Asymmetric aromatic vicarious nucleophilic substitution of hydrogen

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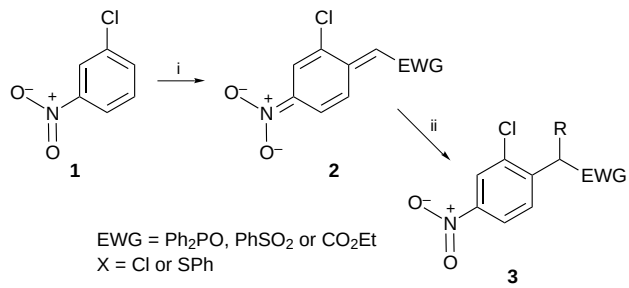
A series of novel one-pot aromatic vicarious nucleophilic substitution of hydrogen/asymmetric alkylation reactions are described; the enolates of several chiral cyclohexyl phenylsulfanylacetates react readily with 3-chloronitrobenzene followed by subsequent stereoselective alkylation.

The aromatic vicarious nucleophilic substitution[1,2] (VNS) of hydrogen provides a useful route to substituted arenes not readily prepared by electrophilic substitution. We recently reported[3,4] that the anion **2**, the initial product of the reaction between a nitrobenzene and a vicarious nucleophile, can be quenched with a variety of electrophiles (**1** → **3**, Scheme 1). It was clear to us that the relative and absolute stereochemical configuration of the newly created stereogenic centre might be controlled by an appropriate auxiliary incorporated into the nucleophile. Here we report an unprecedented asymmetric variant of this type of one-pot VNS–alkylation reaction which enables the stereocontrolled synthesis of a stereocentre adjacent to an electron deficient aryl group.

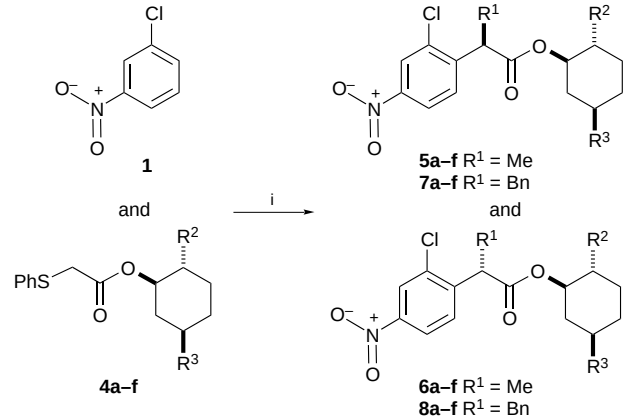
We chose to study the VNS reactions of a series of chiral esters **4a**–**f**. Menthol proved to be a poor auxiliary; reaction of the phenylsulfanylacetate **4a** with **1** followed by benzylation gave a 1 : 1 mixture of diastereoisomers in 60% yield. However the VNS–alkylation reaction of phenylsulfanylacetate **4b** derived from (−)-8-phenylmenthol[5] was much more successful. The enolate of **4b** reacted cleanly with 3-chloronitrobenzene **1** in DMF, with substitution taking place solely in the *para* position. Quenching the reaction mixture at −65 °C with a series of alkylating reagents gave moderate to good stereoselectivity.†,‡ Quenching with methyl iodide generated the corresponding diastereoisomeric esters **5b** and **6b** in a ratio of 3 : 1, in good yield. Benzylation proved to be the most diastereoselective reaction, giving the two α-benzylated diastereoisomers **7b** and **8b** in a ratio of 8 : 1 (Scheme 2, Table 1).

trans-2-Phenylcyclohexan-1-ol[6] has been extensively used in a wide variety of asymmetric reactions and is often used in place of (−)-8-phenylmenthol, since both enantiomeric forms are available by a variety of methods, most notably *via* asymmetric hydroboration[7] or dihydroxylation–reduction[8] of 1-phenylcylohexene. We therefore decided to apply this auxiliary to our VNS–asymmetric alkylation reaction. The enolate of (−)-*trans*-2-phenylcyclohexyl phenylsulfanylacetate **4c** reacted cleanly with 3-chloronitrobenzene, however no stereoselectivity was obtained upon methylation, while only a poor 2 : 1 diastereoselectivity was observed upon benzylation. We next tested the sterically more demanding esters phenylsulfanylacetates **4d**–**f** prepared from (±)-*trans*-2-biphenyl-, (±)-*trans*-2-(1′-naphthyl)- and (±)-*trans*-2-(2′-naphthyl)cyclohexan-1-ol, which are available *via* cuprate ring-opening of cyclohexene oxide.[9] The alcohols were converted to the phenylsulfanylacetates, reacted with 3-chloronitrobenzene under typical VNS conditions, and quenched with methyl iodide and benzyl bromide at −65 °C.§ The *trans*-2-(2′-naphthyl)cyclohex-1-yl group proved to be the most effective auxiliary, giving a 3 : 1 mixture of diastereoisomers **5f** and **6f** upon methylation and a 4 : 1 mixture of **7f** and **8f** upon benzylation.

