Productivity in synthesis: a mixture protocol to raise compound output is demonstrated for asymmetric cyclopropanation of allyl alcohols

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The productivity of conventional chemical reactions can be improved in favourable cases by using a mixture protocol. This concept is demonstrated for the asymmetric cyclopropanation of 3-arylprop-2-en-1-ols. Mixtures of three or four starting materials give products which are separated by flash chromatography. The enantiomeric excess and yield of each pure compound is comparable to that obtained in conventional single-substrate reactions, leading to an overall efficiency gain, especially in experimentalist effort, and reduced hazard.

In both academia and industry, chemists are under pressure to increase productivity using existing resources. The work reported here investigated the question: 'how may organic experimentalists increase their output of compounds?'. Advice and training is available to optimise synthetic efficiency in the sense of planning a short route[1] using safe and reliable techniques.[2] Especially in the process chemistry field, productivity can be increased by telescoping several steps of a sequence into a 'one-pot' transformation.[3] However, there are few guidelines generally applicable to raising the productivity of a given laboratory-scale reaction. A literature search by keyword found sparse reference[4] to research into efficiency of experimentalist's effort, although chemists would be familiar with suggestions such as using otherwise wasted time overnight and fitting the scale of a reaction to its purpose. Many chemicals are initially made at a scale around 0.5 g. Final products from a long route may fall to 5 mg, while repeat synthesis for early steps or for extensive testing might need 50 g. A possible goal is to double or treble the numbers of samples produced in this typical scale range, without increasing the experimentalist's input. It is usually easy to increase the mass throughput of a reaction by carrying it out on a larger scale: in many cases the effort required varies little with scale in the 0.5 to 5 g range. This observation is central to the work reported here.

Much current research on productivity is mixture directed. Compound libraries and the associated science of combinatorial chemistry are in vogue.[4] However, libraries of products are incompatible with many applications. Analogues in a series often have some partial activity and screening cannot rank them efficiently without separation into individual components. The deconvolution of even a few 'hits' from large mixtures can be resource-intensive. Chemists requiring a single target such as a natural product are equally unlikely to benefit from the library approach. Another area in rapid development, particularly in industry, is robotic synthesis.[5] Human productivity is certainly improved; but a robot is expensive and has implications for the robustness and applicability of the reaction under study. Sometimes the medicinal or agrochemical chemist wants only a few analogues, whose biology will guide later synthesis, while a robot-assisted synthesis may only be worth developing for 20–50 analogues.

Although important in some applications such as new lead discovery, neither of the above approaches helps chemists increase productivity in standard experiments. The new developments do, however, suggest trying mixtures of substrates in otherwise conventional reactions. The aim of the present work is to demonstrate the synthesis of a given total quantity of three or more compounds in a single experiment. A conventional procedure was modified by mixing several starting materials. The work-up included chromatography to separate the desired products at the same level of purity and characterisation as the single sample that would normally have been obtained. The goal was to double, approximately, the productivity of the experimentalist. To achieve this, mixtures of just two starting materials are clearly inadequate. Even if the reaction proceeded well, the additional separation step would require a certain effort which could have been avoided by performing the two reactions in separate flasks. Three substrates at least must be prepared per reaction if the protocol is to achieve the productivity target. (A two-substrate approach might deliver a useful but less than doubling of output but it would be more difficult to measure its precise benefit.)

While many chemists might accept the concept of carrying a small pool of starting materials through a conventional reaction, they would probably be reluctant to do so, anticipating that the separation of the products might be difficult. Hence a key issue was to investigate how to select appropriate starting materials from the wider set of choices available.

Results and discussion

Choice of reaction and substrates

The asymmetric cyclopropanation of allylic alcohols, reviewed by Charette and Marcoux,[6] was investigated using a multiple-substrate protocol. There were several factors which made the recently-published modified procedure[7] using $Zn(CH_2I)_2 \cdot DME$ (1,2-dimethoxyethane) and a chiral dioxaborolane auxiliary an attractive reaction for a first study. These are:

(a) The experimentalist's time and skills are heavily used.

(b) The reagents pose hazards and/or require a complex temperature regime (mixtures of starting materials involve fewer exposures and fewer manipulations for a given number of products).

(c) The work-up is complex, and especially so if it requires chromatography.

(d) The reaction is of high added value (new C–C bonds, induction of chirality).

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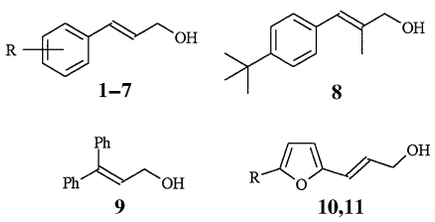
Table 1 Starting materials for the asymmetric cyclopropanation



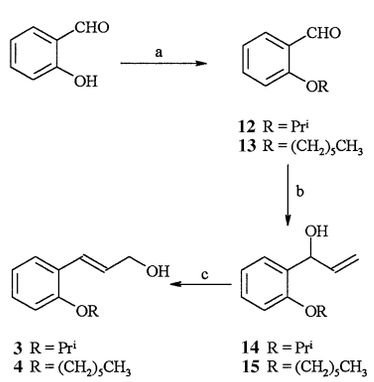
Compound	R	Source
1	H	Purchased
2	2-OMe	Reduction
3	2-OPr^i	As Scheme 1
4	2-O(CH$_2$)$_5$CH$_3$	As Scheme 1
5	2-NO$_2$	Reduction
6	4-NO$_2$	Purchased
7	4-NMe$_2$	Reduction
8	—	Reduction
9	—	Reduction
10	H	Reduction
11	NO$_2$	Reduction

(e) The expected yield (and enantiomeric excess if applicable) is high.

(f) By-products, if present after work-up, are readily separable.

(g) The reaction can accommodate starting materials of varying reactivity.

The substrates chosen for the cyclopropanation were substituted 3-arylprop-2-en-1-ols which would cover a range of reactivity and steric hindrance around the double bond and allow some comparison with the literature for results under conventional single-substrate conditions. The eleven compounds used are listed in Table 1, which also gives their source of supply. Where this is marked as reduction, the compound was prepared by sodium borohydride in ethanol reduction of the corresponding commercially-available aldehyde. Scheme 1



Scheme 1 *Reagents and conditions:* a, R–I, EtOH, EtO$^-$, reflux; b, vinylmagnesium bromide, THF, <12°C; c, Amberlyst A15, aq. THF, reflux

shows the synthesis used for the two substrates which were prepared from salicylaldehyde. The use of Amberlyst A15 for the acid-catalysed rearrangement prevents the formation of allylic chlorides as by-products, which can occur using HCl as in the literature procedure.[8]

Choice of mixture partners

It was anticipated that the standard separation technique of flash chromatography[9] would be applicable to the separation of 'triples' or even 'quadruples' provided appropriate substrate combinations were selected. The hypothesis that starting materials which were separated on TLC by more than 0.1 R_f units would give products which would also be separable by flash chromatography provided a good guide for this series, in which products and starting materials often have nearly identical R_fs (see below). It may also be a robust guide in other series where a single constant fragment is added to a given framework carrying simple substituents. It would not be expected to assist planning the more ambitious combinatorial-type experiment where several substrates are combined in a matrix with several reaction partners. Of course, even in the present case, the chemist must be certain that none of the starting materials contains a functional group which would be incompatible with the desired reaction. This is no different to planning a conventional 'single' reaction, but failure to anticipate problem substrates risks ruining all the products from a 'multiple'!

