*)
9	EtOAc	100	93	93 (*R*)
10	Acetone	100	92	93 (*R*)

[a] *Conditions:* all reactions were performed using 1 mmol of substrate **2**, catalyst loading, 1 mol%.
[b] Conversion determined by ^1H NMR of crude product.
[c] Isolated yield after flash chromatography.
[d] Measured by HPLC analysis on Chiralcel OD-H column.
[e] Not determined.

Table 2 also illustrate that the hydrogen pressure has no impact on the selectivity for the hydrogenation of the *tert*-butyl-substituted substrate **2e**. Finally, attempts to decrease the catalyst loading from 1 to 0.5 mol% gave rise to the hydrogenated compound **1e** with lower 86% *ee* (Table 2, entry 11).

With these results in hand, we set out to determine the optimal solvent for the asymmetric hydrogenation of compound **2e**. The cationic monohydride ruthenium complex $[Ru(H)(\eta^6\text{-cot})SYNPHOS]^+BF_4^-$ **C9** which proved to be the more efficient catalyst system was chosen. All hydrogenations were performed under a hydrogen pressure of 5 bar at room temperature for 23 h. In all cases, except for the reaction run in toluene, complete conversions were reached and compound **1e** was obtained in good to excellent yields ranging from 88 to 98%. The results from these experiments are presented in Table 3. It was found that this reaction was strongly solvent-dependent. The best results were obtained in polar solvent with up to 94% *ee* when the reaction was carried out in methanol whereas all other alcoholic solvents tested gave lower enantioselectivities (Table 3, entries 5–7, 78 to 89% *ee*). The use of acetone and ethyl acetate resulted in similar selectivity (Table 3, entries 9 and 10, 93% *ee*). As mentioned before, toluene was by far the worst solvent for this reaction with only 55% conversion whereas the use of other aprotic apolar solvents such as methyltetrahydrofuran, ether and dichloromethane led to lower selectivities (Table 3, entries 1–4, 66 to 85% *ee*).

With optimal catalyst and solvent conditions established, we decided to study other factors that might improve the selectivity. Toward this end, several commercially available chiral ligands were screened. The results, which are summarized in Table 4, indicated that both the reactivity and the enantioselectivity were highly affected by the electronic and steric properties of the ligand considered. From this screening, we found that atropisomeric diphosphines were in general excellent ligands providing compound **1e** in high isolated yields with good to excellent enantioselectivities (Table 4, entries 1 to 9, 90–98% yields and 80–94% *ee*), except in the cases of the electron-rich isopropyl **L10** and cyclohexyl **L11** MeOBIPHEP derivatives[26] for which 30% conversion was obtained (Table 4, entries 10 and 11). The use of **L4** (SEGPHOS)[27] and **L9** (MeOBIPHEP)[26] ligands resulted in a comparable high enantiodiscrimination to that reached by **L1** (SYNPHOS)[13] (Table 4, compare entries 1 *vs.* 4 and 9) whereas the same reaction catalyzed by the complex containing BINAP **L3**[28] led to a clear drop in selectivity (Table 4, compare entries 1 *vs.* 3). A decrease in enantioselectivity was also observed when the complex containing the electron-poor DIFLUORPHOS ligand **L2**[13a-c,29] was used (Table 4, entry 2, 82% *ee*).

The data in Table 4 also illustrate that the steric properties of the diphosphine, in particular the substituents at the phosphorus atom, mainly influence the stereochemical outcome of the reaction. This steric effect was revealed by comparison of the selectivity of the reaction conducted with catalysts bearing the SUNPHOS[30] family of ligands (Table 4, entries 5–8). In all cases, full conversions were obtained and compound **1e** was isolated in high yields ranging from 90–95%. The unsubstituted diphenyl SUNPHOS **L5** and the corresponding 4-Me-C_6H_4 substituted diphosphine **L6** gave comparable selectivities with, respectively, 91 and 89% *ee* (Table 4, entries 5 and 6) while ligands **L7** and **L8** having bulky substituents led to a significant drop in enantioselectivity (Table 4, entries 7 and 8, 84 and 80% *ee*). Finally, this ligand screening also revealed that non-atropisomeric diphosphines such as CHIRAPHOS **L13**[31] or JOSIPHOS **L14**[32] provided the hydrogenated compound **1e** in high isolated yields but in moderate to low *ee* values (Table 4, entries 13 and 14, 78 and 39% *ee*) whereas almost no catalytic activity was observed with the phosphoramidite PipPHOS monodentate ligand **L12**[33] (Table 4, entry 12).

