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Asymmetric hydrogenation of a 4,4-diaryl-3-butenoate; a novel approach to sertraline

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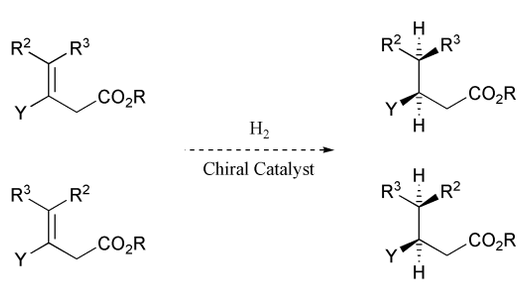
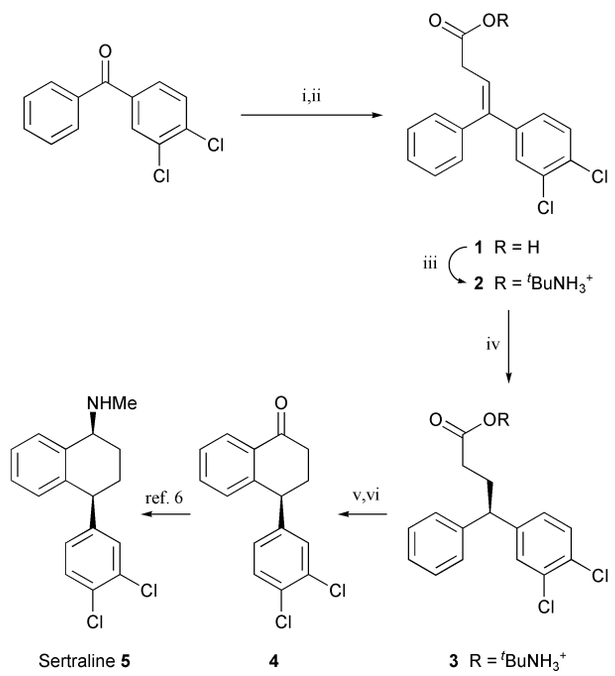
The asymmetric hydrogenation of a selectively crystallised (*E*)-4,4-diaryl-3-butenoate with a rhodium-PhanePhos catalyst is described, providing an intermediate to the anti-depressant sertraline.

Asymmetric hydrogenation of an olefin functionality with rhodium-diphosphine catalysts constitutes a powerful method to construct stereogenic centres. For high enantioselectivity and catalyst reactivity, a suitable substrate contains a fragment of the form C=C–X–C=O where X is any single spacer atom (often carbon or nitrogen) and the carbonyl provides secondary co-ordination to the metal of the catalyst.[1] Frequently the stereocentre is generated at the position of the olefin closest to the carbonyl function; an example from our laboratories is the practical access to 2-alkylsuccinates by the asymmetric hydrogenation of Stobbe derived itaconates (Scheme 1, Y = CO_2Me).[2] Alternatively, a stereocentre can be created at the more distant end of the olefin from the co-ordinating functionality.[3] Then, attainment of a single product enantiomer requires the substrate olefin to be a single geometric isomer, because (*Z*)- and (*E*)-olefin isomers are expected to supply opposite enantiomers with a given catalyst (Scheme 1, Y = H). 4,4-Diarylbutanoates are useful intermediates for pharmaceutical agents, particularly in single enantiomer form, but only a (*Z*)/(*E*) isomeric mixture of olefins is readily available. Sertraline (Zoloft®) **5**, an important commercial pharmaceutical agent for the treatment of depression, can be derived from a 4,4-diarylbutanoate.[4,5] The current published route for the commercial production relies on a racemic synthesis and resolution of the final compound as the mandelic acid salt.[4] A means to establish the chirality much earlier in the synthesis would be preferred economically.[6–8]



Scheme 1 Orientation of asymmetric hydrogenation for mixed-olefin stereoisomers.

Herein we report that an enantiomerically enriched 4,4-diarylbutanoate intermediate for sertraline **5** can be obtained by separating out an olefin geometric isomer by crystallisation, then subjecting it to asymmetric hydrogenation with an appropriate rhodium-diphosphine catalyst (Scheme 2).



Scheme 2 Synthesis of sertraline **5**. *Reagents and conditions:* i) potassium *tert*-butoxide, diethyl succinate, *tert*-butanol; ii) 48% hydrobromic acid, acetic acid, followed by recrystallisation from MTBE, 32% for two steps (17% 19 : 1 ratio, 15% 30 : 1 ratio); iii) *tert*-butylamine, ethyl acetate, 99%; iv) H_2, pre-catalyst, MeOH (see Table 1); v) 2 M sulfuric acid, ethyl acetate; vi) chlorosulfonic acid, dichloromethane, 91% (two steps).

