Practical Access to 2-Alkylsuccinates through Asymmetric Catalytic Hydrogenation of Stobbe-Derived Itaconates[**]

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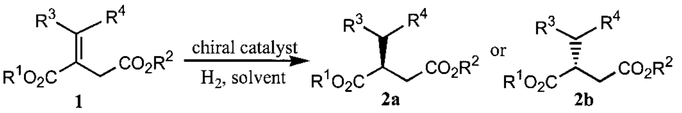
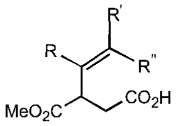
Enantiomerically enriched 2-substituted succinic acid derivatives of general structure **2** have attracted great interest recently because of their utility as chiral building blocks and peptidomimetics in the design of pharmaceuticals, flavors and fragrances, and agrochemicals with improved properties.[1] Asymmetric catalytic hydrogenation of β-substituted itaconic acid derivatives (**1**) potentially offers one of the most convenient and practical routes to this class of compounds. No such catalyst system has yet been developed for the highly enantioselective synthesis of a diverse range of valuable 2-alkylsuccinates of type **2**.



While asymmetric catalytic hydrogenation of the parent itaconates (**1**; R^3, R^4 = H) to 2-methylsuccinate derivatives has been accomplished with considerable cogency,[2] the ability to hydrogenate β-substituted itaconate derivatives with high enantioselectivities has remained challenging. Of the few examples documented thus far only β-phenyl and β-1-naphthylitaconate derivatives have been hydrogenated with reasonably high enantioselectivity, and then only when the substrates **1** were employed as the pure *E*-geometric isomer.[3] The curtailed effectiveness of known asymmetric hydrogenation catalysts is particularly apparent when R^3 or R^4, or both, of **1** is an alkyl group. Yet even less success has been reported for asymmetric hydrogenation of β,β-disubstituted itaconate derivatives (**1**; R^3, R^4 $\neq$ H), where the highest enantioselectivity recorded to date is 78% *ee*.[4]

We herein describe a broadly effective catalyst system that permits highly enantioselective hydrogenation of a wide array of β-substituted itaconate derivatives of type **1**. Both β-aryl and β-alkyl substituents are tolerated, and the substrates may be employed as crude *E*/*Z*-isomeric mixtures. Moreover, a series of β,β-disubstituted itaconate derivatives have been hydrogenated with high enantioselectivites. A practical process has been developed for the production and isolation of enantiomerically pure 2-alkylsuccinates from crude products derived from the Stobbe recation.

Most convenient access to either β-substituted or β,β-disubstituted itaconate derivatives involves a base-promoted Stobbe condensation reaction between dialkylsuccinates and aldehydes or ketones, respectively.[5] Unfortunately, the Stobbe condensation reaction typically leads to a mixture of *E* and *Z* isomeric itaconate products, which often are contaminated with varying quantities of deconjugated isomer (for example **3**). The presence of geometric isomers can cause complications since the (*E*)- and (*Z*)-itaconate derivatives are likely to be hydrogenated with vastly different rates and enantioselectivites.[6,7] Accordingly, separation of the (*Z*)-itaconate derivative from the favored *E* isomer typically is necessary prior to hydrogenation with most current catalysts. Moreover, the presence of isomerized substrate **3** in the mixture is potentially detrimental since any hydrogenation of this material necessarily will afford a racemic succinate product.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We initially surveyed a series of cationic rhodium complexes bearing the DuPHOS and BPE ligands[8,9] (R-DuPHOS and R-BPE = 2′,5′,2″,5″-tetra-R-substituted 1,2-bis(phospholanyl)-benzene (R = Me, Et) and -ethane (R = Me, Et, *i*Pr), respectively) for effectiveness in the asymmetric catalytic hydrogenation of a model substrate **4** (R = *i*Pr, *E*/*Z* ratio 3:1). This substrate was selected for preliminary studies since the highest enantioselectivity achieved thus far in the asymmetric hydrogenation of this itaconate derivative (as the pure *E* isomer) was 76% *ee* with the cationic [(dipamp)Rh]$^+$ catalyst (dipamp = 1,2-ethylene bis[(2-methoxyphenyl)phenylphosphane]).[3e] This screening of the catalysts was performed under a standard set of conditions (MeOH, *c* = 0.5 M, 10% NaOMe, substrate/catalyst ratio S/C = 1000, 20 °C, 5.5 bar H$_2$, 1 h) and revealed a significant influence of the ligand structure upon the level of enantioselectivity attained in the hydrogenation reaction. The [(Et-DuPHOS)Rh]$^+$ catalyst was found to be manifestly superior for this process in which the minor enantiomer could not be detected by chiral GC methods (Table 1). The addition of catalytic amounts of base such as sodium methoxide or 0.1 equivalents of primary or tertiary amines led to significant rate enhancements in these