Conclusions

In conclusion, using the cationic monohydride ruthenium complex $[Ru(H)(\eta^6\text{-cot})SYNPHOS]^+BF_4^-$ we have developed an efficient homogeneous asymmetric

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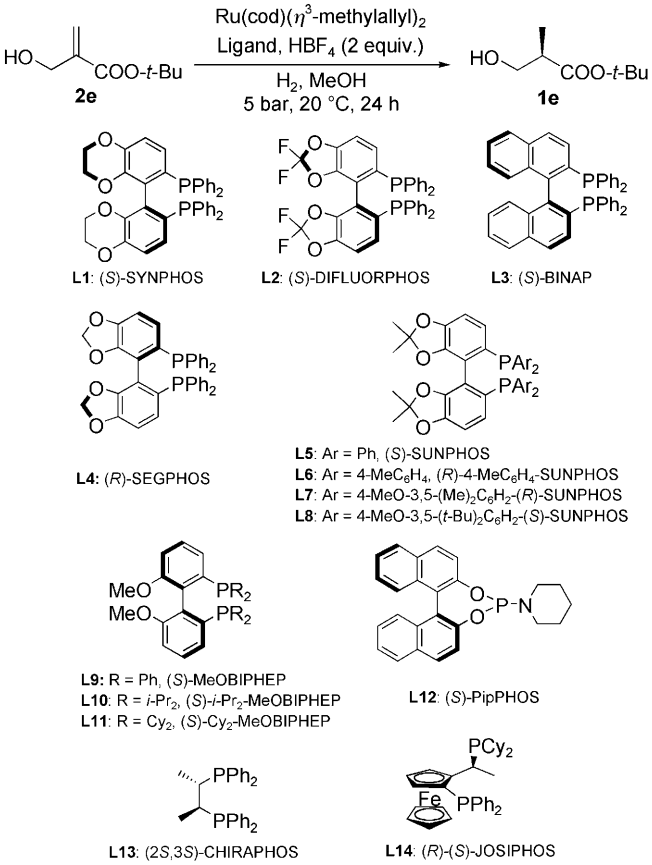
Table 4. Ligand effects for Ru-catalyzed asymmetric hydrogenation of *tert*-butyl acrylate ester **2e**.[a]



Entry	Ligand	Conv. [%][b]	Yield [%][c]	*ee*[d]
1	**L1**, (*S*)-SYNPHOS	100	98	94 (*R*)-**1e**
2	**L2**	100	91	82 (*R*)-**1e**
3	**L3**	100	93	88 (*R*)-**1e**
4	**L4**	100	95	94 (*S*)-**1e**
5	**L5**	100	92	91 (*R*)-**1e**
6	**L6**	100	93	89 (*S*)-**1e**
7	**L7**	100	90	84 (*S*)-**1e**
8	**L8**	100	91	80 (*R*)-**1e**
9	**L9**	100	95	93 (*R*)-**1e**
10	**L10**	30	N/D[e]	N/D[e]
11	**L11**	30	N/D[e]	N/D[e]
12	**L12**	10	N/D[e]	N/D[e]
13	**L13**	100	94	78 (*R*)-**1e**
14	**L14**	100	94	39 (*S*)-**1e**

[a] Conditions: all reactions were performed using 1 mmol of substrate **2e** in methanol for 24 h, catalyst loading, 1 mol%.
[b] Conversion determined by ^{1}NMR analysis of crude product.
[c] Isolated yield after flash chromatography.
[d] Measured by HPLC analysis (see Supporting Information).
[e] Not determined.

hydrogenation of acrylate ester compounds **2** which provides a direct access to synthetically valuable Roche ester derivatives in high yields and selectivities. The robustness and practicability of this highly enantioselective hydrogenation were demonstrated by the synthesis of the 3-hydroxy-2-methylpropanoic acid *tert*-butyl ester **1e** on a multigram scale, starting with 30 mmol of **2e**, and resulting in nearly quantitative yield and *ee* up to 94%. As far as the Ru-catalyzed asymmetric hydrogenation reaction is concerned, we have demonstrated that the yield and enantioselectivity depend on both steric and electronic profiling of ligands **L1–L11** and the bulkiness of the ester function of substrates **2**. As an important complement of our previous study,[11] and among a wide range of chiral ligands and transition metal complexes, we targeted and identified preferred ligand/substrate correspondences leading to the best yield and enantioselectivity and confirmed that atropisomeric ligands and particularly SYNPHOS together with hindered Roche ester derivatives were the most suitable for this reaction.

