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Synthesis of Versatile Building Blocks through Asymmetric Hydrogenation of Functionalized Itaconic Acid Mono-Esters

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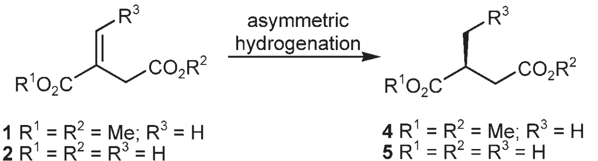
Abstract: The rhodium-catalyzed asymmetric hydrogenation of several β-substituted itaconic acid monoesters, using a library of monodentate phosphoramidite and phosphite ligands is described. Two β-alkyl-substituted substrates were readily hydrogenated by the rhodium complex $Rh(COD)_2BF_4$ in combination with (*S*)-PipPhos as a ligand resulting in *ee*s of 99%. In contrast, the corresponding more hindered β-aryl-substituted substrates did not exhibit acceptable enantioselectivities under these conditions. However, the use of a 48-membered ligand library led to the identification of several suitable ligands for these substrates, resulting in *ee*s of 89–99%. The resulting optically active succinic acid derivatives are potentially useful building blocks for more elaborate compounds, because of the ability to differentiate between the carboxylic acid and the ester groups on either side of the molecule.

Keywords: asymmetric catalysis; asymmetric hydrogenation; itaconic acid; monodentate phosphoramidite ligands; rhodium; succinic acid

Introduction

Over the past decades, homogeneous asymmetric hydrogenation of prochiral olefins has proven to be one of the most powerful methods for the synthesis of enantiomerically pure building blocks. Today, this clean and atom-efficient reaction has a broad scope and is amongst the most studied catalytic transformations. Numerous new catalyst systems are reported each year, thereby continuously increasing the efficiency and scope of this reaction.[1] Dimethyl itaconate (**1**) and – to a lesser extent – itaconic acid (**2**) are commonly used model substrates in the development of new catalyst systems for asymmetric hydrogenation (Scheme 1). The synthetic value of the resulting succinic diesters (**4**) and diacids (**5**) is however limited, since it is virtually impossible to differentiate between the two acid/ester groups. On the other hand, the use of itaconic acid monoesters (e.g., **3**) would result in succinic acid derivatives of type **6**. These compounds would be considerably more useful than **4** or **5**, since carboxylic acids can normally be reduced selectively in the presence of ester groups, thereby discriminating between the two parts of the molecule.[2] These bifunctional, enantiomerically pure compounds could thus be transformed into useful building blocks for a range of (pharmaceutically relevant) natural products.[3]



1 $R^1 = R^2 = Me; R^3 = H$
2 $R^1 = R^2 = R^3 = H$
3 $R^1 = H; R^2 = Me$

4 $R^1 = R^2 = Me; R^3 = H$
5 $R^1 = R^2 = R^3 = H$
6 $R^1 = H; R^2 = Me$

Scheme 1. Asymmetric hydrogenation of itaconic acids and its mono- and diesters.

Surprisingly, the use of such itaconic acid monoesters in asymmetric hydrogenation research has received only moderate attention[4] and particularly examples of substrates with a carboxylic acid moiety in the conjugated position are rare.[3,4b,5] In addition, the asymmetric hydrogenation of substituted itaconate derivatives has remained relatively unexplored.[4a,c,6]

In this paper we wish to report the rhodium-catalyzed asymmetric hydrogenation of β-substituted itaconic acid monoesters, using a monodentate phosphoramidite ligand library, developed by Feringa, Minnaard, de Vries et al. in collaboration with DSM

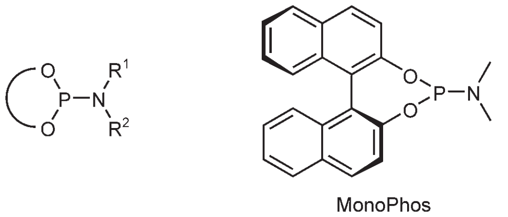
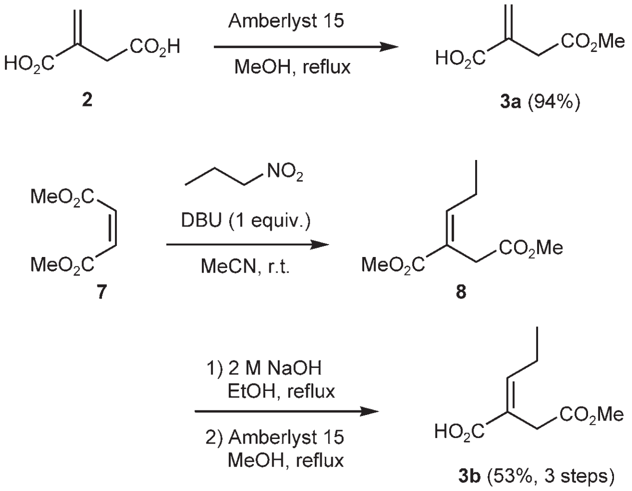


Figure 1. General structure of phosphoramidite ligands and structure of MonoPhos.