Fortunately both products of the VNS reaction of (±)-*trans*-2-(2′-naphthyl)cyclohexyl phenylsulfanylacetate **4f** were crystalline; X-ray crystallography showed the major isomer **7f** to be the (1*RS*,2*SR*,α*RS*) diastereoisomer (Fig. 1).¶,‖ Since both



Scheme 1 *Reagents and conditions*: i, NaH (2 equiv.), EWG–CH_2X (1 equiv), room temp., DMF. ii, RX′ (1 equiv.), room temp.



Scheme 2 *Reagents and conditions*: i, NaH (2 equiv.), 0 °C, DMF; ii, R^1X (MeI or BnBr) (1 equiv.), −65 °C

Table 1 Diastereoselectivity[a] of VNS–asymmetric alkylation reaction **1** + **4** → **5** + **6** or **7** + **8**

Auxiliary	**4**	**5** : **6**[c] R^1 = Me	**7** : **8**[c] R^1 = Bn
(−)-Menthol	**a**	—	1 : 1 (60)
(−)-8-Phenylmenthol	**b**	3 : 1 (67)	8 : 1 (70)
(−)-*trans*-2-Phenylcyclohexan-1-ol	**c**	1 : 1 (55)	2 : 1 (62)
(±)-*trans*-2-(4-Biphenyl)cyclohexan-1-ol	**d**	1 : 1 (64)	4 : 3 (64)
(±)-*trans*-2-(1′-Naphthyl)cyclohexan-1-ol	**e**	3 : 2 (64)	4 : 1 (57)
(±)-*trans*-2-(2′-Naphthyl)cyclohexan-1-ol	**f**	3 : 1 (60)	4 : 1[b] (62)

[a] Measured by ^1H NMR (300 MHz) analysis of the crude reaction mixture. [b] Similar selectivity was obtained when (−)-**4f** was used. [c] Yields shown in parentheses. The relative stereochemistry of the major diastereoisomer is assigned by analogy to **7b** and **7f**.

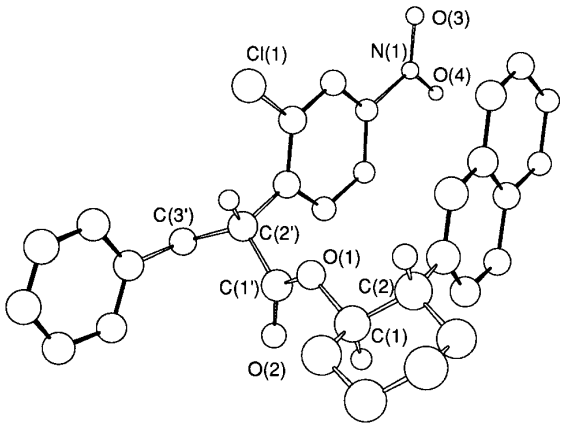
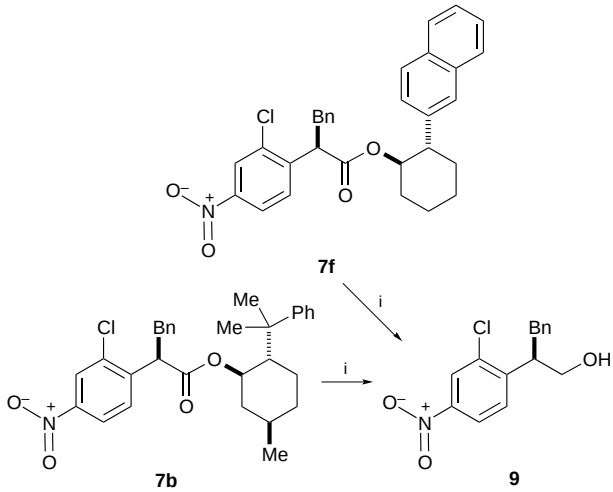


Fig. 1 X-Ray crystal structure of the diastereoisomer **7f**



Scheme 3 *Reagents and conditions*: i, DIBALH (2.1 equiv.), THF, room temp.

products **7b** and **8b** from the (−)-8-phenylmenthol derived VNS nucleophile **4b** were oils the alcohol **9**, obtained from DIBALH reduction of **5b**, was compared with that similarly obtained from (−)-*trans*-2-(2′-naphthyl)cyclohexyl phenylsulfanylacetate **4f** (Scheme 3). Enantiomerically pure (−)-*trans*-2-(2′-naphthyl)cyclohexan-1-ol was prepared from 1-(2′-naphthyl)cyclohexene using Sharpless's procedure.[10] The alcohols **9** derived from the two auxiliaries had the same sign of rotation, $[\alpha]_D$ − 36.4 (from **7f**) and $[\alpha]_D$ − 38.2 (from **7b**),** confirming that configuration of the newly created chiral centre in **7b** was also (*R*). It is interesting to note that the sense of stereochemical induction is the same as that reported for the alkylation of the enolate of 8-phenylmenthyl phenylacetate generated by deprotonation with butyllithium.[11]

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Footnotes

† Diastereoselectivity was determined by ^{1}H NMR spectroscopy (300 MHz). All compounds were fully characterised and gave the expected spectral and analytical data.