Outcomes of mixture reactions

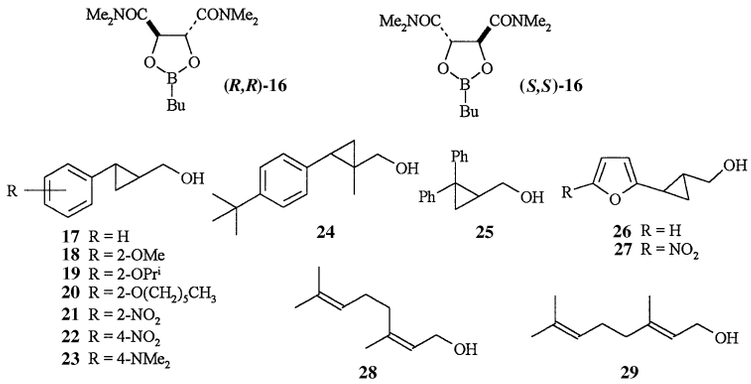
Table 2 lists the experiments done with mixtures and gives the yield and enantiomeric excess (ee) of the isolated products. Both enantiomers of the chiral auxiliary **16** were used, so that both chiral forms of many products were obtained separately. This allowed the ee to be determined by direct HPLC analysis, avoiding mis-assignment owing to minor impurities. Table 2 gives the retention times (t_r) of the individual enantiomers under the conditions used for each analysis. The use of mixtures was found to have little effect on the ee of the products. For example, the parent *trans*-2-phenylcyclopropylmethanol **17** was obtained in 91% ee in experiments 1 and 3 (Table 2), while a separate trial reaction in which it was formed alone gave an ee of 90.6%. The literature value[7] of 93% ee (determined on the derived trifluoroacetate ester by GLC) is comparable.

The reaction conditions[7] require excess reagent to deprotonate the alcohol of the substrate as well as to actually perform the cyclopropanation. Charette *et al.* recommend 3–5 equiv. of reagent for highest enantioselectivity;[7] just under five were used throughout the present study. Substrates with remote double bonds might therefore be susceptible to over-cyclopropanation. To investigate this point, a mixture of nerol **28** and geraniol **29** was used, with cinnamyl alcohol **1** as a control substrate. Molander and Harring have reported alternative conditions[10] for mono-cyclopropanation of the first two. After chromatography, *trans*-2-phenylcyclopropylmethanol **17** was obtained in 95% yield, in an ee of 91.3%. However, NMR of other fractions revealed that over-cyclopropanation of **28** and **29** had occurred. The mixture protocol demonstrated that the control reaction was operating normally, giving one desired product, but that it was not applicable to the other substrates.

A second type of possible failure in the cyclopropanation might result if the substrate's allylic double bond was unreactive. This could be due to steric or reactivity factors. For example, the 4-nitro compound **6** has a double bond relatively deactivated to attack by the electrophilic reagent. The 2-isopropoxy compound **3** has an activated double bond but would be more sterically constrained than the unsubstituted case. These are some of the factors that are probed in an investigation of the scope and limitations of a new reagent. In experiment 2, a 'triple' composed of the 2-methoxy-, 2-isopropoxy- and 4-nitro- compounds **2**, **3** and **6** did not give all three desired products in good yield. When the reaction was warmed to ambient temperature prior to work-up and then immediately quenched, the subsequent chromatography provided acceptable yields of the two alkoxy alcohols **18** and **19**, with no evidence for unreacted starting materials, but only a 26% yield of the 4-nitro product **22** mixed with the unchanged allyl alcohol **6**. As expected, the ee of all three products was unaffected by the poor conversion of the nitro compound. This limited failure, which was also initially observed in a reaction of the 2-nitro compound **5** in experiment 4, was easily avoided merely by allowing a longer reaction time and a higher temperature (see Experimental section).

Two substrates failed to provide any product. In experiment

Table 2 Results of mixture experiments and HPLC determination of ee



						t_r/s		HPLC[b]			
Expt.	Auxiliary	Sm.[a]	Prod.	Yield (%)	Ee (%)	Major	Minor isomer	Column	Polar solvent	% Polar solvent	Flow rate/ cm^3 min^{-1}
1	**(*R*,*R*)-16**	**1**	**17**	39	91.0	781	862	AD	EtOH	3	1
		4	**20**	44	91.8	247	532	OD	Pr^{i}OH	5	2
		6	**22**	58	89.3	1402	1135	AD	EtOH	10	1
2	**(*S*,*S*)-16**	**2**	**18**	68	90.4	1061	498	OD	Pr^{i}OH	5	2
		3	**19**	52	92.6	1301	1415	AD	EtOH	0.5	0.5
		6	**22**	26	87.9	1136	1460	AD	EtOH	10	1
3	**(*S*,*S*)-16**	**1**	**17**	58	91.1	1336	1252	AD	EtOH	4	1
		3	**19**	50	91.9	1059	1143	AD	EtOH	0.5	0.5
		4	**20**	63	91.8	525	250	OD	Pr^{i}OH	5	2
		6	**22**	76	89.6	1270	1674	AD	EtOH	10	1
4	**(*R*,*R*)-16**	**5**	**21**	30	91.9	1707	2156	AD	EtOH	10	1
		8	**24**	77	85.4	962	1433	AD	EtOH	2	1
		10	**26**	41	95.8	1220	1307	AD	EtOH	5	1
5	**(*R*,*R*)-16**	**7**	(**23**)	0	—	—	—	—	—	—	—
		9	**25**	85	93.1	582	1729	AD	EtOH	5	1
		11	**27**	51	85.8	896	1131	AD	EtOH	10	1
6	**(*S*,*S*)-16**	**2**	**18**	83	91.3	1032	490	OD	Pr^{i}OH	5	2
		8	**24**	85	82.9	1274	870	AD	EtOH	2	1
		9	**25**	93	89.3	1867	689	AD	EtOH	5	1
		11	(**27**)	0	—	—	—	—	—	—	—
7	**(*R*,*R*)-16**	**2**	**18**	82	87.7	487	1022	OD	Pr^{i}OH	5	2
		3	**19**	77	91.4	1286	1193	AD	EtOH	0.5	0.5
		4	**20**	80	91.7	247	521	OD	Pr^{i}OH	5	2
		5	**21**	86	88.4	2189	2682	AD	EtOH	10	1

[a] Sm. = starting materials. [b] Samples separated on the OD column had earlier been found not to be adequately resolved on the AD column.