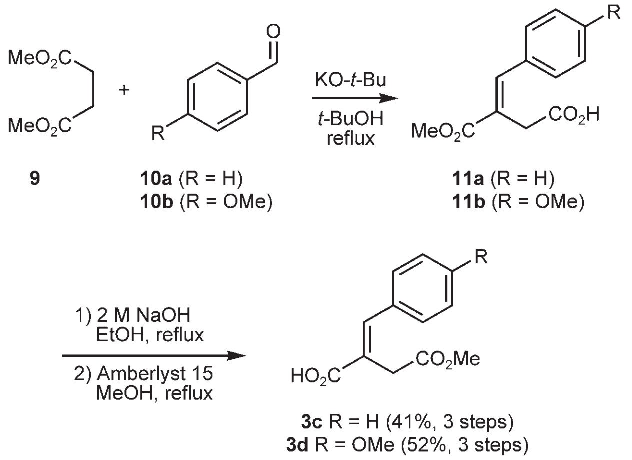
Pharmaceutical Products (e.g., MonoPhos, Figure 1).[7,8] Over the past years, these phosphorus ligands have been successfully applied in the asymmetric hydrogenation of a range of prochiral olefins, including α- and β-dehydroamino acids and esters,[9] itaconic acid and its dimethyl ester,[9b–e] enol acetates and enol carbamates,[10] enamides,[11] acrylic acids[12] and imines.[13] Besides asymmetric hydrogenation, this class of ligands has also been successfully applied in the enantioselective copper-catalyzed conjugate addition of dialkylzinc reagents,[14] in asymmetric hydrosilylation,[15] in asymmetric hydrovinylation,[16] in asymmetric cyclopropanation,[17] in allylic substitution,[18] in the asymmetric Phauson–Khand reaction,[19] in the asymmetric Heck reaction,[20] in asymmetric cycloisomerization,[21] in asymmetric allyl alcohol isomerization,[22] in asymmetric [2+2+2] cycloaddition[23] and in asymmetric arylations using arylboronic acids.[24]

Results and Discussion

We chose to focus our attention on four different itaconic acid derivatives. Besides the unsubstituted monoester **3a**, an ethyl-substituted analogue (**3b**) and two aryl-substituted substrates (**3c** and **d**) were selected as starting points. The preparation of the itaconate derivatives **3** was carried out *via* several methods. The unsubstituted monoester **3a** could be readily synthesized from itaconic acid (**2**) itself. Reaction of **2** in the presence of Amberlyst 15 in methanol under reflux conditions afforded pure **3a** in 94% yield, accompanied by only trace amounts of the corresponding diester (Scheme 2). The synthesis of the β-substituted itaconates required a somewhat larger effort. First of all, ethyl-substituted monoester **3b** was readily synthesized using a reported procedure.[25] Hence, dimethyl maleate (**7**) was reacted with 1-nitropropane in the presence of one equivalent of DBU, resulting in sequential conjugate addition and elimination of HNO_2. The formed (*E*)-diester **8** was then hydrolyzed with aqueous NaOH, followed by selective monoesterification with Amberlyst 15 in methanol, resulting in the formation of **3b** in 53% from **7** (Scheme 2).



Scheme 2. Synthesis of unsubstituted and ethyl-substituted itaconates.



Scheme 3. Synthesis of aryl-substituted itaconates *via* a Stobbe condensation.

Synthesis of aryl-substituted itaconic acid monoesters *via* the previously described route is more laborious, because it would require the preparation of the corresponding nitroalkane reagents, which are not commercially available. Therefore, we chose to prepare **3c** and **3d** through a Stobbe condensation[26] of dimethyl succinate (**9**) with aldehydes **10a** and **b** (Scheme 3).

Condensation of dimethyl succinate with benzaldehyde and 4-methoxybenzaldehyde in refluxing *tert*-butyl alcohol resulted in the formation of monoesters **11a** and **b** as single (*E*)-geometrical isomers. Next, the monoesters were hydrolyzed with 2M NaOH and the resulting diacids were again monoesterified with Amberlyst 15 in methanol, leading to the desired hydrogenation precursors **3c** and **d**.

As already pointed out in the introduction, asymmetric hydrogenations of the four itaconates were performed using a phosphoramidite ligand library. Their good accessibility and modular nature makes

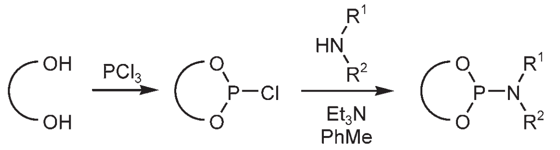


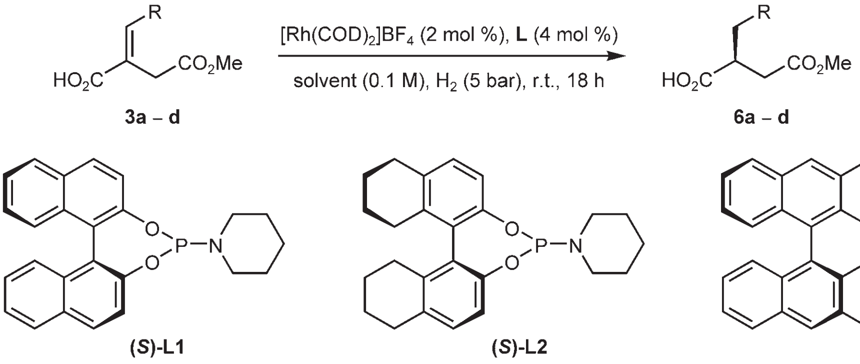
Figure 2. General synthetic route for phosphoramidite ligands.

these ligands particularly suitable for combinatorial applications.[27] Phosphoramidites are essentially built up from two fragments, both of which can be varied to a large extent. In a common synthetic procedure, a (non-)chiral diol is converted into the corresponding chlorophosphite by refluxing in an excess of PCl_3. This chlorophosphite is then reacted with the appropriate (non-)chiral amine in the presence of triethylamine, resulting in the phosphoramidite ligand, which can often be purified by crystallization (Figure 2).

Although MonoPhos (see Figure 1) was the first phosphoramidite ligand that was discovered to induce high enantioselectivities in olefin hydrogenation,[9e] follow-up research has shown other analogous ligands to be better suited for numerous substrates. For instance, PipPhos (**L1**) was identified as an excellent ligand for the asymmetric hydrogenations of a range of compounds, including dehydroamino acid derivatives and dimethyl itaconate,[9b] and enol acetates/carbamates.[10] For this reason we decided to start our investigations into the hydrogenation of **3a–d** with **L1** (Table 1). The hydrogenations were carried out in an Endeavor apparatus,[28] which is essentially an autoclave with eight parallel reaction vessels capable of accommodating 5 mL of solvent. In addition, it allows the continuous monitoring of hydrogen uptake, thereby enabling the reactions to be followed in time. The hydrogenations in Table 1 were carried out at a pressure of 5 bar with 0.5 mmol of substrate, using 2 mol% of $[Rh(COD)_2]BF_4$ and 4 mol% of ligand.

