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Palladium-catalysed enantioselective synthesis of Ibuprofen

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Abstract

A general strategy has been developed for the enantioselective synthesis of α-aryl propanoic acids. Palladium-catalysed asymmetric allylic substitution is used as the key step of the synthesis. Compound **2a** was obtained in 95% ee from the allylic substitution reaction of 1,3-diphenylprop-2-enyl acetate **1a** with *bis*(phenylsulfonyl)methane, catalysed by palladium and oxazoline ligand **9**. Ozonolysis, desulfonylation followed by oxidation furnished (*S*)-2-phenylpropanoic acid **4a** without detectable loss of enantiomeric purity. The same synthetic strategy was employed to obtain Ibuprofen **4b** in 87% ee, starting from acetate **1b**.

Keywords: Palladium-catalysed allylic substitution; α-Aryl propanoic acids; Ibuprofen

1. Introduction

Many enantiomerically pure 2-arylalkanoic acids, natural as well as synthetic, accomplish useful functions as therapeutic, pest control, and other commercially important agents. α-Arylpropanoic acids [1], which have emerged as an important class of non-steroidal anti-inflammatory agents during the past three decades, are an important member of this family of compounds. The important pharmaceutical properties of this class of drugs have been well illustrated by the introduction and extensive use of more than a dozen compounds. Ibuprofen, Naproxen, Ketoprofen, and Flurbiprofen are just a few examples.

Intense research into developing synthetic methods for the preparation of these compounds has been carried out by several groups [2–5].

Ibuprofen was introduced into therapy as a non-steroidal anti-inflammatory analgesic for the treatment of rheumatic and allied conditions in the UK in 1969 by the Boots company and in the US by the Upjohn Co. in 1974 [6]. It is now being marketed in over 120 countries as the racemic mixture, although it is known that it is the (*S*)-enantiomer which is the more potent form.

Our interest in the asymmetric palladium-catalysed allylic substitution reaction [7–12] led us to consider a synthesis of α-arylpropanoic acids utilising this reaction as the key step. Herein we report the use of palladium-catalysed allylic substitution as a method for providing an enantiomerically enriched framework for the synthesis of Ibuprofen. A generalised scheme for the potential synthesis of a range of compounds is given in Scheme 1.

Thus, a suitably substituted allyl acetate **1** can undergo palladium-catalysed allylic substitution with *bis*(phenylsulfonyl)methane **12**, hopefully with good asymmetric induction, to afford the product **2**. Conversion of the alkene into a carboxylic acid **3** via

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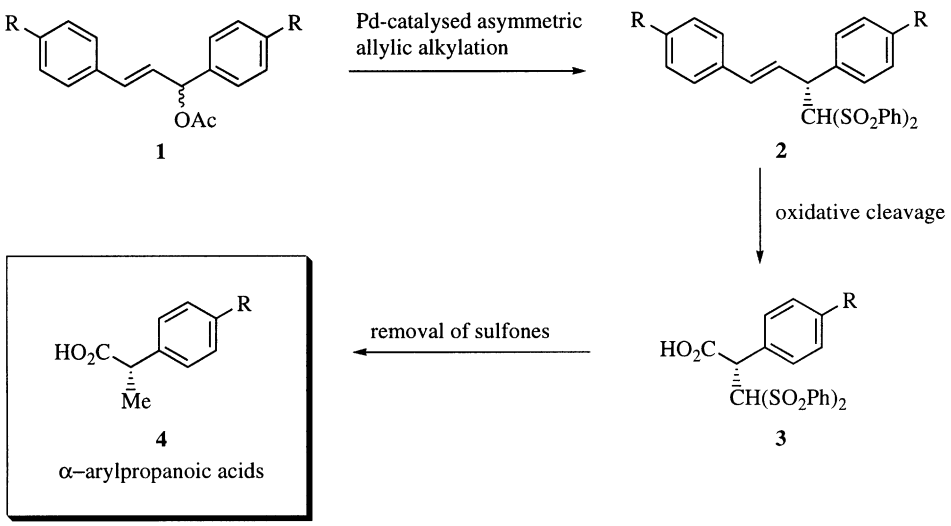


Scheme 1. Generalised scheme for the synthesis of α-arylpropanoic acids.

an oxidative cleavage reaction and subsequent removal of the sulfonyl groups provides a route for the synthesis of α-arylpropanoic acids **4**.

2. Results and discussion

The simple allyl acetate **1a** (R=H) is a well-known compound employed as a model substrate for allylic alkylation reactions. However, the more elaborated variants had to be prepared using a simple strategy indicated in Scheme 2. Aldehyde **5** and methyl ketone **6** were treated with base under Claisen-Schmidt conditions to afford the corresponding chalcone **7**. Luche reduction [13] of the carbonyl group and acetylation afforded the required allyl acetate **1b** in 95% yield from alcohol **8**.