5, the 4-dimethylamino-substituted compound **7** gave a water-soluble product which could not be extracted from the aqueous phase after work-up. This may be due to decomposition through cyclopropane ring-opening. The nitrofuran **11** gave the expected product **27** in experiment 5 but not in experiment 6. This was because **11** had decomposed on storage. The recovery of the five remaining components of these two experiments was good. The failure of one component of the reaction did not lead to irretrievable outcomes in the other components.

Product purification proved possible without resort to resource-intensive methods such as preparative HPLC. The only problem arose from the presence of boron-containing by-products from the chiral auxiliary. In chromatography using solvent mixtures comprising 0–25% ethyl acetate in light petroleum (bp 60–80 °C), the by-product fraction overlapped with several of the cyclopropyl products, particularly as it tended to elute in a broad band. Fortunately, the addition of 1–2% methanol to the solvent systems moved the by-product to a higher R_f than any of the desired products. Table 3 gives the measured R_f values for the starting allyl alcohols and the corresponding cyclopropane products, in sequence from lower to higher R_f in 25% EtOAc–light petroleum. Although there is not a perfect match between the two sets of data, they support the hypothesis that substrates which are well-separated by TLC will give products of similar R_f difference and in roughly the same elution sequence. In practice, a 'quadruple' of compounds **18**–**21** (experiment 7) was readily separable.

Conclusions

The work demonstrates that a mixture of three or four starting materials in a single flask can be treated conventionally through reaction, work-up and separation by column chromatography to provide individual pure products. The extent to which this represents a more efficient process than the alternative of taking each substrate in turn through the same steps (possibly without the need for chromatography) will depend on the chemistry. The factors (a) to (g) listed above are likely to favour the mixture protocol over either the normal one-at-a-time experiment or a multiple-parallel approach in which the reactions are done simultaneously but in separate flasks. The mix-and-separate experimental procedure can lead to substantial savings in experimentalist effort and reduced hazard when, for example, pyrophoric reagents are used. If the reaction must be performed with attention to detail, such as in the drying of solvents and glassware, timing of addition of reagents and temperature profile, then the experimentalist will be committed to only one-third or one-quarter of the effort and observations per compound used. This will often outweigh the potential disadvantage of relying on a chromatographic separation of

Table 3 TLC properties of allyl alcohols and cyclopropane products

Starting allyl alcohol	R_f*	Product cyclopropane	R_f*
6	0.067	**22**	0.05
11	0.072	**27**	0.03
5	0.10	**21**	0.06
2	0.20	**18**	0.16
1	0.20	**17**	0.18
10	0.22	**26**	0.15
3	0.25	**19**	0.23
9	0.28	**25**	0.21
4	0.36	**20**	0.35
8	0.37	**24**	0.26

* R_f determined by TLC using 25% EtOAc in light petroleum as eluent.

the products. The method should find wide applicability in analogue programmes, in which production of three or four products per synthesis will be attractive. In this case, choice of analogues will have taken account of factors such as availability of starting materials and the physical and reactive properties of the intermediates and products. It should be easy to select appropriate partners for each reaction mixture, as the relative chromatographic properties of starting materials and products will be known for a few cases, based on the lead analogues.

Those engaged in investigating the scope and limitations of a new reagent may likewise find the mixture protocol attractive once the basic reaction has been developed. In this case, it may not even be essential to separate the individual products, since mixtures could be examined by NMR, GC–MS or analytical HPLC to establish the fate of each substrate.

Chemists should be able to invent more adventurous applications for the method, once they have been convinced that the separation step is not a problem in the series of interest. For example, when scaling up well-understood sequences, aliquots of new substrates could be added so that the reaction would not only provide the needed amount but would also yield fresh analogues as 'impurities'! There is no reason why the three to four components of the mixture should be taken in equimolar amounts.

The mixture approach to resource-intensive reactions cannot compete with combinatorial methods or robot-assisted synthesis for producing libraries. The generation of large numbers of new compounds for screening as leads is likely to be entirely dominated by these recently-developed techniques. However, the need for 'hand-crafted' chemicals, especially to optimise leads or to develop new methodology, is unlikely to diminish. For these applications, an approach which increases compound output for less experimental effort will be welcome.

Experimental

General

NMR Spectra were recorded in $CDCl_3$ at 270 MHz (^1H) or 67.8 MHz (^{13}C) on a JEOL GSX spectrometer with $SiMe_4$ as internal standard; *J* values are given in Hz. GC–MS Spectra were recorded on a Hewlett Packard 5890 system with a mass detector used in EI mode. Analytical HPLC was performed on an ATI Unicam 'Crystal' instrument fitted with a Daicel Chemical Industries Chiralpack® AD or Chiralcel® OD column (24 cm) using HPLC-grade hexane (Rathburn) as the mobile phase, with ethanol or propan-2-ol as polar modifier. Microanalyses were obtained in the Department of Chemistry microanalytical laboratory at Imperial College. Melting points were determined on a Reichert hot-stage apparatus. Analytical TLC was performed using pre-coated glass-backed plates (Phase Separations, Sorbsil C30, 250 μm) and visualised using UV and I_2. Preparative flash chromatography[9] was performed on E. Merck silica gel 60, 230–420 mesh ASTM, in a column of diameter 65 mm and total length (for silica and solvent reservoir above) of 200 mm. Below the sintered frit was a standard B24 ground-glass joint and gas (vacuum) connector so that fractions of 50 cm^3 could be collected, if necessary by placing the receiving tube under partial vacuum. This was found to be more convenient than the alternative,[9] which places the solvent reservoir under pressure to achieve a satisfactory solvent flow rate, typically 50 cm^3 min^{-1}.

Starting materials from commercial sources (Aldrich) were used as supplied. Standard solvents (BDH) for solvent extraction and chromatography were also used as supplied, except dichloromethane and 1,2-dimethoxyethane for the asymmetric cyclopropanation reactions, which were dried over calcium hydride and distilled under N_2. Light petroleum refers to the fraction bp 60–80 °C.