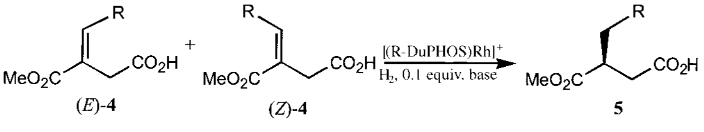

Table 1. Ligand effects in the hydrogenation of **4** (R = *i*Pr).[a]

Ligand (L)	*ee* [%][b] (config.)[c]
{(*R*,*R*)-(Me-DuPHOS)}	94 (*S*)
{(*S*,*S*)-(Et-DuPHOS)}	> 99 (*R*)
{(*S*,*S*)-(Me-BPE)}	47 (*R*)
{(*R*,*R*)-(Et-BPE)}	80 (*S*)
{(*S*,*S*)-(*i*Pr-BPE)}[d]	97 (*S*)

[a] Catalyst precursor = [(L)Rh(cod)]BF$_4$ (cod = cycloocta-1,5-diene). [b] Determined by chiral phase GC. [c] Absolute configuration assigned by comparison with reported optical rotation[3e]. [d] 25% conversion after 3 h.

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reactions, presumably by facilitating coordination of the substrate through the carboxylate group to the catalyst.

On the basis of these auspicious results, we examined the scope of the [(Et-DuPHOS)Rh]$^+$ catalyst for asymmetric hydrogenation of a range of β-itaconates **4**. In many cases, the deconjugated isomer **3** (10–25%) was also present in the substrate mixture but was found unreactive under the conditions employed (see below). The results of these studies are shown in Table 2 and demonstrate the versatility of the [(Et-DuPHOS)Rh]$^+$ catalyst for this transformation.

Table 2. Asymmetric hydrogenation of itaconates **4** with [(Et-DuPHOS)Rh] catalyst.[a]

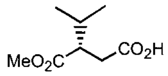
Entry	R (in **4**)[b]	S/C	t [h][c]	*ee* [%][d]
1	H[e]	1000	1	97
2	Et	1000	1	99
3	*n*Bu	1500	2	97
4	CH_2CH_2Ph	2000	2	99
5	(E)-CHCHPh	1000	20	99[f]
6	*i*Pr	3000	2	99
7	cyclopropyl	2000	2	99
8	cyclohexyl	1500	3	98
9	*t*Bu	5000	4	99
10	Ph	3000	12	97
11	1-naphthyl	3000	12	98
12	2-naphthyl	3000	12	97
13	2-thienyl	1000	15	99

[a] Conditions: catalyst precursor = [{(*S*,*S*)-(Et-DuPHOS)Rh}(cod)]BF_4, room temperature, 5.5 bar H_2, MeOH, 10% NaOMe per mol of **4**. [b] Most substrates **4** employed as crude *E*/*Z* mixtures ranging from 2/1 to > 10/1. [c] Reaction time over which complete conversion was observed. [d] Determined on chiral phase (cyclodextrin) GC columns after conversion of crude product **5** to dimethyl ester. [e] Dimethyl itaconate substrate used. [f] *tert*-Butylammonium salt of substrate employed.

Hydrogenation of crude itaconate derivatives **4**, prepared conveniently and economically by Stobbe condensation reactions, produced a wide variety of 2-alkylsuccinates **5** with very high enantioselectivities. This process directly yields valuable succinate derivatives **5** that possess differentially protected carboxyl functionalities. In all cases examined, the *R*,*R* catalyst afforded (*S*)-2-alkylsuccinates, while the *S*,*S* catalyst furnished the *R* isomer. The [(Et-DuPHOS)Rh]$^+$ catalysts tolerate many different types of β-substituents on **4**, including linear alkyl, branched alkyl, aromatic, and heteroaromatic groups. In addition to the high enantioselectivity observed, the hydrogenation is highly regioselective: only the itaconate unit is reduced while the aliphatic double bond of a γ,δ-styrenyl function is unaffected (Table 2, entry 5).[10]

Although this process remains unoptimized, high catalytic efficiency was demonstrated with S/C ratios as high as 5000 and with average turnover frequencies of up to 2000 cycles/h. Itaconate derivatives bearing β-alkyl substituents ($E/Z = 2/1-5/1$) were ostensibly hydrogenated more rapidly than the β-aryl itaconates (predominantly *E* isomers) obtained from the Stobbe condensation reaction.