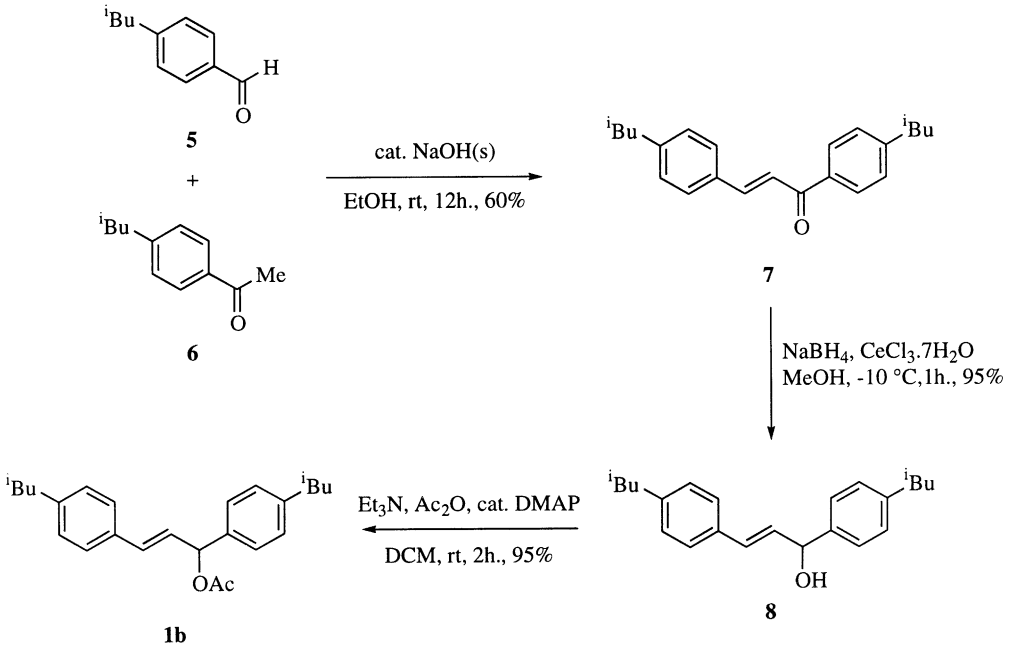
Substrates **1a** and **1b** were then examined in the palladium-catalysed asymmetric allylic substitution reaction, using the ligand **9**, which has a good pedigree for exerting high levels of enantiocontrol in related reactions [14,15]. We chose to use *bis*(phenylsulfonyl)methane as the nucleophile, since once present the sulfone functionality is easily manipulated Schemes 3 and 4.

The enantioselectivity of the reaction was found to be dependent upon the reaction conditions, and these results are summarised in Tables 1 and 2. As illustrated in Table 1, the use of a palladium to ligand ratio of 1:2 is crucial for good selectivity and the use of a 1:1 ratio of palladium to ligand gives diminished enantioselectivity. The use of BSA (N,O-*bis*(trimethylsilyl)acetamide) as a promoter for these reactions generally gave the most consistent results, and we were pleased to be able to obtain

Table 1
Enantioselective allylic substitution of allylic acetate **1a** with bis(phenylsulfonyl)methane **12**

Catalyst (mol%)	Solvent[a]	Nucleophile/base	Yield (%)	ee[b] of **2a** (%)
5 (Pd) 5 (**9**)	THF	BSA/**12** CsOAc	60	31
6 (Pd) 6 (**9**)	1,4-Dioxane	$NaCH(SO_2Ph)_2$	70	65
2 (Pd) 4 (**9**)	THF	BSA/**12** NaOAc	70	91
2 (Pd) 4 (**9**)	THF	BSA/**12** KOAc	77	89
2 (Pd) 4 (**9**)	THF	BSA/**12** CsOAc	65	95
2 (Pd) 4 (**9**)	1,4-Dioxane	$NaCH(SO_2Ph)_2$	78	93

[a] All reactions were run at 73 °C.
[b] Determined by HPLC.

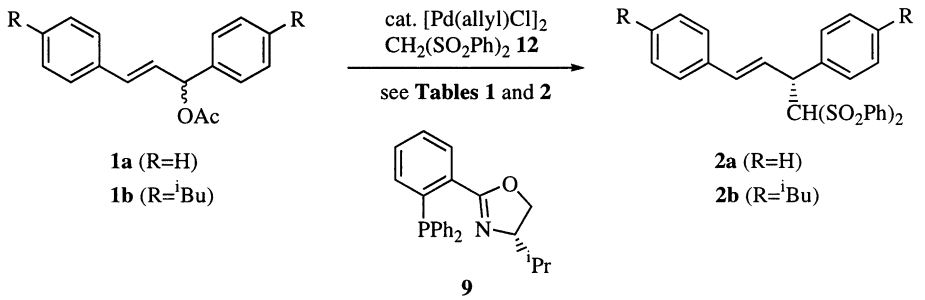


Scheme 2. Synthesis of a substituted allylic acetate.