Experimental Section

Typical Procedure for Asymmetric Hydrogenation of Acrylate Esters 2

Chiral ligand (0.011 mmol) and (1,5-cyclooctadiene)Ru(η^3-methylallyl)$_2$ (3.2 mg, 0.010 mmol, commercially available from Acros), were placed in a round-bottomed tube, degassed by three vacuum/argon cycles at room temperature, and dissolved in degassed dichloromethane (1 mL). To this suspension was added dropwise at 0 °C, a freshly prepared solution of HBF_4·Me_2O in dichloromethane (130 μL, 0.022 mmol, 0.17 N). The reaction mixture was stirred at room temperature for 30 min and a resulting orange suspension was observed. After evaporation of the solvent under vacuum, a solution of the desired substrate **2** (1 mmol) in 3 mL of MeOH was added to the ruthenium catalyst. The resulting mixture was placed under the desired hydrogen pressure and temperature for 23 h. After removal of the solvent, the residue was purified by flash chromatography on silica gel to afford the hydrogenated product **1**.

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References

[1] H.-U. Blaser, B. Pugin, F. Spindler, in: *Applied Homogeneous Catalysis with Organometallic Compounds*, 2nd

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edn., (Eds.: B. Cornils, W. A. Herrmann), Wiley-VCH, Weinheim, **2000**.

[2] a) E. N. Jacobsen, A. Pfaltz, H. Yamamoto, (Eds.), *Comprehensive Asymmetric Catalysis*, Springer, Berlin, **1999**; Vols. I–III; b) T. Ohkuma, M. Kitamura, R. Noyori, in: *Catalysis Asymmetric Synthesis*, 2nd edn., (Ed.: I. Ojima), Wiley-VCH, New York, **2000**, pp 1–110.

[3] a) S. J. Mickel, G. H. Sedelmeier, D. Niederer, F. Schuerch, G. Koch, E. Kuesters, R. Daeffler, A. Osmani, M. Seeger-Weibel, E. Schmid, A. Hirni, K. Schaer, R. Gamboni *Org. Process Res. Dev.* **2004**, *8*, 107; b) I. Paterson, O. Delgado, G. J. Florence, I. Lyothier, M. O'Brien, J. P. Scott, N. Sereinig, *J. Org. Chem.* **2005**, *70*, 150.

[4] a) C. T. Goodhue, J. R. Schaeffer, *Biotechnol. Bioeng.* **1971**, *13*, 203; b) F. Molinari, R. Gandolfi, R. Villa, E. Urban, A. Kiener, *Tetrahedron: Asymmetry* **2003**, *14*, 2041; c) H. Ohta, H. Tetsukawa, N. Noto, *J. Org. Chem.* **1982**, *47*, 2400.

[5] B. A. Czeskis, A. M. Moissenkov, *J. Chem. Soc. Perkin Trans.* 1 **1989**, 1353.

[6] C. H. Senanayake, R. D. Larsen, T. J. Bill, J. Liu, E. J. Corley, P. J. Reider, *Synlett* **1994**, 199.

[7] W. Choy, P. Ma, S. Masamune, *Tetrahedron Lett.* **1981**, *22*, 3555.

[8] H. Shimizu, T. Saito, H. Kumobayashi, *Adv. Synth. Catal.* **2003**, *345*, 185.

[9] J. Wassenaar, M. Kuil, J. N. H. Reek, *Adv. Synth. Catal.* **2008**, *350*, 1610.

[10] Y. Keiji, N. Koichi, (Nippon Shokubai Co. Ltd.), Japanese Patent, 2000128832, **2000**.