2-(1-Methylethoxy)benzaldehyde 12

Sodium (2.8 g, 0.12 mol) was dissolved in EtOH (100 cm^3) (hydrogen evolution) and salicylaldehyde (12.2 g, 0.1 mol) was added, forming a precipitate. 2-Iodopropane (18.7 g, 0.11 mol) was added and the mixture stirred at the reflux temperature for 80 h, then cooled. The EtOH was removed by evaporation at reduced pressure and EtOAc (150 cm^3) and water (150 cm^3) were added. The product was extracted into the EtOAc and the organic phase washed with 2 M aqueous NaOH (2 × 50 cm^3), water (2 × 50 cm^3) and brine (50 cm^3). The extract was dried ($MgSO_4$), filtered and evaporated. The residue was purified by flash chromatography (elution with 10% EtOAc–light petroleum) to afford the aldehyde (9.2 g, 56%) whose spectroscopic properties were identical with those previously reported.[11]

2-Hexyloxybenzaldehyde 13

Salicylaldehyde (12.2 g, 0.1 mol) was added to KOH (6.2 g, 0.11 mol) in EtOH (100 cm^3), forming a precipitate. 1-Bromohexane (15.4 cm^3, 0.11 mol) and KI (1 g) were added and the mixture stirred at the reflux temperature for 32 h, then cooled. The EtOH was removed by evaporation at reduced pressure and EtOAc (150 cm^3) and water (150 cm^3) were added. The product was extracted into the EtOAc and the organic phase washed with 2 M aqueous NaOH (2 × 50 cm^3), water (2 × 50 cm^3) and brine (50 cm^3). The extract was dried ($MgSO_4$), filtered and evaporated. The residue was purified by flash chromatography (elution with 10% EtOAc–light petroleum) to afford the aldehyde (20.9 g, 100%) as an oil (lit.,[12] oil); δ_H 0.91 (3 H, t, *J* 6.2, Me), 1.28–1.4 (4 H, m, alkylCH_2), 1.40–1.55 (2 H, m, alkylCH_2), 1.84 (2 H, m, OCH_2CH_2), 4.06 (2 H, t, *J* 6.2, OCH_2), 6.93–7.02 (2 H, m, ArH), 7.51 (1 H, dt, *J* 7.9 and 2, 4-H), 7.81 (1 H, dt, *J* 7.6 and 2, 6-H) and 10.5 (1 H, s, CHO); *m/z* 206 (M^+, 26%), 122 (100), 121 (96) and 65 (20).

α-Ethenyl-2-(1-methylethoxy)benzenemethanol 14

An ice-bath cooled solution of aldehyde **12** (13.1 g, 0.08 mol) in dry THF (50 cm^3) under a nitrogen atmosphere was treated dropwise with vinylmagnesium bromide (88 cm^3 of a 1 M solution in THF) which was transferred from its storage container using a cannula and a slight pressure of dry nitrogen, at a rate to maintain the reaction temperature below 12 °C. When complete (90 min) the mixture was left to warm to the ambient temperature overnight and worked up by addition of saturated aqueous ammonium chloride (75 cm^3) with ice-cooling to maintain the temperature below 20 °C. The product was extracted into diethyl ether and the organic phase washed with brine, then dried ($MgSO_4$), filtered and evaporated. The residual oil (15.3 g, 100%) was shown by NMR and GC–MS to be suitable for use directly in the next step; δ_H 1.33 (6 H, d, *J* 6.5, 2 × Me), 3.26 (1 H, br s, OH), 4.59 (1 H, septet, *J* 6.1, $OCHMe_2$), 5.10 (1 H, d, *J* 10, $C{=}CH_AH_B$), 5.28 (1 H, d, *J* 17, $C{=}CH_AH_B$), 5.35 (1 H, br t, CHOH), 6.09 (1 H, ddd, *J* 17, 10 and 5.8, $CH{=}CH_2$), 6.83–6.93 (2 H, m, ArH), 7.19 (1 H, dt, *J* 8 and 1.5, 4-H) and 7.27 (1 H, dd, *J* 7.6 and 1.8, 6-H); *m/z* 192 (M^+, 8.5%), 132 (30), 131 (100), 121 (17) and 77 (20).

α-Ethenyl-2-hexyloxybenzenemethanol 15. Compound **15** was similarly prepared from aldehyde **13** as an oil; δ_H 0.90 (3 H, t, *J* 6.9, Me), 1.30–1.40 (4 H, m, 2 × alkylCH_2), 1.40–1.54 (2 H, m, alkylCH_2), 1.80 (2 H, m, OCH$_2$CH_2), 3.02 (1 H, br d, *J* 4.4, OH), 4.00 (2 H, t, *J* 6.5, ArOCH_2), 5.15 (1 H, d, *J* 10.9, C=CH_AH$_B$), 5.30 (1 H, d, *J* 17, C=CH$_A$$H_B$), 5.38 (1 H, br t, C*H*OH), 6.12 (1 H, ddd, *J* 17, 10 and 5.8, C*H*=CH$_2$), 6.84–6.96 (2 H, m, ArH) and 7.19–7.30 (2 H, m, ArH); *m/z* 234 (M^+, 15%), 149 (26), 132 (32), 131 (100) and 121 (49).

Preparation of 3-arylprop-2-en-1-ols

(*E*)-3-[2-(1-Methylethoxy)phenyl]prop-2-en-1-ol 3. The allylic alcohol **14** (4.3 g, 0.022 mol) was dissolved in THF (20 cm^3). Water (3 cm^3) and Amberlyst A15 resin (1.5 g) were added and the mixture stirred at the reflux temperature for 5 h and then cooled. The resin was removed by filtration and washed with EtOAc. The combined organic phases were washed with saturated aqueous $NaHCO_3$ and brine, then dried ($MgSO_4$), filtered and evaporated to give an orange oil (4.1 g) which was purified by flash chromatography (5% EtOAc–light petroleum) to afford the isomeric alcohol **3** (2.34 g, 54%) as an oil; δ_H 1.34 (6 H, d, *J* 6.5, 2 × Me), 1.8–2.0 (1 H, br s, OH), 4.30 (2 H, d, *J* 6, CH$_2$O), 4.54 (1 H, septet, *J* 6.3, C*H*Me$_2$), 6.35 (1 H, dt, *J* 16 and 6, C=C*H*CH$_2$), 6.85 (1 H, d, *J* 16, ArC*H*=C), 6.85–6.95 (2 H, m, ArH), 7.3–7.4 (1 H, dt, *J* 7.6 and 1.7, 4-H) and 7.42 (1 H, dd, *J* 8 and 1.5, 6-H); *m/z* 192 (M^+, 15%), 131 (100), 91 (27) and 77 (24).

(*E*)-3-(2-Hexyloxyphenyl)prop-2-en-1-ol 4. Compound **4** (2.46 g, 49%) was similarly prepared from its isomer **15** as a white solid, mp 47–50 °C; δ_H 0.9 (6 H, t, *J* 7, 2 × Me), 1.25–1.4 (4 H, m, 2 × alkylCH_2), 1.42–1.53 (2 H, m, alkylCH_2), 1.76–1.87 (2 H, m, OCH$_2$CH_2), 3.98 (2 H, t, *J* 6.5, ArOCH_2), 4.32 (1 H, d, *J* 6, CH_2OH), 6.40 (1 H, dt, *J* 16 and 6, C=C*H*CH$_2$), 6.84–6.96 (3 H, m, ArC*H*=C, 3-H and 5-H), 7.20 (1 H, dt, *J* 8 and 1.5, 4-H) and 7.42 (1 H, dd, *J* 7.6 and 1.8, 6-H).