We were pleased to find that the hydrogenation of **3a** and **3b** in dichloromethane proceeded nearly quantitatively and with excellent *ee*s of 97 and 94% (entries 1 and 2), thus eliminating the need for extensive optimization for these substrates. On the other hand, the reactions of **3c** and **3d** under the same conditions resulted in lower conversions[29] and *ee*s of 52 and 46% (entries 3 and 4). A striking difference in reactivity was observed when carrying out the hydrogenations of **3a–d** in methanol instead of dichloromethane. No significant hydrogen uptake was observed for **3b–d**, indicating that no reaction had taken place (entries 6–8). The reaction of **3a** was found to proceed quantitatively, however, hardly any enantiomeric excess was observed (entry 5). This extreme solvent

Table 1. Asymmetric hydrogenation in Endeavor apparatus.



3a – d **6a – d**

(*S*)-L1 **(*S*)-L2** **(*S*)-L3**

Entry	Substrate	R	Ligand	Solvent	Product	Conversion [%][a]	*ee* [%][a,b]
1	**3a**	H	(*S*)-**L1**	CH_2Cl_2	**6a**	>99	97
2	**3b**	Et	(*S*)-**L1**	CH_2Cl_2	**6b**	98	94
3[c]	**3c**	Ph	(*S*)-**L1**	CH_2Cl_2	**6c**	91	52
4	**3d**	*p*-$MeOC_6H_4$	(*S*)-**L1**	CH_2Cl_2	**6d**	60	46
5	**3a**	H	(*S*)-**L1**	MeOH	**6a**	>99	-7
6	**3b**	Et	(*S*)-**L1**	MeOH	**6b**	n.d.[d]	n.d.
7	**3c**	Ph	(*S*)-**L1**	MeOH	**6c**	n.d.[d]	n.d.
8	**3d**	*p*-$MeOC_6H_4$	(*S*)-**L1**	MeOH	**6d**	n.d.[d]	n.d.
9	**3d**	*p*-$MeOC_6H_4$	(*S*)-**L2**	CH_2Cl_2	**6d**	86	62
10	**3d**	*p*-$MeOC_6H_4$	(*S*)-**L3**	CH_2Cl_2	**6d**	78	-51

[a] Determined by HPLC.
[b] (*S*)-configuration.
[c] Pressure slowly raised to 25 bar.
[d] No significant H_2-consumption was observed; n.d. = not determined.

Table 2. Influence of lower catalyst loadings.[a]

Entry	Substrate	R	Catalyst [mol %]	Ligand	Concentration [M]	Product	Conversion [%][b]	*ee* [%][b,c]
1	**3a**	H	0.5	(*S*)-**L1**	0.2	**6a**	>99	99.7
2	**3b**	Et	0.5	(*S*)-**L1**	0.2	**6b**	>99	58
3	**3a**	H	1	(*S*)-**L2**	0.1	**6a**	>99	98
4	**3b**	Et	1	(*S*)-**L2**	0.1	**6b**	>99	91

[a] Conditions: $Rh(COD)_2BF_4$/ligand (1:2), CH_2Cl_2, H_2 (5 bar), r.t., 18 h.
[b] Determined by HPLC.
[c] (*S*)-configuration.

dependency has been observed before with these catalyst systems and in many cases the use of non-protic solvents appears to give the best results;[8] known exceptions are the hydrogenations of (*Z*)-*N*-acetyl-β-dehydroamino acid esters[9d] and α-substituted cinnamic acids[12] which proceed best in 2-propanol and 2-propanol/water mixtures, respectively. Additionally, we investigated whether different ligand backbones had an influence on the enantioselectivity in the hydrogenation of the aryl-substituted substrate **3d** (entries 9 and 10). We employed an octahydro analogue of **L1** (i.e., **L2**) and a ligand with a 3,3′-dimethylBINOL moiety (**L3**). Unfortunately, these two ligands offered only a slight improvement in terms of enantioselectivity. The result from entry 10 is remarkable, since the opposite enantiomer is formed, possibly due to a different coordination mode of substrate and/or ligands to the rhodium.

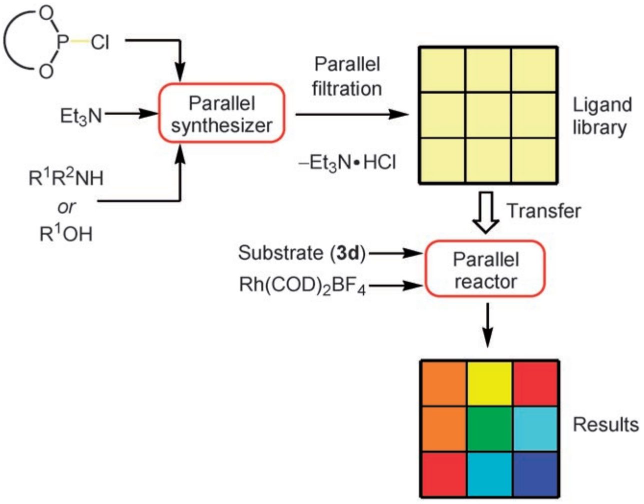


Figure 3. Schematic representation of the automated ligand synthesis and subsequent hydrogenation.

Furthermore, we decided to study the influence of lower catalyst loadings on the conversion and enantioselectivity of the hydrogenations of **3a** and **3b** (Table 2). Lowering the amount of catalyst from 2 mol% to 0.5 mol% actually improved the *ee* of **6a** somewhat (99.7%, entry 1). On the other hand, the *ee* of **6b** was found to be surprisingly low (58%, entry 2), indicating that for this substrate at least 2 mol% of catalyst is required to obtain an acceptable *ee*. This latter result can probably be ascribed to the presence of minor impurities in the starting material.