[11] S. Jeulin, T. Ayad, V. Ratovelomanana-Vidal, J. P. Genêt, *Adv. Synth. Catal.* **2007**, *349*, 1592.

[12] a) J. P. Genêt, *Acc. Chem. Res.* **2003**, *36*, 908; b) R. Leroux, N. Desroy, P. Phansavath, J. P. Genêt, *Synlett* **2005**, 429; c) O. Labeeuw, P. Phansavath, J. P. Genêt, *Tetrahedron: Asymmetry* **2004**, *15*, 1899; d) O. Labeeuw, D. Blanc, P. Phansavath, V. Ratovelomanana-Vidal, J. P. Genêt, *Eur. J. Org. Chem.* **2004**, 2352; e) C. Mordant, S. Reymond, V. Ratovelomanana-Vidal, J. P. Genêt, *Tetrahedron* **2004**, *60*, 9715; f) R. Touati, V. Ratovelomanana-Vidal, B. Ben Hassine, J. P. Genêt, *Tetrahedron: Asymmetry* **2006**, *17*, 3400; g) D. Blanc, J. Madec, F. Popowyck, T. Ayad, P. Phansavath, V. Ratovelomanana-Vidal, J.-P. Genêt, *Adv. Synth. Catal.* **2007**, *349*, 943; h) C. Mordant, S. Reymond, H. Tone, D. Lavergne, R. Touati, B. Ben Hassine, V. Ratovelomanana-Vidal, J. P. Genêt, *Tetrahedron* **2007**, *63*, 6115.

[13] a) S. Duprat de Paule, N. Champion, V. Ratovelomanana-Vidal, J. P. Genêt, P. Dellis, French Patent 2830254, **2001**; b) S. Duprat de Paule, N. Champion, V. Ratovelomanana-Vidal, J. P. Genêt, P. Dellis, WO Patent 03029259, **2003**; c) S. Duprat de Paule, S. Jeulin, V. Ratovelomanana-Vidal, J. P. Genêt, N. Champion, G. Deschaux, P. Dellis, *Org. Process. Res. Dev.* **2003**, *7*, 399; d) S. Duprat de Paule, S. Jeulin, V. Ratovelomanana-Vidal, J. P. Genêt, N. Champion, P. Dellis, *Eur. J. Org. Chem.* **2003**, 1931; e) S. Duprat de Paule, S. Jeulin, V. Ratovelomanana-Vidal, J. P. Genêt, N. Champion, P. Dellis, *Tetrahedron Lett.* **2003**, *44*, 823.

[14] a) D. Basavaiah, A. J. Rao, T. Satyanarayana, *Chem. Rev.* **2003**, *103*, 811; b) E. Ciganek, *Org. React.* **1997**, *51*, 201; c) P. Langer, *Angew. Chem. Int. Ed.* **2000**, *39*, 3049.

[15] R. Shelkov, M. Nahmany, A. Melman, *J. Org. Chem.* **2002**, *67*, 8975.

[16] J. Villieras, M. Rambaud, *Synthesis* **1982**, *39*, 924; J. Villieras, M. Rambaud, *Synthesis* **1983**, *40*, 300.

[17] a) C. González-Arellano, A. Corma, M. Iglesia, F. Sánchez, *Chem. Commun.* **2005**, 3451; b) M. P. Muñoz, J. Adrio, J. C. Carretero, A. M. Echavarren, *Organometallics* **2005**, *24*, 1293.

[18] a) Y.-Q. Wang, S.-M. Lu, Y.-G. Zhou, *Org. Lett.* **2005**, *7*, 3235; b) Y.-Q. Wang, S.-M. Lu, Y.-G. Zhou, *J. Org. Chem.* **2007**, *72*, 3729; c) Y.-Q. Wang, C.-B. Yu, D.-W. Wang, X.-B. Wang, Y.-G. Zhou, *Org. Lett.* **2008**, *10*, 2071; d) Q. Yang, G. Shang, W. Gao, X. Zhang, *Angew. Chem. Int. Ed.* **2006**, *45*, 3832.

[19] S. Jeulin, N. Champion, P. Dellis, V. Ratovelomanana-Vidal, J. P. Genêt, *Synthesis* **2005**, 3666.