In addition to β-substituted itaconates, preliminary studies also indicate that the β,β-disubstituted itaconates **1** ($R^3,R^4 \neq H$) may be hydrogenated with high enantioselectivities. Given the sterically encumbered nature of the disubstituted itaconates (tetrasubstituted alkenes), it is not surprising that the most effective catalysts identified were derived from Me-BPE, the least hindered ligand of our bis(phospholane) collection.[8] As an example, the two succinate derivatives **6** and **7** were prepared from the corresponding itaconate with the cationic [{(*S*,*S*)-(Me-BPE)Rh}]$^+$ catalyst.



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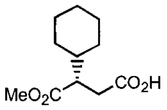

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Relative to **4**, hydrogenation of the disubstituted itaconates used higher catalyst loadings (S/C = 500) and higher hydrogen pressures (11 bar H_2) to achieve reasonable rates of conversion (15–20 h). Under otherwise standard conditions, **6** and **7** were obtained in 91% *ee* and 88% *ee*, respectively.[11] Interestingly, hydrogenation of the *tert*-butylammonium salts of these β,β-disubstituted substrates proceeded readily at 0°C to furnish the products in 96% *ee*. The enantioselectivities listed are by far the highest ever reported for this challenging class of substrates.[4]

Our objective was to develop a proficient and practical route to 2-alkylsuccinates **2** through asymmetric hydrogenation of crude Stobbe condensation products. Demonstration that catalysis proceeded smoothly despite the use of unpurified substrates was encouraging. However, as alluded to above, Stobbe condensation reactions involving alkyl aldehydes often afford varying amounts of the deconjugated isomer **3**, which upon hydrogenation would lead to a racemic succinate. Importantly, we have found that the cationic catalysts [(R-DuPHOS)Rh]$^+$ and [(R-BPE)Rh]$^+$ specifically hydrogenate the itaconate substrates without affecting **3**. Moreover, we have established that isomer **3** may be removed simply by treatment of the hydrogenation product mixture with basic iodine solution (leading to iodolactonization of **3**) and extraction. Subsequent acidification afforded the pure succinates (for example **5**) in high yield. It is noteworthy that in most cases examined, enantiomerically pure succinates were obtained in 500 g quantities through simple crystallization of the corresponding *tert*-butylammonium salts (see *Experimental Section*).

Overall, we have developed a versatile asymmetric catalytic process for the synthesis of valuable 2-alkylsuccinate derivatives. We have demonstrated that crude isomeric mixtures of itaconate substrates obtained directly from the Stobbe condensation reaction may be hydrogenated with high catalytic efficiencies and high enantioselectivities.

Experimental Section

4 (R = *i*Pr): Potassium *tert*-butoxide (988 g, 8.8 mol) was dissolved in *tert*-butyl alcohol (6 L). A mixture of isobutyraldehyde (577 g, 8 mol) and dimethyl succinate (1.46 kg, 10 mol) in *tert*-butyl alcohol (1 L) was added to this solution over a period of 1 h. The mixture was heated to 50°C for 2 h, and stirring was continued at room temperature overnight. The solvent was removed under reduced pressure and the residue dissolved in water (5 L) and extracted with ethyl acetate (2 × 1 L). The aqueous phase was acidified (conc. HCl) and the organic layer separated off. The aqueous phase was extracted with ethyl acetate (2 × 2 L). The combined organic phases were dried over magnesium sulfate, filtered, and the solvent was removed under reduced pressure to yield a yellow oil. Treatment of this crude material with pentane (2 L) induced crystallization. The crystals were filtered off, washed twice with 300 mL pentane, and dried in vacuo to afford a light yellow, sticky solid (658 g, 44 %). ^{1}H NMR analysis indicated a mixture of approximately 82 % *(E)*-itaconate, 7 % *(Z)*-itaconate, and 11 % **3**. This material was used in the hydrogenation reaction without further purification.