The use of ligand **L2**, which already slightly improved the enantioselectivity for **3c** (see Table 1), resulted in comparable *ee*s for the hydrogenation of **3a** and **3b** (entries 3 and 4). It should be noted that these two experiments were performed with 1 mol% of catalyst, making comparison in the case of **3b** more complicated, in view of the influence of catalyst loading discussed earlier (see above).

Because the hydrogenation experiments conducted so far with **3c** and **3d** did not result in satisfactory enantioselectivities, we decided to carry out a high-throughput experiment with a solution phase library of 48 ligands. Figure 3 shows a schematic representation of the parallel ligand synthesis and subsequent hydrogenation. The ligands were prepared in a fully automated fashion by a liquid handling robot, which was placed inside a glove-box. Stock solutions of the chlorophosphite, triethylamine and the amine or the alcohol (for the preparation of phosphites rather than phosphoramidites) were dispensed into a microtiter plate, which was shaken for 2 h followed by parallel filtration, affording the different ligands in solution. Next, fractions of the ligand solutions were transferred to 48 vials, alongside with the solutions of $Rh(COD)_2BF_4$ and the substrate (**3d**).[30] The 48 parallel hydrogenations were performed in dichloromethane in a Premex 96-Multi Reactor,[31] using 4 mol% of catalyst and 25 bar of H_2 at room temperature for 6 h. Afterwards, conversions and *ee*s were determined by chiral HPLC.

The 48 ligands that were selected for the parallel hydrogenation experiment are depicted in Figure 4 a. Besides eight secondary amines, we decided to include five primary amines, because we envisaged that the steric hindrance of **3c** and **d** can possibly be compensated for by using less hindered ligands. Phosphoramidite ligands derived from primary amines are generally known to be somewhat unstable, especially towards column chromatography purification used in traditional synthesis. The mild purification used in the automated synthesis and the immediate coordination of the

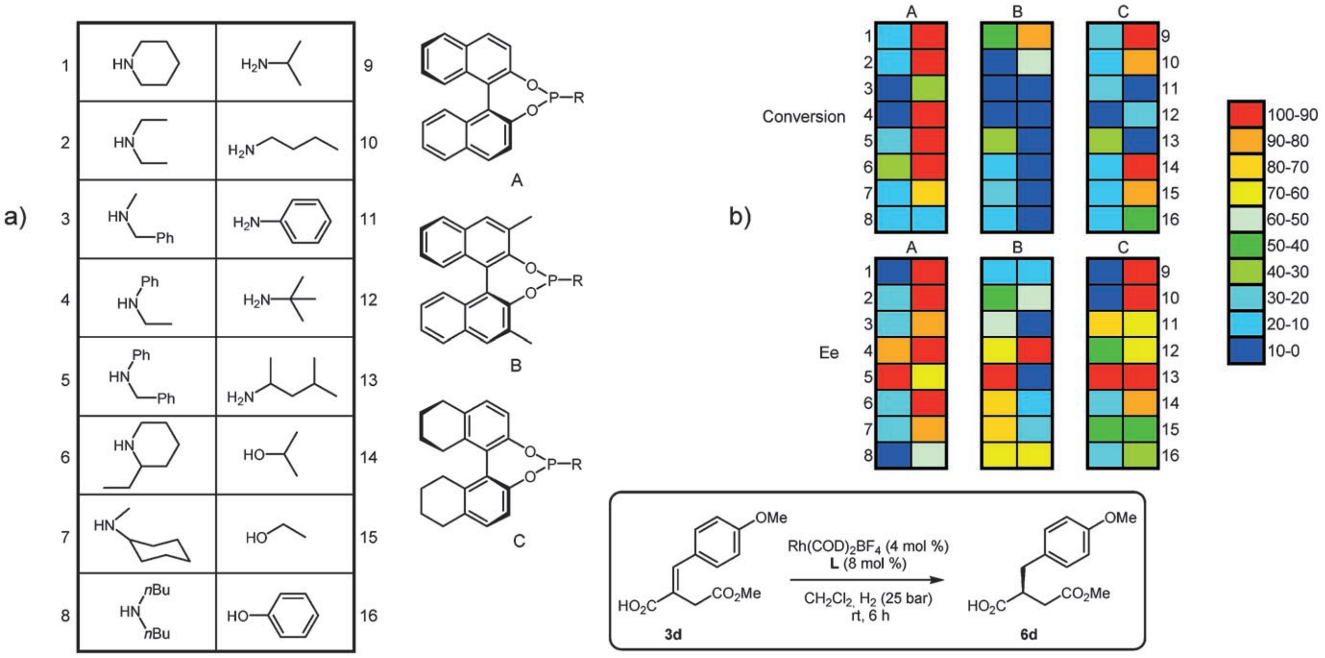


Figure 4. Asymmetric hydrogenation of **3d. a)** List of amines/alcohols and backbones used in ligand library. **b)** Conversions and (absolute) *ee* values.

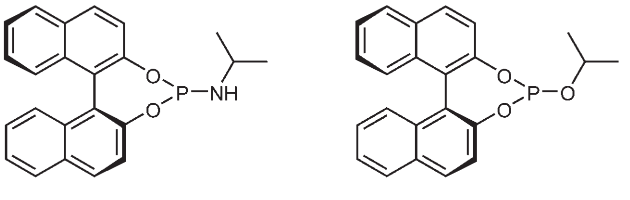
ligand to the metal makes these ligands easily available. We have previously shown that these NH ligands lead to the formation of very fast rhodium catalysts that have hydrogenation rates comparable to or better than the best rhodium bisphosphine complexes.[32]

In addition, we used three different alcohols instead of amines, resulting in the corresponding phosphite ligands – a class of ligands reported by Reetz and coworkers[33] – which are also excellent ligands for asymmetric hydrogenation. Moreover, we chose to study three different BINOL-type ligand backbones (i.e., **A**–**C**), which in combination with the 16 amine/alcohol fragments eventually resulted in a library of 48 different ligands.