[20] J. P. Genêt, C. Pinel, V. Ratovelomanana-Vidal, S. Mallart, X. Pfister, M. C. Caño de Andrade, J. A. Laffitte, *Tetrahedron: Asymmetry* **1994**, *5*, 665.

[21] The putative structure of cationic monohydride $[Ru(H)(\eta^6\text{-cot})SYNPHOS]^+BF_4^-$ **C9** has been assigned by analogy with our previous work, see ref.[22a].

[22] a) D. A. Dobbs, K. P. M. Vanhessche, E. Brazi, V. Rautenstrauch, J. Y. Lenoir, J. P. Genêt, J. A. Wiles, S. H. Bergens, *Angew. Chem. Int. Ed.* **2000**, *39*, 1992; b) J. A. Wiles, S. H. Bergens, K. P. M. Vanhessche, D. A. Dobbs, V. Rautenstrauch, *Angew. Chem. Int. Ed.* **2001**, *40*, 914.

[23] a) K. E. Koenig, M. J. Sabacky, G. L. Bachman, W. C. Christopfel, H. D. Barnstorff, R. B. Friedman, W. S. Knowles, B. R. Stults, B. D. Vineyard, D. J. Weinkauff, *Ann. N. Y. Acad. Sci.* **1980**, *333*, 16; b) S. Feldgus, C. R. Landis, *J. Am. Chem. Soc.* **2000**, *122*, 12714.

[24] A. Karlström, A. Undén, *Tetrahedron Lett.* **1995**, *36*, 3909.

[25] A. Karlström, A. Undén, *Tetrahedron Lett.* **1996**, *37*, 4243.

[26] a) M. Cereghetti, J. Foricher, B. Heiser, R. Schmid, European Patent 398,132, **1990**; b) R. Schmidt, J. Foricher, M. Cereghetti, P. Schönholzer, *Helv. Chim. Acta* **1991**, *74*, 370; c) R. Schmidt, E. A. Broger, M. Cereghetti, Y. Crameri, J. Foricher, M. Lalonde, R. K. Müller, M. Scalone, G. Schoettel, U. Zutter, *Pure Appl. Chem.* **1996**, *68*, 131.

[27] a) T. Saito, T. Yokozawa, X. Zhang, N. Sayo, European Patent 850,945, **1998**; b) T. Saito, T. Yokozawa, T. Ishizaki, T. Moroi, N. Sayo, T. Miura, H. Kumobayashi, *Adv. Synth. Catal.* **2001**, *343*, 264.

[28] a) A. Miyashita, A. Yasuda, H. Takaya, K. Toriumi, T. Ito, T. Souchi, R. Noyori, *J. Am. Chem. Soc.* **1980**, *102*, 7932; b) A. Miyashita, H. Takaya, T. Souchi, R. Noyori, *Tetrahedron* **1984**, *40*, 1245.

[29] S. Jeulin, S. Duprat de Paule, V. Ratovelomanana-Vidal, J. P. Genet, N. Champion, P. Dellis, *Angew. Chem. Int. Ed.* **2004**, *43*, 320.

[30] a) Y. Sun, X. Wan, G. Minjie, D. Wang, X. Dong, Y. Pan, Z. Zhang, *Tetrahedron: Asymmetry* **2004**, *15*, 2185; b) Y. Sun, X. Wan, J. Wang, Q. Meng, H. Zhang, L. Jiang, Z. Zhang, *Org. Lett.* **2005**, *7*, 5425; c) Q.

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Meng, Y. Sun, V. Ratovelomanana-Vidal, J. P. Genet, Z. Zhang, *J. Org. Chem.* **2008**, *73*, 3842.
[31] M. D. Fryzuk, B. J. Bosnich, *J. Am. Chem. Soc.* **1977**, *99*, 6262.
[32] a) A. Togni, C. Breutel, A. Schnyder, F. Spindler, H. Landert, A. Tijani, *J. Am. Chem. Soc.* **1994**, *116*, 4062; b) A. Togni, *Angew. Chem. Int. Ed.* **1996**, *35*, 1475.
[33] H. Bernsmann, M. van den Berg, R. Hoen, A. J. Minnaard, G. Mehler, M. T. Reetz, J. G. De Vries, B. L. Feringa, *J. Org. Chem.* **2005**, *70*, 943.

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