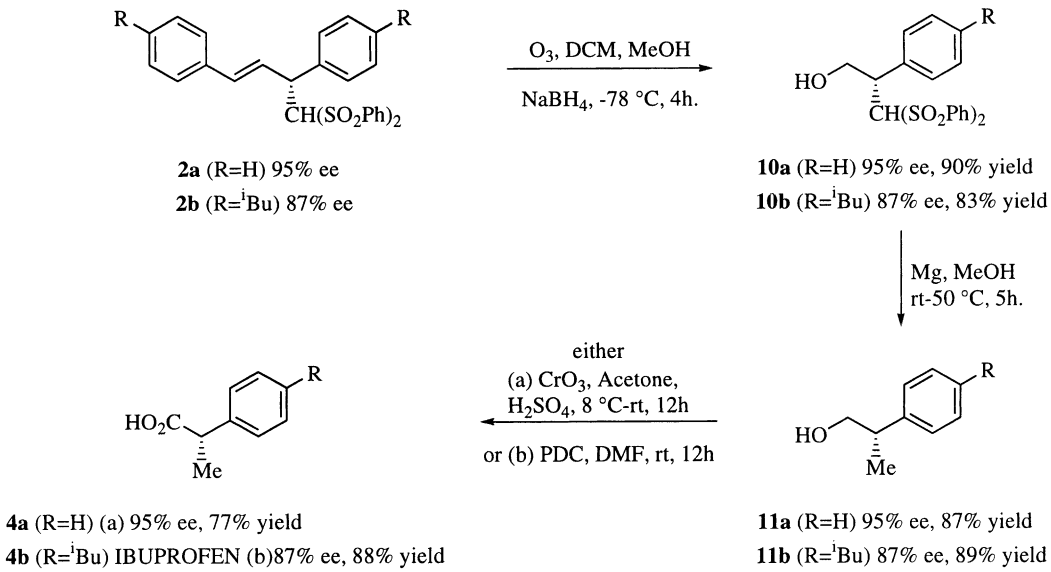
enantioselectivity of up to 95% ee. However, the use of sodio*bis*(phenylsulfonyl)methane in 1,4-dioxane provided the substituted product **2a** with higher yield (78%) and very good enantiomeric excess (93%).

Therefore, the use of sodio*bis*(phenylsulfonyl)methane in 1,4-dioxane formed the isobutyl substituted analogue **2b** with 75% yield and with a slightly lower ee of 87% (see Table 2).

The oxidative cleavage of the alkenes **2a** and **2b** was found to be unsatisfactory, leading to a mixture of products. Several methods were employed including $RuCl_3/NaIO_4$, the Lemieux–Von Ruoloff reaction as well as ozonolysis followed by oxidative work-up. The latter method gave the best result, forming carboxylic acid **3** (R=H) but with only 7% yield. We are unsure of the reasons for this since the closely related compound derived from substitution of 1,3,3-triphenylprop-2-enyl acetate with malonyl esters readily undergoes oxidative cleavage under a variety of conditions [14]. We also found the acetate **1a** itself undergoes oxidative cleavage to give the correspond-



Scheme 3. Palladium catalysed allylic substitution.



Scheme 4. Synthesis of (*S*)-2-phenylpropanoic acid and (*S*)-Ibuprofen.

Table 2
Enantioselective allylic substitution of allylic acetate **1b** with bis(phenylsulfonyl)methane **12**

Catalyst (mol%)	Solvent[a]	Nucleophile/base	Yield (%)	ee[b] of **2b** (%)
2.5 (Pd) 5 (**9**)	THF	$NaCH(SO_2Ph)_2$	60	76
3 (Pd) 6 (**9**)	THF	$NaCH(SO_2Ph)_2$	96	79
2 (Pd) 4 (**9**)	1,4-Dioxane	$NaCH(SO_2Ph)_2$	75	87
3 (Pd) 6 (dppe)	THF	$NaCH(SO_2Ph)_2$	96	–

[a] All reactions were run at 73 °C.
[b] Determined by HPLC.

ing carboxylic acid. However, ozonolysis followed by a reductive work-up with sodium borohydride afforded the alcohols **10a** and **10b** in 90% and 83% yield, respectively. The sulfone groups were readily removed at this stage by treatment with magnesium metal in methanol. Subsequent oxidation back to the carboxylic acid afforded the arylpropanoic acids **4a** and **4b** (Ibuprofen) without concomitant racemisation of the chiral centre.

3. Conclusion

In summary, palladium-catalysed allylic substitution with *bis*(phenylsulfonyl)methane can be achieved with good asymmetric induction. Simple modification of the enantiomerically enriched substitution products provides a convenient route for the synthesis of arylpropanoic acids including Ibuprofen. Therefore analogous compounds should also be accessible *via* this general strategy.

4. Experimental

Commercially available solvents and reagents were used throughout without further purification, except for THF which was distilled from sodium benzophenone ketyl under nitrogen prior to use. Anhydrous methanol and 1,4-dioxane were used for reactions and were purchased from Aldrich. Other solvents for reactions were HPLC grade, whereas during work-up and purification standard grade solvents were used. 4-Isobutylbenzaldehyde was purchased from TCI (Japan). Analytical thin layer chromatography was carried out using plastic backed plates coated with Merck Kieselgel 60 GF_{254}. Plates were visualised

using UV light (at 254 nm) and/or by staining with potassium permanganate or vanillin followed by heating. Flash chromatography was carried out using Merck Kieselgel 60 H silica or 50–200 μm neutral aluminum oxide, as specified. Infra red spectra were recorded in the range 4000–600 cm^{-1} using a Perkin-Elmer 1605 FT-IR spectrometer. Spectra were recorded as Nujol mulls or as neat samples. Elemental analysis was carried out on a Carbo-Erba Stametazione EA 1506 analyser. Melting points were measured on a Gallenkamp single stage apparatus and were uncorrected. HPLC analysis were performed with a SpectraSeries P200 instrument. ^{1}H and ^{13}C NMR spectra were recorded using Jeol GX 270, and Bruker GX 400 instruments at the frequency indicated and are referenced to TMS. Magnesium turnings were activated by vigorous stirring under an argon atmosphere.