(*E*)-3-(2-Methoxyphenyl)prop-2-en-1-ol 2

3-(2-Methoxyphenyl)prop-2-enal (9.72 g, 0.06 mol) was stirred in EtOH (100 cm^3) until mostly dissolved, then cooled in an ice-bath while an aqueous solution of $NaBH_4$ (0.76 g in 20 cm^3, 0.02 mol) was added dropwise. After 1 hour, TLC indicated complete conversion and the EtOH was therefore removed by evaporation. The residue was extracted with EtOAc, the organic layer washed with water, 1 M HCl (H_2 evolution from excess borohydride), saturated aqueous $NaHCO_3$ and brine, then dried ($MgSO_4$), filtered and evaporated to afford a pale yellow oil (9.43 g, 96%). A small quantity was covered in light petroleum and cooled. Scratching provided a solid, and this was used to seed the oil, which was stirred with light petroleum (100 cm^3) for 16 h to give the alcohol **2** (8.53 g, 87%) as a white powder, mp 36–37 °C (lit.,[13] oil); δ_H 1.73 (1 H, br s, OH), 3.84 (3 H, s, OMe), 4.31 (2 H, dd, *J* 5.8 and 1.5, CH_2OH), 6.38 (1 H, dt, *J* 16 and 5.8, C=C*H*CH$_2$), 6.85–6.96 (3 H, m, ArC*H*=C, 3-H and 5-H), 7.23 (1 H, dt, *J* 6 and 1.8, 4-H) and 7.43 (1 H, dd, *J* 7.6 and 1.8, 6-H); *m/z* 164 (M^+, 52%), 131 (60), 121 (65), 108 (100) and 91 (89).

The following compounds were prepared from their corresponding commercially-available aldehydes by the above procedure.

(*E*)-3-(2-Nitrophenyl)prop-2-en-1-ol 5. Orange oil (lit.,[14] mp 60.5–61 °C); δ_H 1.9 (1 H, br s, OH), 4.38 (2 H, dd, *J* 5 and 1.5, CH_2OH), 6.35 (1 H, dt, *J* 16 and 5, C=C*H*CH$_2$), 7.08 (1 H, dt, *J* 16 and 1.5, ArC*H*=C), 7.4 (1 H, dt, *J* 7.5 and 2.2, 4-H), 7.54–7.63 (2 H, m, 5-H and 6-H) and 7.92 (1 H, d, *J* 7.5, 3-H); *m/z* 179 (M^+, 1.5%), 132 (36), 104 (58), 92 (52) and 77 (100).

(*E*)-3-(4-Dimethylaminophenyl)prop-2-en-1-ol 7. Brown solid, mp 66–68 °C; δ_H 1.57 (1 H, br s, OH), 2.95 (6 H, s, NMe$_2$), 4.26 (2 H, d, *J* 6, CH_2OH), 6.16 (1 H, dt, *J* 16 and 6, C=C*H*CH$_2$), 6.50 (1 H, d, *J* 16, ArC*H*=C), 6.65 (2 H, d, *J* 9, 3-H and 5-H) and 7.26 (2 H, d, *J* 9, 2-H and 6-H); *m/z* 177 (M^+, 46%), 160 (17), 144 (17), 134 (100) and 121 (20).

(*E*)-3-[4-(1,1-Dimethylethyl)phenyl]-2-methylprop-2-en-1-ol 8. Oil; δ_H 1.32 (9 H, s, Bu^t), 1.68 (1 H, br s, OH), 1.92 (3 H, s, 2-Me), 4.18 (2 H, s, CH$_2$O), 6.48 (1 H, br s, 3-H), 7.23 (2 H, d, *J* 8, ArH) and 7.36 (2 H, d, *J* 8, ArH); *m/z* 204 (M^+, 26%), 189 (100), 147 (33), 131 (48) and 115 (26).

3,3-Diphenylprop-2-en-1-ol 9. White powder, mp 61–63 °C (lit.,[15] 65–67 °C); δ_H 1.45 (1 H, br s, OH), 4.22 (2 H, d, *J* 7, CH_2OH), 6.25 (1 H, t, *J* 7, C=C*H*CH$_2$) and 7.14–7.41 (10 H, m, ArH); *m/z* 210 (M^+, 57%), 192 (92), 178 (36), 167 (100) and 165 (89).

(*E*)-3-(Furan-2-yl)prop-2-en-1-ol 10. Oil (lit.,[16] oil); δ_H 2.44 (1 H, br s, OH), 4.26 (2 H, d, *J* 5, CH_2OH), 6.1–6.4 (2 H, m, 3-H and 4-H), 6.3 (1 H, dt, *J* 16 and 5, C=C*H*CH$_2$), 6.42 (1 H, d, *J* 16, ArC*H*=C) and 7.34 (1 H, d, *J* 1.5, 5-H); *m/z* 124 (M^+, 47%), 81 (69), 77 (60), 68 (100) and 67 (56).

(*E*)-3-(5-Nitrofuran-2-yl)prop-2-en-1-ol 11. Orange solid, mp 52–55 °C (lit.,[17] oil); δ_H 2.62 (1 H, br s, OH), 4.38 (2 H, m, CH_2OH), 6.44 (1 H, d, *J* 4, 3-H), 6.55 (1 H, dt, *J* 16 and 1.8, ArC*H*=C), 6.68–6.78 (1 H, dt, *J* 16 and 4.4, C=C*H*CH$_2$) and 7.31 (1 H, d, *J* 4, 4-H).

Preparation of chiral auxiliary 16

The enantiomers of dioxaborolane **16** were prepared from diethyl D-tartrate and diethyl L-tartrate, following the literature method[7] *via* the respective amides.[18] NMR Analysis confirmed their identity.

General cyclopropanation procedure for experiments 1–7

Experiments 1–7 (Table 2) were all done on the same scale, using 5 cm^3 of diethylzinc, and 10 mmol in total of three or four substrate allyl alcohols. The following protocol was typical (experiment 7).

Synthesis of a mixture of compounds 18, 19, 20 and 21 enriched in their (*S*,*S*) enantiomeric forms. CAUTION: Diethylzinc is pyrophoric and must be maintained under an atmosphere of dry nitrogen.