Figure 4 b shows the results obtained in the asymmetric hydrogenation of **3d**. To our delight, several entries resulted in both a conversion and an *ee* of $\geq$90%. In general, the ligands based on the regular BINOL backbone (**A**) appeared to be the most suitable. Entries A9, A10, A12 and A14 showed the best results, with conversions of 90–100% and *ee*s of 94–98%.[34] The ligands that were based on the octahydro-BINOL backbone (**C**) gave lower conversions and *ee*s, with the exception of those used in entries C9 and C10, which produced data comparable to those from the analogous ligands in entries A9 and A10. Clearly, the use of phosphoramidite ligands based on primary amines is the key to success for the hydrogenation of **3d**. While these ligands in a number of cases gave excellent *ee*s and conversions, the ligands based on secondary amines led to poor conversions and in most cases low *ee*s. A noteworthy exception is presented by the ligands based on *N*-benzylaniline (entries A5, B5 and C5). Although the conversions obtained with these ligands are poor (26–34%), the observed *ee*s are surprisingly high (99–100%). In addition, the isopropyl-substituted phosphite ligand in entry A14 also gave a high conversion (95%) and *ee* (94%), suggesting that monodentate phosphite ligands are also suitable for the hydrogenation of these substrates. Finally, the more hindered 3,3′-dimethyl-BINOL-based ligands (**B**) were found to be less suited for this specific substrate, generally exhibiting poor conversions and at best only moderate *ee*s. This is again in agreement with the observation that less hindered ligands are required for the hydrogenation of more hindered substrates.

In the end, two ligands were selected from the library to be scaled up to a 0.5-mmol scale and to test if similar results could be obtained with substrate **3c**. First of all, phosphoramidite ligand **L4**[35] was selected based on the results in entry A9 in Figure 4. In addition, we chose to use the analogous phosphite ligand **L5**[36] in view of possible instability issues with **L4** (Figure 5).

Table 3 shows the application of **L4** and **L5** in the hydrogenation of **3c** and **d** on a 0.5-mmol scale in the Endeavor reactor. The ligands were prepared in a similar fashion as in the library experiment, namely in a glove-box and using the same stock solutions as used in the parallel synthesizer. First of all, we were pleased to see that the behaviour of **3c** in terms of reactivity and enantioselectivity was almost identical to that of **3d**. The use of phosphite ligand **L5** resulted in



(S)-L4 **(S)-L5**

Figure 5. Isopropyl-substituted phosphoramidite (**L4**) and phosphite (**L5**) ligands.

Table 3. Translation of library results to 0.5-mmol Endeavor experiments.[a]

Entry	Substrate	L[b]	Product	Conversion [%][c]	*ee* [%][c,d]
1	**3c**	(*S*)-**L4**	**6c**	>99	91
2	**3d**	(*S*)-**L4**	**6d**	>99	92
3	**3c**	(*S*)-**L5**	**6c**	>99	97
4	**3d**	(*S*)-**L5**	**6d**	>99	96

[a] Conditions: $Rh(COD)_2BF_4$ (1 mol%), ligand (2 mol%), solvent (0.1 M), H_2 (25 bar), r.t., 2 h.

[b] Ligands were prepared in a glove box and not further purified.

[c] Determined by HPLC.

[d] (*S*)-configuration.

quantitative conversions and *ee*s of 96 and 97% (entries 3 and 4), which are slightly better than the results obtained in the library experiment. However, phosphoramidite ligand **L4** was found to give somewhat lower *ee*s than those observed in the library experiment (91–92% compared to 96%, entries 1 and 2). Preforming the catalyst complex $[(\mathbf{L})_2Rh(COD)BF_4]$ prior to the hydrogenation did not improve the results for both substrates and ligands. Therefore, it was decided to select **L5** as the ligand for the gram-scale hydrogenation of **3c** and **d** and to prepare a stock solution of this ligand in the glove-box, as was done with the experiments in Table 3.

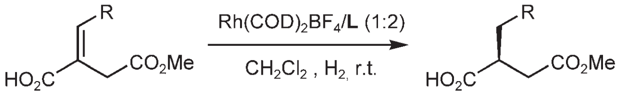
Since the monoacids **6a–d** are intended as building blocks for more elaborate synthetic targets,[2] the asymmetric hydrogenations of **3a–d** evidently need to be carried out on a preparative scale. Thus, gram-scale hydrogenations of **3a–d** were performed in an autoclave vessel, using ligand **L1** for substrates **3a** and **b** and ligand **L5** for substrates **3c** and **d** (Table 4). The hydrogenations of **3a** and **b** (entries 1 and 2) were carried out under 10 bar of H_2 pressure using a relatively low amount of catalyst (0.5 mol%) for **3a**, since lower catalyst loadings were found not to diminish the conversion and *ee* for this substrate (see Table 2). Gratifyingly, both reactions resulted in complete conversion of the starting material within 3 h and a product with an *ee* of 99%.

For the hydrogenation of **3c** and **d**, a solution of ligand **L5** was synthesized in a glove-box under identical conditions as employed in the library experiment. Next, the appropriate amount of this solution, the $Rh(COD)_2BF_4$ and the dichloromethane were transferred into the high-pressure vessel and the hydrogenation was performed under 25 bar of H_2 (entries 3 and 4). The conversions of the starting materials were again quantitative, however, the *ee*s were somewhat lower than those observed in the library and Endeavor experiments. In the end, compounds **6c** and **6d** were isolated with *ee*s of 94 and 89%, respectively.

Conclusions

Rhodium(I)-catalyzed asymmetric hydrogenation of β-substituted itaconic acid monoesters proceeded

Table 4. Autoclave hydrogenations on a gram-scale.