The preparation of ligand **9** has been detailed elsewhere [16].

4.1. (2E)-1,3-bis(4-isobutylphenyl)-2-propen-1-one 7

To a solution of 4-isobutylacetophenone **6** (19.10 g, 108.35 mmol, 1.0 equiv.) and 4-isobutylbenzaldehyde **5** (17.50 g, 108.35 mmol, 1.0 equiv.) in absolute ethanol (150 ml), either in a closed atmosphere or under N_2 at room temperature, was added a catalytic amount of NaOH (*S*) (2–3 pellets) and the mixture was vigorously stirred. The reaction was placed in an ice bath to initiate precipitation of product. The ice bath was then removed and the reaction carried out at room temperature. The reaction was left to stir for 24 h. Following this the product was filtered off, washed with cold ethanol, water and cold ethanol again, and dried in a vacuum oven to give a pale yellow powder (20.8 g, 65.01 mmol, 60%). R_f 0.57 (20% EtOAc/light petroleum); mp 62–65 °C; (Found M^+, 320.2129. $C_{23}H_{28}O$ requires M^+, 320.2140); (Found: C, 85.9; H, 8.82. $C_{23}H_{28}O$ requires C, 86.20; H, 8.81%); ν_{max} (film)/cm^{-1} 1661(C=O), 1596 (C=C); δ_H (270 MHz, $CDCl_3$) 0.91 (6H, d, $J = 6.6$, CH_3), 0.92 (6H, d, $J = 6.6$, CH_3), 1.86–1.94 (2H, m, 2*x*CH), 2.51 (2H, d, $J = 7.2$, CH_2), 2.55 (2H, d, $J = 7.3$, CH_2), 7.20 (2H, d, $J = 7.6$, Ar), 7.27 (2H, d, $J = 7.8$, Ar), 7.51 (1H, d, $J = 15.6$, CH=CH), 7.56 (2H, d, $J = 8.1$, Ar), 7.80 (1H, d, $J = 15.8$, CH=CH), 7.9 (2H, d, $J = 8.2$, Ar); δ_C (100.6 MHz, $CDCl_3$) 22.8, 30.5, 30.6, 45.7, 45.8, 121.5, 128.7, 128.9, 129.7, 130.1, 132.9, 136.5, 144.9, 145.2, 147.6, 190.5; *m/z* (EI) 320 (M^+, 30%), 263 (100), 161 (50).

4.2. (2E)-1,3-bis(4-isobutylphenyl)-2-propen-1-ol 8

(2*E*)-1,3-*bis*(4-isobutylphenyl)-2-propen-1-one 7 (10.00 g, 31.20 mmol, 1.0 equiv.) in MeOH (40 ml) along with $CeCl_3 \cdot 7H_2O$ (11.62 g, 31.20 mmol, 1.0 equiv.) was cooled to −10 °C whilst sodium borohydride (1.18 g, 31.20 mmol, 1.0 equiv.) was added gradually over 15 min. After an hour the reaction was quenched with distilled water (30 ml) and extracted with dichloromethane (5 × 40 ml). The organic extracts were combined and dried over Na_2SO_4 and the solvent removed in vacuo to give the product as a pale yellow oil (9.56 g, 29.64 mmol, 95%). This compound was unstable, therefore, it was used in the *next* step as soon as possible. R_f 0.42 (20% EtOAc/light petroleum); (Found (EI) M^+, 322.2290. $C_{23}H_{30}O$ requires M^+, 322.2296); ν_{max} (film)/cm^{-1} 3356; δ_H (400 MHz; $CDCl_3$) 0.88 (6H, d, $J = 6.4$, 2*x*CH_3), 0.89 (6H, d, $J = 6.7$, 2*x*CH_3), 1.78–1.89 (2H, *m*, 2*x*CH), 2.03 (1H, s, OH), 2.44 (2H, d, $J = 7.6$, CH_2), 2.46 (2H, d, $J = 7.6$, CH_2), 5.33 (1H, d, $J = 6.6$, CHOH), 6.34 (1H, dd, $J = 6.6$, 15.9, CH=CHCH), 6.65 (1H, d, $J = 15.9$, CH=CHCOH), 7.07 (2H, d, $J = 8.2$, Ar), 7.13 (2H, d, $J = 7.9$, Ar), 7.29 (2H, d, $J = 8.2$, Ar), 7.32 (2H, d, $J = 7.9$, Ar); δ_C (100.6 MHz; $CDCl_3$) 22.4, 30.2, 45.2, 75.1, 126.1, 126.4, 129.2, 129.3, 130.3, 130.7, 134.1, 140.2, 141.3, 141.5; *m/z* (EI) 322 (M^+, 12%), 279 (45), 161 (100), 91 (45), 43 (40).