Dry 1,2-dimethoxyethane (5 cm^3, 0.0486 mol) and dry CH_2Cl_2 (40 cm^3) in a 100 cm^3 three-necked flask was cooled to an internal temperature of −15 °C. Diethylzinc (5 cm^3, 0.0486 mol) was transferred to a calibrated dropping funnel using a transfer cannula with a slight pressure of N_2 and then added dropwise to the cold, stirred mixture. The dropping funnel was rinsed with more CH_2Cl_2 (5 cm^3). The resulting solution was kept below −15 °C as CH_2I_2 (7.8 cm^3, 0.097 mol) was added over 0.5 h. Meanwhile, the four alcohols (**2**, 0.41 g; **3**, 0.48 g; **4**, 0.59 g and **5**, 0.45 g, each 0.0025 mol) and dioxaborolane **(*R*,*R*)-16** (2.9 g, 0.0107 mol) were dissolved in dry CH_2Cl_2 (50 cm^3) under N_2 in a 250 cm^3 flask fitted with a septum inlet and magnetic stirrer. This flask was cooled below −35 °C (bath temperature) as the cold zinc complex was added using a transfer cannula, initially under a positive nitrogen pressure and then by siphon. The addition was complete in 0.5 h and CH_2Cl_2 (10 cm^3) was used to wash through the last traces of reagent. The mixture was stirred as it warmed to ambient temperature over 1.5 h, and was then heated at its reflux temperature for 1.5 h to ensure complete conversion of the nitro compound **5**. The reaction flask was next cooled in an ice-bath while aqueous NH_4Cl (100 cm^3) was added with stirring (initial exotherm). After 1 h, the initially-formed white precipitate had redissolved. The lower organic layer was separated and stirred with 2 M aqueous NaOH (100 cm^3) for 4 h to hydrolyse the borolane auxiliary. Then the organic phase was washed with H_2O, dried ($MgSO_4$) and evaporated to afford a mixture of the products along with some boron-containing by-products (total 3.35 g). Flash chromatography then gave the individual pure products.

The purification method for experiment 7 was optimised using experience gained from experiments 1–6 in an attempt to maximise the total yield, at the cost of extra chromatography. In particular, the troublesome boron-containing by-products were found to have an R_f of about 0.8 (*i.e.* greater than products

17–**27**) when the solvent system (0–30% EtOAc in light petroleum for a gradient elution) also contained 1–2% MeOH. The following procedure was effective.

The above oil (3.35 g) was subjected to flash chromatography on silica (150 g) in a column of diameter 65 mm. Gradient elution (5–30% EtOAc–light petroleum with 2% MeOH) of 50 cm^3 aliquots at a flow rate of about 50 cm^3 min^{-1} (suction controlled) gave 40 fractions which were examined by TLC. Fractions containing product **21** (the product of lowest R_f, eluted last) were combined, evaporated and the material (0.77 g) recolumned on a conventional column (20 mm diameter) using 40–60 μm silica (15 g) and eluting with a constant solvent mixture (15% EtOAc, 2% MeOH and 83% light petroleum). This gave cyclopropanemethanol **21** (0.420 g, 86%) as a pale yellow oil. The appropriate early-eluting fractions from this column were combined with those from the original column which contained product **18** (0.52 g total) and these were subjected to a further conventional column, as before. Two further columns, for the fractions containing compounds **19** and **20** were performed using 10% and 5% EtOAc respectively, together with 1% MeOH (remainder light petroleum). The final recovery consisted of cyclopropanemethanols **18** (0.363 g, 82%), **19** (0.394 g, 77%) and **20** (0.504 g, 80%) as colourless oils of high purity.

The yields of the other compounds shown in Table 2 refer to the pure fractions isolated after chromatography. In most cases where the quoted yield was below 70% there were other mixed chromatography fractions which were not processed further.

Spectral data for cyclopropanation products

These data refer to the compound and experiment number quoted. Where an identical or enantiomeric compound was prepared in separate experiments, these samples had the same properties, except for the ees which are shown in Table 2. The absolute stereochemistry of the major isomer from a given experiment was not established but was inferred from published data on the parent 2-phenylcyclopropylmethanol **17**.[7] The assumption made was that the absolute stereochemistry of products would be *S*,*S* when dioxaborolane **(*R*,*R*)-16** derived from (+)-*N*,*N*,*N*′,*N*′-tetramethyltartaric acid diamide was used.

(1*R*)-*trans*-2-Phenylcyclopropylmethanol 17 from experiment 3. Oil (lit.,[19] oil); δ_H 0.87–0.98 (2 H, m, 3-H), 1.37–1.49 (1 H, m, 1-H), 1.80 (1 H, m, 2-H), 1.99 (1 H, br s, OH), 3.53–3.64 (2 H, m, CH_2O), 7.05 (2 H, m, 2′-H and 6′-H), 7.15 (1 H, m, 4′-H) and 7.25 (2 H, m, 3′-H and 5′-H); *m/z* 148 (M^+, 17%), 130 (22), 117 (100), 115 (69), 104 (51) and 91 (53).

(1*R*)-*trans*-2-(2-Methoxyphenyl)cyclopropylmethanol 18 from experiment 6. Oil (Found: C, 74.07; H, 7.70. $C_{11}H_{14}O_2$ requires C, 74.13; H, 7.92%); δ_H 0.82–0.89 (1 H, m, 3-H_A), 1.02–1.09 (1 H, m, 3-H_B), 1.15–1.25 (1 H, m, 1-H), 1.86–1.93 (1 H, m, 2-H), 2.44 (1 H, br s, OH), 3.29 (1 H, dd, *J* 11 and 8.5, CH_AH_BOH), 3.82–3.87 (1 H, m, CH_AH_BOH), 3.87 (3 H, s, OMe), 6.82–6.96 (3 H, m, ArH) and 7.14–7.20 (1 H, m, 4′-H); δ_C 158.4 (C), 130.1 (C), 127.2 (CH), 126.7 (CH), 120.8 (CH), 110.2 (CH), 67.3 (CH_2), 55.6 (CH_3), 24.3 (CH), 16.6 (CH) and 10.8 (CH_2); *m/z* 178 (M^+, 16%), 159 (21), 147 (51), 115 (39) and 91 (100).

(1*R*)-*trans*-2-[2-(1-Methylethoxy)phenyl]cyclopropylmethanol 19 from experiment 3. Oil (Found: C, 75.51; H, 8.92. $C_{13}H_{18}O_2$ requires C, 75.69; H, 8.80%); δ_H 0.84 (1 H, m, 3-H_A), 1.06–1.20 (2 H, m, 3-H_B and 1-H), 1.37 (3 H, d, *J* 6, $CHMe_AMe_B$), 1.41 (3 H, d, *J* 6, $CHMe_AMe_B$), 1.82–1.90 (1 H, m, 2-H), 2.36 (1 H, br s, OH), 3.23 (1 H, t, *J* 10.8, CH_AH_BOH), 3.88 (1 H, dd, *J* 10.8 and 5, CH_AH_BOH), 4.65 (1 H, septet, *J* 6, $CHMe_2$), 6.83–6.88 (2 H, m, ArH), 6.96 (1 H, dd, *J* 7.6 and 1.5, 6′-H) and 7.15 (1 H, dt, *J* 7.7 and 1.5, 4′-H); *m/z* 206 (M^+, 14%), 145 (55), 133 (100), 131 (43) and 91 (33).