3a – d **6a – d**

Entry	Substrate	R	Catalyst [%]	Ligand	Concentration [M]	Pressure [bar]	Product	Conversion [%][a]	*ee* [%][b]
1	**3a**	H	0.5	(*S*)-**L1**	0.28	10	**6a**	>99	99 (*S*)
2	**3b**	Et	2	(*S*)-**L1**	0.11	10	**6b**	>99	99 (*S*)
3	**3c**	Ph	2	(*R*)-**L5**[c]	0.10	25	**6c**	>99	94 (*R*)
4	**3d**	*p*-$MeOC_6H_4$	2	(*R*)-**L5**[c]	0.12	25	**6d**	>99	89 (*R*)

[a] Determined by ^1H NMR.

[b] Determined by HPLC.

[c] Ligand synthesized by hand in a glove-box; (*R*)-isomer was prepared.

readily and resulted in high *ee*s, using a monodentate phosphoramidite/phosphite ligand library. Unsubstituted and β-ethyl-substituted substrates could be converted into the corresponding succinic acid derivatives on a gram-scale, using (*S*)-PipPhos as a ligand. Under 5 bar of H_2 the conversions were complete within 3 h with *ee*s of 99%. On the other hand, the reaction of the corresponding aryl-substituted substrates under identical conditions proceeded significantly slower and with lower *ee*s, thus demanding further optimization. Investigation of the hydrogenation of one of these latter substrates with a 48-membered ligand library, resulted in the discovery of a number of suitable ligands, that exhibited *ee*s up to 99%. Finally, gram-scale hydrogenation of all itaconates under 25 bar of H_2 produced the corresponding succinic acid derivatives quantitatively and with *ee*s of 94 and 89%, respectively. The resulting optically active succinic acid derivatives are potentially useful building blocks for more elaborate compounds, because of the difference in reactivity between the carboxylic acid and ester groups on either side of the molecule. An example from our group illustrating the synthetic use of these scaffolds is described in the following article in this issue.[2]

Experimental Section

General

All reactions were carried out under an atmosphere of dry argon, unless stated otherwise. Argon was dried over SICAPENT®, $CaCl_2$ and KOH. Infrared (IR) spectra were obtained using an ATI Mattison Genesis Series FTIR spectrometer and wavelengths (ν) are reported in cm^{-1}. Optical rotations were measured on a Perkin–Elmer 241 polarimeter, using concentrations (*c*) in g/100 mL in the indicated solvents. ^1H and ^{13}C nuclear magnetic resonance (NMR) spectra were determined in $CDCl_3$, unless indicated otherwise, using a Bruker DMX200 (200 MHz) or a Bruker DMX300 (300 MHz) spectrometer. Chemical shifts (δ) are given in ppm downfield from tetramethylsilane. HR-MS measurements were carried out using a Fisons (VG) Micromass 7070E or a Finnigan MAT900S instrument. Column chromatography was performed with Acros Organics silica gel (0.035 ± 0.070 nm) or Merck silica gel 60 (0.040–0.063 mm). Unless stated otherwise, all commercially available reagents were used as received. Ligands **L1**–**L3** were synthesized through a procedure reported in the literature.[37]

4-Methoxy-2-methylene-4-oxobutanoic Acid (3a)

Amberlyst-15H$^+$ (2.4 g) was washed to neutral with MeOH and added to a solution of itaconic acid (2.03 g, 15.6 mmol) in MeOH (40 mL). After gentle stirring for 6 d at room temperature, the suspension was filtered over Celite and the solvent evaporated. The resulting light brown solid was dissolved in CH_2Cl_2 and filtered over Celite after which the solvent was evaporated yielding a white solid. The crude product was recrystallized (heptane/toluene, 3:2) affording pure **3a** as white crystals; yield: 2.11 g (94%). The analytical data agreed with those reported in the literature.[38] ^1H NMR ($CDCl_3$, 300 MHz): $\delta = 6.48$ (m, 1H), 5.84 (m, 1H), 3.71 (s, 3H), 3.35 (s, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 171.2$, 171.1, 133.3, 131.1, 52.3, 37.2.

(*E*)-2-(2-Methoxy-2-oxoethyl)pent-2-enoic Acid (3b)

To a solution of dimethyl maleate (5.03 g, 33.5 mmol) in MeCN (100 mL) were added 1-nitropropane (3.05 mL, 33.5 mmol) and DBU (5.05 mL, 33.6 mmol). The mixture was stirred at room temperature for 20 h, after which the volatiles were removed under vacuum. The crude product was purified by column chromatography (EtOAc/heptane, 1:6). The resulting diester was dissolved in EtOH (30 mL) and aqueous NaOH (0.5 M, 150 mL) was added. The mixture was stirred at reflux temperature for 1 h, followed by evaporation of most of the EtOH under reduced pressure. Extra H_2O (100 mL) was added and the mixture was washed with EtOAc (3 × 100 mL). Next, the aqueous layer was acidified (pH ~ 1) with 2 M HCl, extracted with EtOAc (2 × 150 mL) and the organic layers were dried ($MgSO_4$) and concentrated. The resulting diacid was dissolved in MeOH (150 mL), Amberlyst-15H$^+$ (3.5 g) was added and the reaction mixture was refluxed for 7 h. The mixture was filtered over Celite and concentrated under vacuum, resulting in crude **3b**. The product was recrystallized from toluene/heptane, yielding **3b** as a white crystalline solid. The overall yield was 3.06 g (53%). The analytical data agreed with those reported in the literature.[25a] ^1H NMR ($CDCl_3$, 300 MHz): $\delta = 7.09$ (t, $J = 7.6$ Hz, 1H), 3.68 (s, 3H), 3.34 (s, 2H), 2.22 (m, 2H), 1.07 (t, $J = 7.6$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 172.3$, 171.1, 150.0, 124.3, 52.1, 31.7, 22.5, 12.8.