4.3. (2E)-1,3-bis(4-isobutylphenyl)-2-propenyl acetate 1b

(2*E*) - 1,3 - *bis*(4 - isobutylphenyl) - 2-propen-1-ol 8 (9.00 g, 27.90 mmol, 1.0 equiv.) was dissolved in dichloromethane (100 ml) and DMAP (30 mg) was added to this mixture, followed by triethylamine (3.10 g, 4.28 ml, 30.69 mmol, 1.1 equiv.) and acetic anhydride (5.26 ml, 5.69 g, 55.8 mmol, 2.0 equiv.). After stirring the solution at room temperature for 2 h, it was washed with water (100 ml), 2 M NaOH (100 ml), dried over Na_2SO_4 and filtered. The solvent was then evaporated in vacuo to give the product as a pale

yellow oil (9.66 g, 26.50 mmol, 95%). R_f 0.65 (20% EtOAc/light petroleum); (Found (EI) M^+, 364.2394 $C_{23}H_{30}O$ requires M^+, 364.2402). (Found: C, 81.9; H, 8.71. $C_{23}H_{30}O$ requires C, 82.37; H, 8.71%); ν_{max} (film)/cm^{-1} 1739; δ_H (400 MHz; $CDCl_3$) 0.89 (6H, d, J = 6.7, 2*x*CH_3), 0.87 (6H, d, J = 6.7, 2*x*CH_3), 1.77–1.95 (2H, m, 2*x*CH), 2.11 (3H, s, OAc), 2.44 (2H, d, J = 7.0, CH_2), 2.46 (2H, d, J = 7.3, CH_2), 6.30 (1H, dd, J = 7.1, 15.9, CH=CHCH), 6.41 (1H, d, J = 7.1, CHOAc), 6.61 (1H, d, J = 15.9, CH=CHCH), 7.07 (2H, d, J = 8.2, Ar), 7.13 (2H, d, J = 7.9, Ar), 7.29 (2H, d, J = 7.9, Ar), 7.30 (2H, d, J = 7.6, Ar); δ_C (100.6 MHz; $CDCl_3$) 21.8, 22.7, 22.8, 30.6, 45.5, 76.6, 126.9, 127.1, 127.3, 129.7, 132.8, 134.1, 137.0, 142.1, 142.2, 170.5; *m/z* (EI) 364 (M^+, 10%), 304 (25), 261 (65), 43 (100).

4.4. (S)-[(1E)-3-phenyl-4,4-bis(phenylsulfonyl)-1-butenyl]benzene 2a

(4*S*)-2-(2-diphenylphosphinophenyl)-4-isopropyl-1,3-oxazoline **9** (42 mg, 0.112 mmol, 4 mol%) and [{Pd ($\eta^3C_3H_5$)Cl}$_2$] (10 mg, 0.028 mmol, 2 mol% in Pd) were heated at reflux in THF (2 ml) under an argon atmosphere for 15 min [17]. Following this *rac*-1,3-diphenylprop-2-enyl acetate **1a** (0.70 g, 2.8 mmol, 1.0 equiv.), N,O-*bis*(trimethylsilyl)acetamide (1.38 ml, 1.14 g, 5.6 mmol, 2.0 equiv.) and *bis*(phenylsulfonyl)methane **12** (0.829 g, 2.8 mmol, 1.0 equiv.) in 8 ml THF along with a catalytic amount of anhydrous caesium acetate (10 mg) were added to the refluxing catalyst. The reaction was heated at reflux for 48 h. After cooling to room temperature, the contents of the flask were diluted with dichloromethane (50 ml) and then washed with saturated aqueous ammonium chloride (50 ml), saturated brine (50 ml) and water (50 ml). The combined extracts were dried (Na_2SO_4), filtered and evaporated under reduced pressure. Column chromatography (10% EtOAc/light petroleum) of the residue on aluminum oxide afforded a colourless solid (0.89 g, 1.82 mmol, 65%), 95% ee [by HPLC (chiralpac AD, hexane:^{i}PrOH (70:30), 1 ml/min, 254 nm, t_R 14/17 min.)]; $[\alpha]_D^{30}$ − 5.3 (c = 1.0, $CHCl_3$), (Lit. [17] (*R*)-**2a** $[\alpha]_D^{25}$ +5.6 (c = 1.0, $CHCl_3$); mp 163–164 °C (Found (FAB$^+$) MH$^+$, 489.1199. $C_{28}H_{25}O_4S_2$ requires MH$^+$, 489.1149); ν_{max} (Nujol)/cm^{-1} 1331 and 1150; δ_H (400 MHz; $CDCl_3$) 4.71 (1H, dd, J = 2.4 and 9.3, CH=CH–CH), 5.09 (1H, d, J = 2.4, CH($SO_2Ph)_2$), 6.20 (1H, d, J = 15.6, CH=CH–CH), 6.88 (1H, dd, J = 9.3 and 15.6, CH=CH-CH), 7.20–8.33 (18H, m, Ar), 8.04 (2H, m, Ar); δ_C (100.6 MHz; $CDCl_3$) 47.6, 89.1, 124.2, 126.6, 127.3, 127.8, 128.2, 128.4, 128.7, 128.9, 128.9, 130.2, 134.0, 134.6, 134.9, 136.5, 137.9, 140.6, 140.6; *m/z* (FAB$^+$) 489 (MH$^+$, 50%), 346 (40), 205 (100), 193 (60).