(1*S*)-*trans*-2-(2-Hexyloxyphenyl)cyclopropylmethanol 20 from experiment 1. Oil (Found: C, 77.51; H, 9.75. $C_{16}H_{24}O_2$ requires C, 77.38; H, 9.74%); δ_H 0.81–0.91 (1 H, m, 1-H), 0.90 (3 H, t, *J* 7, Me), 1.05–1.25 (2 H, m, 3-H), 1.30–1.40 (4 H, m, 2 × alkylCH_2), 1.40–1.50 (2 H, m, alkylCH_2), 1.77–1.92 (3 H, m, 2-H and OCH_2CH_2), 2.2 (1 H, br s, OH), 3.29 (1 H, dd, *J* 10.9 and 8.5, CH_AH_BOH), 3.84 (1 H, br dd, *J* 10.8 and 5.4, CH_AH_BOH), 3.93–4.10 (2 H, m, $ArOCH_2$), 6.80–6.90 (2 H, m, 3′-H and 5′-H), 6.96 (1 H, dd, *J* 7.4 and 1.8, 6′-H) and 7.15 (1 H, dt, *J* 7.6 and 1.8, 4′-H); *m/z* 248 (M^+, 14%), 145 (51), 133 (100), 131 (35) and 91 (30).

(1*S*)-*trans*-2-(2-Nitrophenyl)cyclopropylmethanol 21 from experiment 7. Oil (Found: C, 61.88; H, 5.56; N, 6.97. $C_{10}H_{11}NO_3$ requires C, 62.17; H, 5.74; N, 7.25%); δ_H 0.96–1.12 (2 H, m, 3-H), 1.3–1.42 (1 H, m, 1-H), 2.19 (1 H, br s, OH), 2.26–2.33 (1 H, m, 2-H), 3.56 (1 H, dd, *J* 11.4 and 7.3, CH_AH_BOH), 3.75 (1 H, dd, *J* 11.4 and 5.8, CH_AH_BOH), 7.22 (1 H, d, *J* 8, 6′-H), 7.33 (1 H, t, *J* 8, 4′-H), 7.51 (1 H, dt, *J* 8 and 1.3, 5′-H) and 7.86 (1 H, dd, *J* 8 and 1.3, 3′-H); *m/z* 135 ($M^+ - C_3H_6O$, 100%), 115 (39), 91 (89), 79 (55) and 77 (69).

(1*S*)-*trans*-2-(4-Nitrophenyl)cyclopropylmethanol 22 from experiment 1. Pale orange needles, mp 94–96 °C (Found: C, 61.87; H, 5.55; N, 7.20. $C_{10}H_{11}NO_3$ requires C, 62.17; H, 5.74; N, 7.25%); δ_H 1.05–1.17 (2 H, m, 3-H), 1.52–1.62 (2 H, m, 1-H and OH), 1.95 (1 H, m, 2-H), 3.63 (1 H, dd, *J* 11.6 and 6.5, CH_AH_BOH), 3.72 (1 H, dd, *J* 11.6 and 6.2, CH_AH_BOH), 7.17 (2 H, d, *J* 9, 2′-H and 6′-H) and 8.11 (2 H, d, *J* 9, 3′-H and 5′-H); *m/z* 193 (M^+, 6%), 150 (37), 116 (100), 115 (98), 91 (48) and 77 (46).

(1*S*)-*trans*-2-(4-Dimethylaminophenyl)cyclopropylmethanol 23 from experiment 5. This product was not recovered. It is assumed that it partitioned into the aqueous layer on work-up when aqueous NH_4Cl was added. However, subsequent extraction after this layer had been made alkaline to pH 14 with NaOH did not provide any appreciable amount of extractable material.

(1*S*)-*trans*-2-[4-(1,1-Dimethylethyl)phenyl]-1-methylcyclopropylmethanol 24 from experiment 4. White solid, mp 63–66 °C (lit.,[20] mp 45–46 °C for racemate) (Found: C, 82.28; H, 10.29. $C_{15}H_{22}O$ requires C, 82.52; H, 10.16%); δ_H 0.83 (1 H, t, *J* 6, 3-H_A), 0.91 (3 H, s, 1-Me), 0.92 (1 H, dd, *J* 8 and 6, 3-H_B), 1.31 (9 H, s, Bu^t), 1.48 (1 H, br s, OH), 2.0 (1 H, dd, *J* 8 and 6, 2-H), 3.53 (2 H, s, CH_2O), 7.10 (2 H, d, *J* 8, 2′-H and 6′-H) and 7.30 (2 H, d, *J* 8, 3′-H and 5′-H); δ_C 148.9 (C), 135.9 (C), 128.9 (CH), 125.1 (CH), 72.1 (CH_2), 34.5 (C), 31.6 (CH_3), 26.5 (CH), 25.3 (C), 16.0 (CH_3) and 15.4 (CH_2); *m/z* 218 (M^+, 25%), 145 (96), 143 (48), 131 (58) and 57 (100).

(1*S*)-2,2-Diphenylcyclopropylmethanol 25 from experiment 5. Oil (lit.,[21] oil); δ_H 1.26 (1 H, dd, *J* 8.9 and 5, 3-H_A), 1.37 (1 H, t, *J* 5, 3-H_B), 1.41 (1 H, br s, OH), 2.00 (1 H, m, 1-H), 3.35 (1 H, dd, *J* 11.4 and 7.8, CH_AH_BOH), 3.46 (1 H, dd, *J* 11.4 and 6.4, CH_AH_BOH) and 7.1–7.40 (10 H, m); *m/z* 224 (M^+, 5%), 206 (78), 193 (89), 178 (60), 165 (67) and 115 (100).

(1*S*)-*trans*-2-(Furan-2-yl)cyclopropylmethanol 26 from experiment 4. Oil; δ_H 0.81–0.88 (1 H, m, 3-H_A), 1.00–1.07 (1 H, m, 3-H_B), 1.46–1.58 (1 H, m, 1-H), 1.80 (1 H, br s, OH), 1.82–1.87 (1 H, m, 2-H), 3.56 (1 H, dd, *J* 11 and 7, CH_AH_BOH), 3.61 (1 H, dd, *J* 11 and 7, CH_AH_BOH), 5.95 (1 H, dt, *J* 3.2 and 0.7, 3′-H), 6.26 (1 H, dd, *J* 3.2 and 1.9, 4′-H) and 7.24 (1 H, dd, *J* 1.9 and 0.7, 5′-H); δ_C 156.0 (C), 140.7 (CH), 110.5 (CH), 103.9 (CH), 66.1 (CH_2), 23.0 (CH), 14.6 (CH) and 11.5 (CH_2); *m/z* 138 (M^+, 41%), 107 (63), 94 (51), 79 (100) and 77 (94).