(*E*)-2-Benzylidene-4-methoxy-4-oxobutanoic Acid (3c)

To a refluxing suspension of KO*t*Bu (16.5 g, 140.5 mmol) in *t*-BuOH (100 mL) was carefully added a solution of dimethyl succinate (23.3 g, 159 mmol) and benzaldehyde (13.6 g, 127 mmol) in *t*-BuOH (100 mL). The reaction mixture was stirred at reflux temperature for 18 h, after which the solvent was removed under vacuum. The residue was dissolved in 1 M HCl (100 mL) and this solution was extracted with EtOAc (3 × 100 mL). The organic layers were dried (Na_2SO_4) and concentrated. The resulting monoacid was dissolved EtOH (50 mL) and aqueous NaOH (2 M, 100 mL) was added. The reaction was stirred at reflux temperature for 1 h, followed by evaporation of most of the EtOH under reduced pressure. Extra H_2O (100 mL) was added and the mixture was washed with EtOAc (3 × 100 mL). Next, the aqueous layer was acidified (pH ~ 1) with 2 M HCl, extracted with EtOAc (2 × 100 mL) and the organic layers were dried (Na_2SO_4) and concentrated. The resulting diacid was dissolved in MeOH (170 mL), Amberlyst-15H$^+$ (5.8 g) was added and the reaction mixture was refluxed for 16 h. The mixture was filtered over Celite and concentrated under vacuum, resulting in crude **3c**. The product was recrystallized from toluene/heptane, yielding **3c** as a white solid. The overall yield was 11.5 g (41%). The analytical data agreed with those reported in the literature.[39] ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 8.03$ (s, 1H), 7.38 (m, 5H), 3.75 (s, 3H), 3.56 (s, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 172.7$, 171.4, 144.3, 134.6, 129.3, 129.2, 128.7, 125.2, 52.3, 33.2.

(*E*)-4-Methoxy-2-(4-methoxybenzylidene)-4-oxobutanoic Acid (3d)

To a refluxing suspension of KO-*t*-Bu (16.8 g, 150 mmol) in *t*-BuOH (60 mL) was carefully added a solution of dimethyl succinate (17.5 g, 120 mmol) and 4-methoxybenzaldehyde (13.6 g, 100 mmol) in *t*-BuOH (60 mL). The reaction mixture was stirred at reflux temperature for 18 h, after which the solvent was removed under vacuum. The residue was dissolved in 1 M HCl (80 mL) and this solution was extracted with EtOAc (3×75 mL). The organic layers were dried (Na_2SO_4) and concentrated. The resulting monoacid was dissolved EtOH (40 mL) and aqueous NaOH (2 M, 100 mL) was added. The reaction mixture was stirred at reflux temperature for 2 h, followed by evaporation of most of the EtOH under reduced pressure. Extra H_2O (100 mL) was added and the mixture was washed with EtOAc (3×100 mL). Next, the aqueous layer was acidified (pH ~ 1) with 2 M HCl, extracted with EtOAc (3×150 mL) and the organic layers were dried (Na_2SO_4) and concentrated. The resulting diacid was dissolved in MeOH (200 mL), Amberlyst-15H$^+$ (8.5 g) was added and the reaction mixture was refluxed for 18 h. The mixture was filtered over Celite and concentrated under vacuum, resulting in crude **3d**. The product was recrystallized from toluene/heptane, yielding **3d** as an off-white crystalline solid. The overall yield was 13.1 g (52%). ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 7.96$ (s, 1H), 7.35 (d, $J = 8.8$ Hz, 2H), 6.93 (d, $J = 8.8$ Hz, 2H), 3.83 (s, 3H), 3.74 (s, 3H), 3.59 (s, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta =$ 172.6, 171.6, 160.6, 144.0, 131.2, 127.1, 122.8, 114.2, 55.4, 52.3, 33.3; HR-MS (CI$^+$): $m/z = 250.0835$, calcd. for $C_{13}H_{14}O_5$, [M]$^+$: 250.0841.

Endeavor Experiments

The substrate, $Rh(COD)_2BF_4$ and the ligand were weighed into the glass reaction vessels. The vessels were placed in the reactors and 5 mL of solvent were added. The reactors were then purged for 30 min with N_2 before applying a hydrogen atmosphere. The pressure was kept constant during the reaction and the hydrogen uptake was monitored. After completion of the reaction, the reactors were opened and samples were taken, which were filtered over a short silica column and subjected to *ee* determination by GC or HPLC. Conversions were determined by ^{1}H NMR.

Library Synthesis and Hydrogenation

General: The library was synthesized using a Zinsser Lissy liquid handling robot equipped with 4 probes and placed inside a glove-box. Whatman PKP 2 mL 96-well filter plates in combination with the UniVac 3 vacuum manifold were used to perform the parallel filtration of the ligand library. The hydrogenation reaction was carried out in a Premex 96-Multi Reactor[31] that can accommodate 96 reactions vessels at the same temperature and hydrogen pressure.

Conditions: Into 48 wells of the filter plate were transferred a solution of the desired chlorophosphite (0.15 M, 333 μL, 0.05 mmol), a triethylamine solution (0.50 M, 100 μL, 0.05 mmol) and solutions of the selected amines and alcohols (0.15 M, 333 μL, 0.05 mmol). The microplate was shaken for 2 h, after which parallel filtration was performed to remove the precipitated salts, yielding 48 solutions of the different ligands (0.065 M). The appropriate amounts of the ligand solutions (93 μL, 8 mol%) were transferred into 48 vials, equipped with stirring bars and the toluene was allowed to evaporate overnight. Next, a stock solution of $Rh(COD)_2BF_4$ in CH_2Cl_2 (0.020 M, 150 μL, 4 mol%) was added to each of the vials, allowing the formation the different catalysts. A solution of **3d** in CH_2Cl_2 (0.03 M, 2.5 mL, 75 μmol) was then added to each vial and the resulting mixtures were transferred under a N_2 atmosphere to the parallel hydrogenation apparatus. The mixtures were hydrogenated under 25 bar of H_2 for 6 h and the conversions and *ee*s were determined by chiral HPLC (Chiralcel OD column; heptane/2-propanol/TFA, 95:5:0.05). The conversions and (absolute) *ee*s are depicted in Figure 4.