Following the known route, Stobbe condensation of 3,4-dichlorobenzophenone and diethyl succinate and then acidic treatment of the crude reaction residue afforded allylic acid **1** as a 1 : 1 mixture of geometric isomers.[5a] We discovered that subsequent recrystallisation from methyl *tert*-butyl ether (MTBE) provided isomer enrichment. Two crops of crystals [19 : 1 and 30 : 1 (*E*) : (*Z*) isomeric ratio respectively] were obtained in a combined yield of 32% overall from the starting dichlorobenzophenone (Scheme 2). In an attempt to obtain additional isomeric enrichment, various amine salts of the crude material were screened. However, no significant improvement was observed.

For the hydrogenation reactions we chose to use *tert*-butyl ammonium salt **2** due to its favourable physical form and because a carboxylate salt was expected to give better secondary co-ordination to the catalyst than the free acid. Thus hydrogenation of salt **2** (19 : 1 (*E*) : (*Z*) isomeric ratio) was screened with a variety of rhodium and ruthenium pre-catalysts (Table 1 and Fig. 1).† Initially the achiral pre-catalyst [DiPFc Rh COD]BF_4 was used to prepare a racemic sample, on which a supercritical fluid chromatography (SFC) analytical method for enantiomeric excess (ee) was developed for the saturated free acid.[9d]

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Table 1 Summary of results for the catalytic asymmetric hydrogenation of *tert*-butyl ammonium salt **2**

Entry	Pre-catalyst	Temp./°C	Pressure/psi	Time/h [a]	Conversion (%)	ee (%) [bc]
1	[DiPFc Rh COD]BF_4	22	120	1	100	*rac*
2	[(*R*,*R*)-Me-DuPHOS Rh COD]BF_4	22	120	16	77	nd [d]
3	[(*R*,*R*)-Et-DuPHOS Rh COD]BF_4	22	120	16	86	nd [d]
4	[(*R*,*R*)-^{i}Pr-DuPHOS Rh COD]BF_4	22	120	16	100	−1
5	[(*S*,*S*)-Me-BPE Rh COD]BF_4	22	120	4	100	20
6	[(*R*,*R*)-Me-BPE Rh COD]BF_4	22	120	16	100	9
7	[(*S*,*S*)-^{i}Pr-BPE Rh COD]BF_4	22	120	16	100	−13
8	[(*R*,*R*)-Me-FerroTANE Rh COD]BF_4	22	120	16	100	−30
9	[(*S*,*S*)-Et-FerroTANE Rh COD]BF_4	22	120	16	100	46
10	[(*S*,*S*)-^{n}Pr-FerroTANE Rh COD]BF_4	22	120	16	100	33
11	[(*S*,*S*)-^{i}Pr-FerroTANE Rh COD]BF_4	22	120	16	100	−53
12	[(*R*,*R*)-Me-5-Fc Rh COD]BF_4	22	120	16	100	−65
13	[(*R*,*R*)-^{i}Pr-5-Fc Rh COD]BF_4	22	120	16	100	82
14	[(*R*,*R*)-^{t}Bu-5-Fc Rh COD]BF_4	22	120	16	93	nd [d]
15	[(*R*)-PhanePhos Rh COD]BF_4	22	120	16	100	90
16 [e]	[(*R*)-PhanePhos Rh COD]BF_4	22	120	16	100	84
17	[(*S*)-Xyl-PhanePhos Rh COD]BF_4	22	120	16	100	−77
18	[(*S*)-Xyl-PhanePhos Rh COD]BF_4	0	120	16	100	−72
19	[(*S*)-Xyl-PhanePhos Rh COD]BF_4	0	180	64	100	−89
20	[(*S*)-Xyl-PhanePhos Rh COD]BF_4	22	60	64	100	−89
21	[(*R*)-Cl-MeO-BIPHEP Rh COD]BF_4	40	120	16	100	3
22	[(*R*)-Cl-MeO-BIPHEP Rh COD]BF_4	22	120	16	100	36
23	[(*R*,*R*)-^{i}Pr-DuPHOS Ru $(OCOCF_3)_2$]	22	120	16	100	−44
24 [f]	[(*R*,*R*)-^{i}Pr-BPE Ru (2-methylallyl)$_2$]	22	120	16	100	−50

[a] Time is not necessarily for complete reduction. [b] Negative ee corresponds to *R* enantiomer of product (by comparison of optical rotation). [c] *rac* = racemic. [d] Not determined, starting olefin interferes in analytical assay if conversion is incomplete. [e] Dibenzylammonium salt used. [f] Free acid used.