(1*S*)-*trans*-2-(5-Nitrofuran-2-yl)cyclopropylmethanol 27 from experiment 5. Oil (Found: C, 52.25; H, 4.68; N, 7.74. $C_8H_9NO_4$ requires C, 52.46; H, 4.95; N, 7.65%); δ_H 1.08–1.15 (1 H, m, 3-H_A), 1.22–1.29 (1 H, m, 3-H_B), 1.68–1.77 (1 H, m, 1-H), 1.96–2.03 (1 H, m, 2-H), 2.29 (1 H, br s, OH), 3.58 (1 H, dd, *J* 11.4 and 6.5, CH_AH_BOH), 3.74 (1 H, dd, *J* 11.4 and 5.8, CH_AH_BOH), 6.25 (1 H, d, *J* 3.8, 3′-H) and 7.25 (1 H, d, *J* 3.8, 4′-H); *m/z* 183 (M^+, 19%), 166 (52), 139 (89), 123 (63), 109 (80) and 78 (100). This product was not observed by TLC of the crude reaction mixture after work-up from experiment 6. It was concluded that the starting material had decomposed or poly-

merised on standing. This was confirmed when the remaining starting material **11** was found to have become non-crystalline and sticky.

Cyclopropanation of nerol and geraniol

A mixture of nerol **28** (0.45 g, 0.0029 mol), geraniol **29** (0.54 g, 0.0035 mol) and (*E*)-3-phenylprop-2-en-1-ol **1** (0.43 g, 0.0032 mol) were used in the cyclopropanation procedure described above. After work-up with aqueous NH_4Cl, the CH_2Cl_2 solution of products was stirred with 2 M aqueous NaOH (100 cm^3) containing mannitol (4 g) for 4 h to hydrolyse the chiral auxiliary and attempt to render the boron-containing by-products water soluble.[22] Then the organic phase was washed with water, dried ($MgSO_4$) and evaporated to afford a pale yellow oil (2.35 g) comprising the products and a reduced quantity of by-products. Flash chromatography using a gradient elution of 0–20% EtOAc in light petroleum provided a number of fractions derived from nerol and geraniol, and finally, pure cyclopropylmethanol **17** (0.45 g, 95%) whose spectral properties were identical with those reported above. ^{1}H NMR Spectroscopy of the early fractions all showed low integrals for signals at δ 4.9–5.2 (the allylic proton) and at δ 1.4–1.6 (the allylic methyl groups) with additional methyl groups evident at δ 0.9–1.2. Comparison with the published NMR spectra of authentic mono-cyclopropanated products[10] confirmed the over-reaction.

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References

1 E. J. Corey and X.-M. Cheng, *The Logic of Chemical Synthesis*, Wiley, New York, 1989; T. Hudlicky, *Chem. Rev.*, 1996, **96**, 3.
2 H. J. E. Loewenthal, *A Guide for the Perplexed Organic Experimentalist*, Wiley, Chichester, 2nd edn., 1990; A. I. Vogel, *Vogel's Textbook of Practical Organic Chemistry*, Longman, Harlow, 5th edn., 1989.
3 S. A. Lee and G. E. Robinson, *Process Development: Fine Chemicals from Grams to Kilograms*, Oxford University Press, Oxford, 1995. Recent work aimed at achieving more complex transformations in a single step is reviewed in L. F. Tietze, *Chem. Rev*., 1996, **96**, 115; P. J. Parsons, C. S. Penkett and A. J. Shell, *Chem. Rev*., 1996, **96**, 195.
4 I. Amato, *Science*, 1992, **257**, 5068; N. Hall, *Science*, 1994, **266**, 5182; N. K. Terrett, M. Gardner, D. W. Gordon, R. J. Kobylecki and J. Steele, *Tetrahedron*, 1995, **51**, 8135; L. A. Thompson and J. A. Ellman, *Chem. Rev*., 1996, **96**, 555; A. Lubineau, *Chem. Ind.* (*London*), 1996, 123.
5 J. N. Little, *Chemom. Intell. Lab. Syst*., 1993, **21**, 199; D. G. Vogt, *J. Autom. Chem*., 1994, **16**, 231; S. H. DeWitt and A. W. Czarnik, *Acc. Chem. Res.*, 1996, **29**, 114.
6 A. B. Charette and J.-F. Marcoux, *Synlett*, 1995, 1197.
7 A. B. Charette, S. Prescott and C. Brochu, *J. Org. Chem.*, 1995, **60**, 1081.
8 R. G. Salih and M. Y. Shandala, *Collect. Czech. Chem. Commun.*, 1976, **41**, 262.
9 W. C. Still, M. Kahn and A. Mitra, *J. Org. Chem.*, 1978, **43**, 2923.
10 G. A. Molander and L. S. Harring, *J. Org. Chem*., 1989, **54**, 3525.
11 T. Horaguchi, C. Tsukada, E. Hasegawa, T. Shimizu, T. Suzuki and K. Tanemura, *J. Heterocycl. Chem.*, 1991, **28**, 1261.
12 M. R. Stillings, A. P. Wellbourn and D. S. Walker, *J. Med. Chem.*, 1986, **29**, 2280.
13 H.-L. Pan, C.-A. Cole and T. L. Fletcher, *Synthesis*, 1980, 813.
14 H. Meerwein, B. van Bock, B. Kirschnick, W. Lenz and A. Migge, *J. Prakt. Chem*., 1936, **147**, 211.
15 S. Ohki and F. Hamaguchi, *Yakugaku Zasshi*, 1965, **85**, 971 (*Chem. Abstr.*, 1966, **64**, 5199g).
16 R. J. Rallings and J. C. Smith, *J. Chem Soc.*, 1953, 618.
17 T. Sasaki, *Pharm. Bull.*, 1953, **1**, 343 (*Chem. Abstr.*, 1955, **49**, 14727b).
18 D. Seebach, H.-O. Kalinowski, W. Langer, G. Crass and E.-M. Wilka, *Org. Synth.*, Coll. Vol. VII, 41.
19 (Chiral products) H. Takahashi, M. Yoshioka, M. Shibasaki, M. Ohno, N. Imai and S. Kobayashi, *Tetrahedron*, 1995, **51**, 12 013; (racemic product) S. E. Denmark and J. P. Edwards, *J. Org. Chem.*, 1991, **56**, 6974.
20 C. J. Urch, BP 2191 774/1987 (*Chem. Abstr.*, 1989, **110**, P7720h).
21 H. M. Walborsky, L. Barash, A. E. Young and F. J. Impastato, *J. Am. Chem. Soc.*, 1961, **83**, 2517.
22 Professor A. G. M. Barrett suggested using mannitol to minimise the amount of by-products carried through to the chromatography.

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