General Procedure A for the Hydrogenation of 3a–d in an Autoclave Vessel

To a Schlenk tube were added $Rh(COD)_2BF_4$, the ligand and dry CH_2Cl_2 (5 mL) under a nitrogen atmosphere. The resulting orange solution was stirred at room temperature for 10 min. In a Parr Hastelloy C autoclave were sequentially added **3**, CH_2Cl_2 (45 mL) and the catalyst solution. Next, the vessel was closed and the reaction mixture was stirred by an overhead turbine stirrer at room temperature and under nitrogen. Then, hydrogen pressure was applied and the mixture was stirred for the specified time. After that, the conversion was measured by ^{1}H NMR and the *ee* was determined by chiral HPLC. The solvent was evaporated and the product was purified by column chromatography (EtOAc/heptane, 1:2).

(*S*)-4-Methoxy-2-methyl-4-oxobutanoic Acid (6a)

This compound was prepared from **3a** (2.01 g, 13.9 mmol) following general procedure A [0.5 mol% $Rh(COD)_2BF_4$, 1.0 mol% **L1**, 10 bar H_2, 3 h]. The conversion was >99%, the isolated yield was 1.88 g (92%). The *ee* was determined by HPLC to be 98.6% (Chiralpak AD column; heptane/*n*-butanol/TFA, 95:5:0.05). Analytical data agreed with those reported in the literature.[3] ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta =$ 3.69 (s, 3H), 3.02–2.91 (m, 1H), 2.75 (dd, $J = 8.1$, 16.7 Hz, 1H), 2.43 (dd, $J = 6.0$, 16.7 Hz, 1H), 1.26 (d, $J = 7.2$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 181.5$, 172.3, 51.8, 37.1, 35.7, 16.8; $[\alpha]_D^{22}$: -10.6 (*c* 0.8, $CHCl_3$).

(*S*)-2-(2-Methoxy-2-oxoethyl)pentanoic Acid (6b)

This compound was prepared from **3b** (0.94 g, 5.45 mmol) following general procedure A [2.0 mol% $Rh(COD)_2BF_4$, 4.0 mol% **L1**, 10 bar H_2, 3 h]. The conversion was >99%, the isolated yield was 0.88 g (93%). The *ee* was determined by HPLC to be 98.5% (Chiralpak AD column; heptane/ethanol/TFA, 95:5:0.05). Analytical data agreed with those reported in the literature.[25a] A small amount was converted into the diacid[40] in order to compare the sign of the optical rotation and thereby determine the absolute stereochemistry. ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 3.68$ (s, 3H), 2.87 (m, 1H), 2.70 (m, 1H), 2.44(dd, J=5.1, 16.6 Hz, 1H), 1.73–1.46 (m, 2H), 1.43–1.21 (m, 2H), 0.92 (t, $J=7.2$ Hz, 3H); ^{13}C NMR (CDCl$_3$, 75 MHz): $\delta=180.7$, 172.4, 51.9, 40.8, 35.4, 33.8, 20.1, 13.8; $[\alpha]_D^{22}$: −15.2 (c 0.6, CHCl$_3$).

(*R*)-2-Benzyl-4-methoxy-4-oxobutanoic Acid (6c)

This compound was prepared from **3c** (1.11 g, 5.04 mmol) following general procedure A [2.0 mol% Rh(COD)$_2$BF$_4$, 4.0 mol% **L5**, 25 bar H$_2$, 16 h]. The conversion was >99%, the isolated yield was 1.05 g (94%). The *ee* was determined by HPLC to be 93.7% (Chiralpak AD column; heptane/ethanol/TFA, 95:5:0.05). Analytical data agreed with those reported in the literature.[41] A small amount was converted into the diacid,[42] in order to compare the sign of the optical rotation and thereby determine the absolute stereochemistry. ^{1}H NMR (CDCl$_3$, 300 MHz): $\delta=7.33$–7.16 (m, 5H), 3.64 (s, 3H), 3.21–3.10 (m, 2H), 2.79 (m, 1H), 2.65 (dd, $J=8.8$, 16.9 Hz, 1H), 2.41 (dd, $J=4.7$, 16.9 Hz, 1H). ^{13}C NMR (CDCl$_3$, 75 MHz): δ 179.5, 172.2, 137.9, 129.0, 128.6, 126.8, 51.8, 42.7, 37.3, 34.4; $[\alpha]_D^{22}$: +11.1 (c 0.5, CH$_2$Cl$_2$).

(*R*)-4-Methoxy-2-(4-methoxybenzyl)-4-oxobutanoic Acid (6d)

This compound was prepared from **3d** (1.49 g, 5.95 mmol) following general procedure A [2.0 mol% Rh(COD)$_2$BF$_4$, 4.0 mol% **L5**, 25 bar H$_2$, 2 h]. The conversion was >99%, the isolated yield was 1.41 g (94%). The *ee* was determined by HPLC to be 89.0% (Chiralcel OD column; heptane/2-propanol/TFA, 95:5:0.05). ^{1}H NMR (CDCl$_3$, 300 MHz): $\delta=7.09$ (d, $J=8.7$ Hz, 2H), 6.83 (d, $J=8.7$ Hz, 2H), 3.78 (s, 3H), 3.64 (s, 3H), 3.17–3.03 (m, 2H), 2.76–2.60 (m, 2H), 2.40 (dd, $J=4.8$, 16.9 Hz, 1H); ^{13}C NMR (CDCl$_3$, 75 MHz): $\delta=178.6$, 172.3, 158.4, 130.0, 129.8, 114.0, 55.2, 51.8, 42.8, 36.6, 34.4; $[\alpha]_D^{22}$: +17.4 (c 0.4, CHCl$_3$); HR-MS (CI$^+$): $m/z=252.0988$, calcd. for C$_{13}$H$_{16}$O$_5$, [M]$^+$: 252.0998.

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