5 (R = *i*Bu): Sodium methoxide (96 g, 172 mol) was added to a solution of the mixture from above (532 g, 2.86 mol) in methanol (4.5 L), and the mixture transferred to a 7 L hydrogenation vessel. After degassing the solution with a nitrogen sparge, the reactor was subjected to five pressurization/release cycles; each pressurization step involved stirring for 5 min under 5.2 bar hydrogen. Subsequently, a solution of [{(*R*,*R*)-(Me-DuPHOS)}Rh(COD)]BF_4 (540 mg, 0.89 mmol, S/C = 3200) in degassed methanol (20 mL) was added, and the mixture was allowed to stir under a hydrogen atmosphere (5.2 bar) for 4 h. ^{1}H NMR analysis revealed that both *E* and *Z* isomers were hydrogenated and the deconjugated methyl 2-isobutenylsuccinate **3** remained unaffected. The enantiomeric excess of the crude methyl 2-isobutylsuccinate was 94 % *ee* (see Table 1 and method below). The reaction mixture was concentrated to approximately 1 L, followed by addition of water (500 mL), $NaHCO_3$ (101 g, 1.2 mol), and iodine (119 g, 0.47 mol), and allowed to stir at room temperature for 16 h. Solid sodium sulfite (slight excess) was added to the mixture in destroy excess iodine. The mixture was concentrated under reduced pressure to a approximately 1 L and extracted with ethyl acetate (3 × 0.5 L). The aqueous phase was acidified (conc. HCl) and again extracted with ethyl acetate (3 × 300 mL). Analysis of aliquots from the latter organic layers showed only the presence of monomethyl 2-isobutylsuccinate with an enantiomeric excess of 94 %. ^{1}H NMR ($CDCl_3$): $\delta = 11.05$ (s, 1 H), 3.70 (s, 3 H), 2.96 – 2.86 (m, 1 H), 2.74 (dd, $J = 16.7$, 9.9 Hz, 1 H), 2.48 (dd, $J = 17.2$, 4.9 Hz, 1 H), 1.66 – 1.53 (m, 2 H), 1.39 – 1.28 (m, 1 H), 0.93 (d, $^{3}J = 6.4$ Hz, 3 H), 0.90 (d, $^{3}J = 5.9$ Hz, 3 H); ^{13}C NMR ($CDCl_3$): $\delta = 177.8$ (s), 175.6 (s), 51.7 (q), 40.9 (t), 38.9 (d), 36.0 (t), 25.6 (d), 22.3 (q), 22.0 (q).

Further purification was accomplished by formation of an ammonium salt as follows: The organic layers from above (about 900 mL) were combined and further diluted with ethyl acetate (1 L). A solution of *tert*-butylamine (219 g, 3 mol) in ethyl acetate (200 mL) was added over 2 h. The ammonium salt rapidly precipitated to form a very thick mixture that was allowed to stir for an additional 2 h at room temperature. The precipitated solid was filtered, washed with ethyl acetate (3x2 L), and dried in vacuo to afford 465 g (71 % yield from substrate mixture) of the desired product **5** (R = *i*Bu) as a colorless powder (> 99 % *ee*); $[\alpha]_D = -12.8^{\circ}$ ($c = 6.07\ g\,dm^{-3}$, MeOH, 20 °C); ^{1}H NMR (CD_3OD): $\delta = 5.06$ (s, 3 H), 3.66 (s, 3 H), 2.94 – 2.85 (m, 1 H), 2.47 (dd, $J = 17.2/9.9$ Hz, 1 H), 2.25 (dd, $J = 17.2/5.3$ Hz, 1 H), 1.63 – 1.46 (m, 2 H), 1.36 (s, 9 H), 1.37 – 1.25 (m, 1 H), 0.94 (d, $^{3}J = 5.3$ Hz, 3 H), 0.90 (d, $^{3}J = 5.3$ Hz, 3 H); ^{13}C NMR (CD_3OD): $\delta = 179.9$ (s), 178.7 (s), 52.2 (s), 51.9 (q), 42.8 (t), 42.3 (d), 41.7 (t), 28.0 (q, 3C), 27.2 (d), 23.3 (q), 22.5 (q). The enantiomeric excess was determined, after conversion of crude **5** to the dimethyl ester by treatment with trimethylsilyldiazomethane, by chiral phase GC; GC parameters: capillary GC column Chirasildex-CB (25 m × 0.25 mm), 80 °C for 35 min then heated to 200 °C at 4 °C min^{-1}, helium 1.4 bar, $t_1(S) = 39.98$ min, $t_2(R) = 40.31$ min).

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[11] The [(Me-DuPHOS)Rh]$^{+}$ catalyst was found to provide the 2-isopropylsuccinate derivative **6** in only 71 % *ee*, compared to 91 % *ee* with [(Me-BPE)Rh]$^{+}$ at 20 °C. This result highlights the strong relationship between the steric and conformational constitution of the ligand and the enantioselectivities achieved in these reactions.