Alternative procedure: (4*S*)-2-(2-diphenylphosphinophenyl)-4-isopropyl-1,3-oxazoline **9** (42 mg, 0.112 mmol, 4 mol%) and [{Pd ($\eta^3C_3H_5$)Cl}$_2$] (10 mg, 0.028 mmol, 2 mol% in Pd) were heated at 73 °C in 1,4-dioxane (2 ml) under an argon atmosphere for 15 min. Following this *rac*-1,3-diphenylprop-2-enyl acetate **1a** (0.70 g, 2.8 mmol, 1.0 equiv.) and sodium salt of *bis*(phenylsulfonyl)methane (0.829 g, 2.8 mmol, 1.0 equiv.) in 8 ml 1,4-dioxane were added to the refluxing catalyst which was then treated as above.

4.5. (S)-1-isobutyl-4-[(1E)-3-(4-isobutylphenyl)-4,4-bis(phenylsulfonyl)-1-butenyl]benzene 2b

The same procedure as that for (*S*)-[(1*E*)-3-phenyl-4,4-*bis*(phenylsulfonyl)-1-butenyl]benzene **2a** was employed, starting from acetate **1b**. Title compound was obtained as a colourless solid (1.26 g, 2.10 mmol, 75%), 87% ee [by HPLC (chiralpac AD, hexane:^{i}PrOH (70:30), 1 ml/min., 254 nm, t_R 13/17 min.)] $[\alpha]_D^{30}$ + 20 (c = 1.5, $CHCl_3$); mp 119–122 °C; R_f 0.47 in 20% EtOAc/light petroleum; (Found (FAB$^+$) MH$^+$, 601.2438. $C_{36}H_{41}O_4S_2$ requires MH$^+$, 601.2446); (Found: C, 71.9; H, 6.88. $C_{36}H_{40}O_4S_2$ requires C, 71.97; H, 6.71%); ν_{max} (film)/cm^{-1} 1320, 1154 (S=O), 1145 (S=O); δ_H (400 MHz; $CDCl_3$) 0.89 (6H, d, J = 6.3, 2*x*CH_3), 0.90 (6H, d, J = 6.8, 2*x*CH_3), 1.79–1.88 (2H, m, 2*x*CH), 2.42 (2H, d, J = 6.8, CH_2), 2.45 (2H, d, J = 6.8, CH_2), 4.66 (1H, dd, J = 2.4, 9.3, CH=CH-CH), 5.08 (1H, d, J = 2.4, CH($SO_2Ph)_2$), 6.17 (1H, d, J = 15.8, CH=CH–CH), 6.81 (1H, dd, J = 9.3, 15.8, CH=CH–CH), 7.01 (2H, d, J = 8.3, Ar), 7.05 (2H, d, J = 8.3, Ar), 7.18 (2H, d, J = 7.8, Ar), 7.19 (2H, d, J = 7.8, Ar), 7.35–8.02 (10H, m, Ar); δ_C (100.6 MHz; $CDCl_3$) 22.3, 30.1, 30.2, 44.9, 45.1, 47.3, 89.3, 123.4, 126.4, 127.9, 128.7, 128.9, 128.8, 129.2, 129.3, 130.3, 133.9, 134.0, 134.4, 134.7, 137.9, 138.0, 140.7, 141.4; *m/z* (CI) 600 (M^+, 10%), 318 (60), 305 (50), 142 (100).

4.6. (S)-2-phenyl-3,3-bis(phenylsulfonyl)-1-propanol 10a

(*S*)-[(1*E*)-3-phenyl-4,4-*bis*(phenylsulfonyl)-1-butenyl]benzene **2a** (1.06 g, 2.16 mmol, 1.0 equiv.) dissolved in MeOH (10 ml) and dichloromethane (45 ml) was cooled to −78 °C with O_2 gas bubbled through the solution for 5 min. Ozone was generated and bubbled through the reaction mixture until the reaction solution turned blue and TLC analysis revealed no more starting material was present (usually about 4 h.). Oxygen was bubbled through the mixture again for 5 min and then sodium borohydride (0.164 g, 4.33 mmol, 2.0 equiv.) was added and the mixture was allowed to warm to room temperature overnight. The solvent was evaporated under reduced pressure and the crude product taken up in dichloromethane (80 ml) and then washed with saturated ammonium chloride (50 ml), saturated brine (50 ml) and water (50 ml). The organic layer was dried (Na_2SO_4), filtered and solvent evaporated under reduced pressure. Column chromatography (65% ether/light petroleum) of the residue on silica gel afforded a colourless solid (0.80 g, 1.93 mmol, 90%), 95% ee[1] $[\alpha]_D^{30}$ + 83 (c = 1.0, $CHCl_3$); R_f 0.19 (65% Ether/light petroleum); mp 75–76 °C; (Found (FAB^+) MH^+ 417.0819. $C_{21}H_{21}O_5S_2$ requires 417.0785); (Found: C, 60.2; H, 4.83. $C_{21}H_{20}O_5S_2$ requires C, 60.56; H, 4.84%); ν_{max} (Nujol)/cm^{-1} 3610 (OH); δ_H (270 MHz; $CDCl_3$) 2.28 (1H, s, OH), 4.05–4.09 (1H, m, CH), 4.32–4.41(2H, m, CH_2), 5.11 (1H, d, J = 2.44, CH), 7.21–7.83 (15H, m, Ar); δ_C (67.9 MHz; $CDCl_3$) 47.8, 62.5, 86.1, 128.2, 129.1, 129.3, 129.4, 129.5, 129.6, 129.7, 134.7, 134.9, 137.6, 138.9, 140.1; *m/z* (FAB^+) 417 (MH^+, 100%), 399 (85), 245 (55).