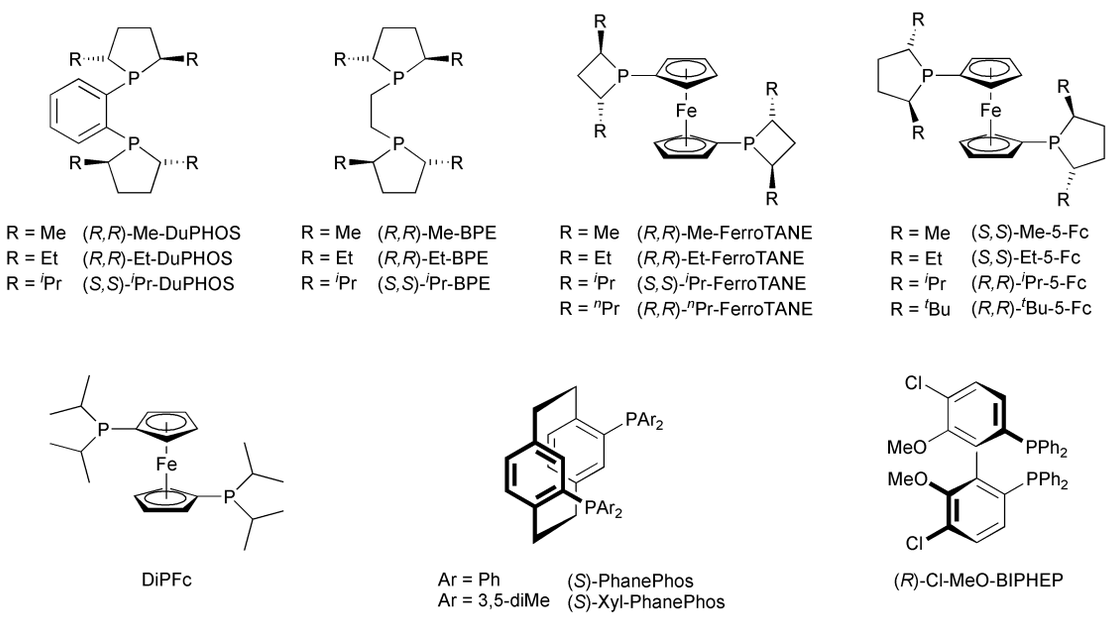

Fig. 1 Structure of chiral diphosphine ligands used during the hydrogenation screen.[9,10]

The majority of reactions performed gave full conversion to acid salt **3** over 16 hours at 22 °C and 120 psi hydrogen pressure with 1 mol% catalyst. Unlike our experience with the hydrogenation of itaconates,[2] DuPHOS, BPE and FerroTANE based rhodium catalysts showed little enantioselectivity for this substrate (entries 2–11).[9a–c] The ferrocenylphospholane ligands used for entries 12, 13 and 14 showed some increased selectivity. Unexpectedly, rhodium-PhanePhos, a catalyst that typically shows lower selectivity than other diphosphine complexes, proved the most useful for this particular substrate, with 90% ee being achieved (entry 15).[10] The parent diphenylphosphinyl ligands provided slightly better selectivity than the corresponding xylyl analogue. Lowering the temperature and pressure slightly increased the enantioselectivity for the xylyl catalyst albeit with a lowering of the reaction rate (entries 18, 19 and 20). Hydrogenation of free acid **1** rather than the salt **2** gave consistently worse results under rhodium catalysis. A variety of ruthenium pre-catalysts were examined against salt **2** and free acid **1**, the best of these results are presented in the table (entries 23 and 24) but selectivities were moderate.

In order to verify the enantioenriched diarylbutanoate salt **3** as an intermediate for sertraline, the hydrogenation product was cyclised by treatment firstly with 2 M sulfuric acid to liberate the free carboxylic acid and then with chlorosulfonic acid to afford tetralone **4** in 91% yield, with no loss of enantiopurity as judged by HPLC analysis (Scheme 2).[6] It was found that catalysts with the (*S*)-PhanePhos ligand provided the required (*R*)-enantiomer of the diarylbutanoate and from that the (*S*)-tetralone **4**, which has been used for the synthesis of sertraline **5** by reductive amination with methylamine.[7f] The stereochemistry of the major component of the enriched olefin mixtures used for the hydrogenation screen was determined to be the (*E*)-isomer by X-ray crystallographic analysis and ^{1}H NMR (Fig. 2).‡

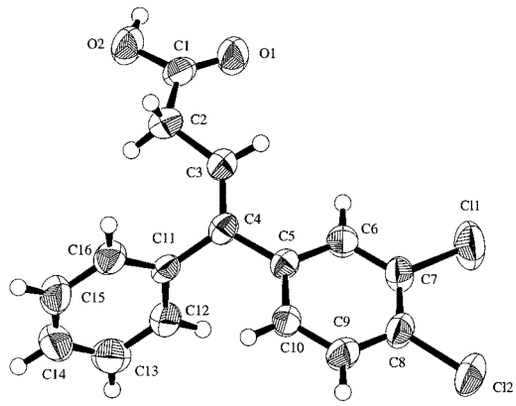

Fig. 2 ORTEP diagram of the molecular structure of allylic acid **1**. Thermal ellipsoids shown at the 50% probability level.