‡ *Typical procedure*: To a nitrogen flushed slurry of sodium hydride (2.0 mmol) in dry DMF (3 cm^3) at 0 °C was added dropwise a mixture of phenylsulfanylacetate **4** (1 mmol) and 3-chloronitrobenzene (1.1 mmol) in dry DMF (3 cm^3). The mixture was allowed to reach room temperature over 2 h then cooled to −65 °C. The alkyl halide (1.0 mmol) was added and the reaction left to reach room temperature. The mixture was poured into dilute hydrochloric acid (20 ml) and extracted with chloroform (3 × 20 cm^3). The combined extracts were washed with distilled water, dried (magnesium sulfate) and concentrated *in vacuo*. The diastereoisomeric mixture of esters was separated by chromatography (silica, 1 : 1 chloroform–hexane, v/v).

§ *Selected data* for **7f**: $[\alpha]_D$ −71 (*c* 0.5, $CHCl_3$); R_f 0.45 (silica, 1 : 1, chloroform–hexane, *v/v*); mp 89–91 °C. (Found: C, 72.3; H, 5.5; N, 2.8; Cl, 7.1; $C_{31}H_{28}ClNO_4$ requires C, 72.4; H, 5.5; N, 2.7; Cl, 6.9%); ν_{max}(liquid film on CsI plates)/cm^{-1} 2940 (m), 2860 (w), 1735 (s), 1530 (s), 1350 (s), 1170 (m), 1020 (w), 820 (w), 750 (m); δ_H(300 MHz; $CDCl_3$) 1.26–1.65 (4 H, m, cyclohexyl), 1.76–1.90 (3 H, m, cyclohexyl), 2.02 (1 H, m, cyclohexyl), 2.65 (1 H, dt, *J* 4, 12 Hz, C*H*CHO), 2.66 (1 H, dd, *J* 7, 14 Hz, PhCH_aH_b), 3.14 (1 H, dd, *J* 9, 14 Hz, PhCH_aH_b), 4.23 (1 H, dd, *J* 7, 9 Hz, CHC=O) 5.09 (1 H, dt, *J* 4, 11 Hz, CHO), 6.73 (1 H, d, *J* 9 Hz, aromatic), 6.98–7.62 (14 H, cm, aromatic); δ_C(75 MHz; $CDCl_3$) 24.71 (CH_2), 25.62 (CH_2), 32.20 (CH_2), 33.59 (CH_2), 38.54 (CH_2), 48.86 (CH), 50.14 (CH), 77.00 (CH), 121.07 (CH), 123.86 (CH), 125.15 (CH), 125.71 (CH), 125.93 (CH), 126.06 (CH), 126.57 (CH), 127.13 (CH), 127.53 (CH), 127.93 (CH), 128.30 (CH), 128.70 (CH), 132.08 (C), 132.79 (C), 133.73 (C), 137.77 (C), 139.76 (C), 142.69 (C), 146.03 (C), 171.00 (C=O); *m/z* (FAB) 552 [(M + K)$^+$, 45%], 513 [(M + H)$^+$, 50], 419 (40), 391 (40), 208 (60), 141 (100).

¶ *Crystal data* for **7f**. $C_{31}H_{28}ClNO_4$: *M* = 514.0 monoclinic, space group $P2_1/c$, *a* = 14.357(2), *b* = 20.227(3), *c* = 18.643(3) Å, β = 91.56(3)°, *V* = 5411.9(14) Å^3, *Z* = 8, D_c = 1.262 g cm^{-3}, *T* = 293 K, colourless plates, μ = 1.78 cm^{-1}. *Data collection and processing*: A crystal of **7f** having approximate dimensions of 0.40 × 0.30 × 0.3 mm was mounted on a glass fibre. All measurements were made on a Siemens R3m/n diffractometer with graphite-monchromated Mo-Kα X-radiation. The data were collected at a temperature of 20 ± 1 °C using the ω–2θ scanning technique to a maximum of 2θ value of 50.0°. The structure was solved by direct methods using SHELXS-86.[12]

Full-matrix least-squares refinement using SHELXL93[13] yielded final residuals, based on F^2, of wR^2 = 0.207 and R_1 = 0.099 for 5025 observed [$I > 2\sigma(I)$] reflections with $w = 1/[\sigma^2(F_o) + (0.0766p)^2 + 3.2581p]$ where $p = (F_o^2 + 2F_c^2)/3$. In this room temperature study the atoms are undergoing substantial vibration leading to relatively high *R*-factors. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC). See Information for Authors, Issue No. 1. Any request to the CCDC for this material should quote the full literature citation and the reference number 182/326.

‖ The asymmetric unit consists of two chemically identical and similarly configured molecules. For clarity, only one is shown in the Fig. 1.

** Both samples of **9**, derived from diastereoisomerically pure **7b** and **7f** were shown to be enantiomerically pure by ^{1}H and ^{19}F NMR analysis of their α-methoxy-α-(trifluoromethyl)phenylacetates.

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