4.7. (S)-2-(4-isobutylphenyl)-3,3-bis(phenylsulfonyl)-1-propanol 10b

The same procedure as that for 2-phenyl-3,3-*bis*-(phenylsulfonyl)-1-propanol **10a** was employed. Title compound obtained as a colourless solid (1.30 g, 2.75 mmol, 83%), 87% ee[2] $[\alpha]_D^{30}$ 84 (c = 1, $CHCl_3$); R_f 0.05 (20% EtOAc/light petroleum); mp 131–133 °C (Found (FAB^+) MH^+, 473.1447. $C_{25}H_{29}O_5S_2$ requires MH^+ 473.1411); (Found: C, 63.6; H, 6.11. $C_{25}H_{28}O_5S_2$ requires C, 63.54; H, 5.97%); ν_{max} ($CHCl_3$)/cm^{-1} 3445 (OH); δ_H (270 MHz; $CDCl_3$) 0.89 (6H, d, J = 6.6, $CH(CH_3)_2$), 1.77–1.87 (1H, m, $CH(CH_3)_2$), 2.24 (1H, s, OH), 2.42 (2H, d, J = 7.1, $CH_2CH(CH_3)_2$, 4.06 (1H, td, J = 7.2, 2.4, $CHCH(SO_2Ph)_2$), 4.27–4.45 (2H, m, CH_2OH), 5.12 (1H, d, J = 2.4, $CH(SO_2Ph)_2$), 7.01 (2H, d, J = 8.2, Ar), 7.17 (2H, d, J = 8.2, Ar), 7.42–7.52 (4H, m, Ar), 7.58–7.68 (2H, m, Ar), 7.76–7.84 (4H, m, Ar); δ_C (67.9 MHz; $CDCl_3$) 22.4, 30.0, 44.9, 47.1, 62.1, 86.0, 128.7, 128.9, 129.4, 134.2, 134.3, 138.5, 139.7, 141.2; *m/z* (CI) 473 (MH^+, 30%), 455 (100), 161 (70).

4.8. (S)-2-phenyl-1-propanol 11a

Into 25 ml of dry methanol was placed activated magnesium metal (0.30 g) with stirring. The mixture was heated to 50 °C to initiate continuous hydrogen generation [18]. Hydrogen continued to be evolved when the heating source was removed and (*S*)-2-phenyl-3,3-*bis*(phenylsulfonyl)-1-propanol **10a** (0.50 g, 1.20 mmol) was added. The reaction mixture was normally stirred without heating for the rest of the time (temperature remained near 50 °C) and 0.30 g of magnesium was added in portions to maintain the reaction. After 1.0–1.2 g of magnesium had been added, the reduction was normally complete by (TLC). If not more magnesium was added. Once the reaction was complete the cloudy grey mixture was poured into a mixture of 2 M HCl (50 ml) and ice and then extracted with dichloromethane. The organic extracts were combined, dried (Na_2SO_4), filtered and the solvent evaporated in vacuo. The crude product was purified using column chromatography using 33% ether/light petroleum as the eluent. The product was obtained as a yellow oil (0.142 g, 1.04 mmol, 87%), 95% ee [by HPLC (chiralcel OB, Hexane-^{i}PrOH (97:3), 1 ml/min., 254 nm, t_R 15/16 min.) $[\alpha]_D^{30}$ − 15.7 (c = 0.513, $CHCl_3$), (Lit. [18] $[\alpha]_D^{20}$ − 16.09 (c = 0.513, $CHCl_3$); R_f 0.23 (33% ether/light petroleum); (Found M^+, 136.0890. $C_9H_{12}O$ requires M^+, 136.0888); ν_{max} (film)/cm^{-1} 3357 (OH); δ_H (270 MHz; $CDCl_3$) 1.27

[1] We were unable to determine the ee of compounds **10a** and **b**. However, as the ee of the compounds **11a** and **b** have remained the same as the ee of compounds **2a** and **b**, we assume that the ee is retained throughout and is the same for compounds **10a** and **b**, respectively.

[2] See footnote one.

(3H, d, $J = 7.0$, CH_3), 1.54 (1H, brs, OH), 2.92 (1H, sextet, $J = 7.0$, CH), 3.69 (2H, d, $J = 7.0$, CH_2), 7.21–7.36 (5H, m, Ar); δ_C (67.9 MHz; $CDCl_3$) 17.5, 42.4, 68.6, 126.6, 127.5, 128.9, 143.7.