The rhodium-PhanePhos catalysed hydrogenation of a 1 : 1 isomeric mixture of *tert*-butyl ammonium salt **2** using our best conditions (*cf*. run 15) gave racemic product. The successful synthesis of an intermediate for candoxatril,[11] where the stereocentre is created at the more distant end of the olefin from the coordinating carboxylate functionality, is presumably due to the substrate being available as a single geometric isomer.

In summary we have demonstrated the principle of a route to an enantioenriched 4,4-diarylbutanoate using asymmetric hydrogenation, in which unpredictably, a catalyst based on the PhanePhos ligand gave the best results. These findings illustrate the importance of screening a wide range of ligands against any new substrate.[12] The route may have practical utility for sertraline and stereochemically related compounds, particularly when an efficient crystallisation based separation procedure for the olefin isomers can be demonstrated. It may ultimately be possible to recycle the unwanted olefin isomer, or hydrogenate it with the opposite enantiomer of catalyst to converge all the material into one enantiomer of product.

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Notes and References

† General hydrogenation procedure for the preparation of 4-(3,4-dichlorophenyl)-4-phenylbutanoic acid *tert*-butyl ammonium salt **3**. Geometrically enriched (*E*)-4-(3,4-dichlorophenyl)-4-phenylbut-3-enoic acid *tert*-butyl ammonium salt **2** and the hydrogenation pre-catalyst (1 mol%, see Table 1) were placed in a glass liner within a 50 ml stainless steel autoclave and the vessel was assembled. The vessel was pressurised to 120 psi with nitrogen and then the gas was released, this process was repeated a further three times. After the final vent, deoxygenated methanol (5 ml) was introduced into the bomb. The vessel was then charged and vented three times with hydrogen to 120 psi. The vessel was equilibrated to the appropriate temperature and charged with the appropriate pressure of hydrogen. After stirring overnight, the vessel was allowed to cool, the hydrogen pressure was released and the vessel was disassembled. The reaction mixture was concentrated under reduced pressure to afford a crude residue, which was analysed by ^{1}H NMR spectroscopy for conversion and SFC for enantiomeric excess. δ_H(400 MHz; d_4-MeOD; ref. MeOH) 7.40–7.14 (8H, m, Ar), 3.96 (1H, t, *J* 8, C*H*CH$_2$), 2.34–2.28 (2H, m, CHC*H*$_2$), 2.09 (2H, t, *J* 7, CHCH$_2$C*H*$_2$) and 1.33 (9H, s, 3 × CH$_3$); Free acid $[a]_D^{22}$ = +12.4 [*c* = 2.2 in benzene (product from run 15, 90% *ee*)]; δ_H(400 MHz; $CDCl_3$; ref. Me_4Si) 7.36–7.18 (7H, m, Ar), 7.07 (1H, d, *J* 9, Ar), 3.91 (1H, br t, *J* 8, C*H*CH$_2$) and 2.40–2.27 (4H, m, C*H*$_2$C*H*$_2$). Determination of enantiomeric excess was performed using a Gilson SFC system [Diacel Chiralcel OD column, 250 × 4.6 mm, 10 μm particle size, using 95% CO_2, 5% methanol (with 1% v/v TFA modifier), 30 ml min^{-1} flow rate, 3000 psi pressure, 35 °C column temperature, 220 nm UV detection]. Retention times: first enantiomer (*S*) 12.0 minutes, second enantiomer (*R*) 14.1 minutes.

‡ Crystal data for (*E*)-allylic acid **1**, $C_{16}H_{12}Cl_2O_2$, *M* = 307.16: colourless, monoclinic, $P2_1/C$, *a* = 7.474(4) Å, *b* = 12.744(4) Å, *c* = 15.237(3) Å, *β* = 91.49(3)°, *V* = 1450.7(10) Å^3, *Z* = 4, d_{calc} = 1.406 g cm^{-3}, *F*(000) = 632, *μ*(Mo-K*α*) = 0.455 mm^{-1}, *θ* = 6.9–8.2° (Mo-K*α*), 2777 measured reflections on a Rigaku AFC-5R diffractometer, 2567 independent reflections [*R*(int) = 0.0346], structure determination using direct methods (SHELXS86), *R*(F) = 0.0575, *R*w = 0.1135 for 1321 reflections with $I > 2\sigma(I)$, GOF = 1.022. CCDC reference numbers 196474. See http://www.rsc.org/suppdata/ob/b3/b301175p/ for crystallographic data in .cif or other electronic format.

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