4.9. (S)-2-(4-isobutylphenyl)-1-propanol 11b

The same procedure as that for 2-phenyl-1-propanol was employed [19]. Title compound was obtained as a colourless oil (0.41 g, 0.87 mmol, 89%), 87% ee; $[\alpha]_D^{30} - 11.95$ ($c = 1.45$, $CHCl_3$), (Lit. [19] $[\alpha]_D^{20} - 14.8$ ($c = 1.6$, $CHCl_3$); ν_{max}/cm^{-1} 3380; δ_H (400 MHz, $CDCl_3$) 0.90 (6H, d, $J = 6.7$, $CH(CH_3)_2$, 1.26 (3H, d, $J = 7.0$, Me), 1.60 (1H, s, OH), 1.79–1.90 (1H, m, $CH(CH_3)_2$), 2.45 (2H, d, $J = 7.3$, $CH_2CH(CH_3)_2$), 2.91 (1H, m, CHMe), 3.69 (2H, d, $J = 6.9$, CH_2OH), 7.10 (2H, d, $J = 8.3$, Ar), 7.15 (2H, d, $J = 8.3$, Ar); δ_C (100.6 MHz, $CDCl_3$) 18.0, 22.8, 30.6, 42.4, 45.4, 69.1, 126.1, 127.4, 129.5, 140.9.

4.10. (S)-2-phenyl propanoic acid 4a

To a chromium trioxide (0.10 g, 1.00 mmol, 3.8 equiv.) solution in 1.5 M H_2SO_4 (1.6 ml), was added (*S*)-2-phenyl propanol **11a** (36 mg, 0.26 mmol, 1.0 equiv.), dissolved in acetone (3.3 ml) at 8 °C [20]. The reaction was then stirred whilst allowing the temperature to reach room temperature. After stirring the reaction mixture overnight, it was diluted with ether (5 ml) and the organic layer washed with brine (2×5 ml). The organic layers were then combined and extracted with 1 M NaOH (8 ml). The aqueous layer was acidified with H_2SO_4 (1.5 M, 1.6 ml) and then extracted with ether. The organic layer was separated, dried ($MgSO_4$) filtered and the solvent evaporated. Purification by column chromatography on silica using 33% Et_2O/ light petroleum as eluent gave **4a** as a colourless solid (30 mg, 0.20 mmol, 77%), 95% ee [by HPLC (chiralcel OD, Hexane-^{i}PrOH-HCO_2H (98:2.98:0.02), 1 ml/min., 254 nm, t_R 10.5/12 min.) $[\alpha]_D^{30} + 72.3$ ($c = 1$, $CHCl_3$), (Lit. [20] $[\alpha]_D^{20} + 72.8$ ($c = 1$, $CHCl_3$). R_f 0.33 (Ether/light petroleum); ν_{max} (film)/cm^{-1} 3030 (OH), 1704 (C=O); δ_H (270 MHz; $CDCl_3$) 1.49 (3H, d, $J = 7.0$, Me), 3.69 (1H, q, $J = 7.0$, CH), 7.24–7.32 (5H, m, Ar); δ_C (67.9 MHz; $CDCl_3$) 18.1, 45.3, 127.4, 127.6, 128.6, 132.6, 180.7.

4.11. (S)-Ibuprofen 4b

Pyridinium dichromate (1.01 g, 2.69 mmol, 5.18 equiv.) dissolved in anhydrous DMF (8 ml) was added to a solution of the alcohol, (*S*)-2-(4-isobutylphenyl)-1-propanol **11b** (0.10 g, 0.52 mmol, 1.0 equiv.) in DMF (2 ml) [21]. The reaction was then stirred under an inert atmosphere at room temperature for 12 h. The resulting mixture was poured into saturated aqueous sodium bisulfite (30 ml) and acidified to pH 1 with concentrated hydrochloric acid. Sodium chloride was added to make a saturated solution, which was extracted with ether (3×50 ml). The combined organic extracts were dried ($MgSO_4$), filtered and evaporated under reduced pressure. Purification by column chromatography on silica using 40% EtOAc/ light petroleum as eluent gave Ibuprofen as a colourless solid (0.095 g, 0.46 mmol, 88%), 87% ee [by HPLC (chiralcel OD, hexane:*s*-TFA (99:0.9:0.1), 0.5 ml/min., 254 nm, t_R 13.5/14.5 min.) $[\alpha]_D^{30} + 45.5$ ($c = 0.30$, EtOH), (Lit [21] $[\alpha]_D + 60$ ($c = 2$, EtOH). mp 49–51 °C (lit. [21] mp 50–52 °C); ν_{max}/cm^{-1} 3500 (O-H), 1710 (C=O); δ_H (270 MHz; $CDCl_3$) 0.82 (6H, d, $J = 6.6$, $CH(CH_3)_2$), 1.43 (3H, d, $J = 7.1$, Me), 1.75 (1H, m, $CH(CH_3)_2$), 2.37 (2H, d, $J = 7.1$, $CH_2CH(CH_3)_2$), 3.64 (1H, q, $J = 7.2$, CHMe), 7.02 (2H, d, $J = 8.1$, Ar), 7.15 (2H, d, $J = 8.1$, Ar).

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