JOURNAL OF LABELLED COMPOUNDS AND RADIOPHARMACEUTICALS
J Label Compd Radiopharm 2004; **47**: 705–717.
Published online in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/jlcr.860

Review Article

The use of *quasi*-enantiomeric isotopomers as chiral probes for determining stereoisomeric purity

Jason Eames* and Michael J. Suggate
Department of Chemistry, Queen Mary, University of London, London E1 4NS, UK

Summary

This review discusses the use of chiral isotopomers, in particular the use of *quasi*-enantiomeric isotopomers as novel chiral probes for determination of enantio- and diastereoisomeric purity. Copyright © 2004 John Wiley & Sons, Ltd.

Key Words: acyl transfer; [^{13}C]-labelling; covalent nucleophilic catalysis; [^{2}H]-labelling; enantiomeric excess; diastereoisomeric excess; isotopomers; parallel kinetic resolution; *quasi*-enantiomers

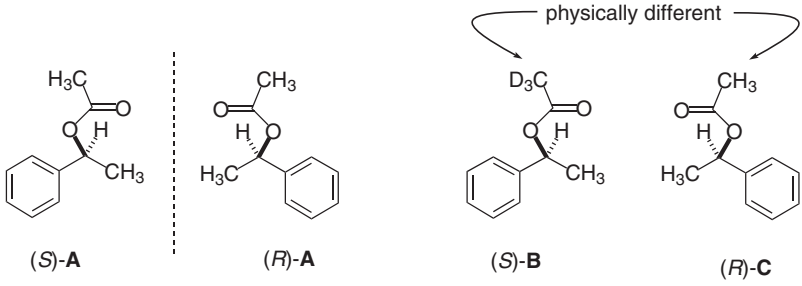
Background

The use of *quasi*-enantiomeric components[†] [e.g. (*S*)-**B** and (*R*)-**C**] within *Organic Synthesis* is developing into a fascinating area.[1] These species are synthetically unusual since they behave as if they were a pair of enantiomers [e.g. (*S*)-**A** and (*R*)-**A**], but are in fact physically separable without the need for an additional chiral reagent (Scheme 1). Of these reports,[2] the majority have used *quasi*-enantiomers as chiral auxiliaries [e.g. (*R*)-**1** and (*S*)-**2**,[3] and (*R*)-**3** and (*S*)-**4**[4]] to improve the levels of enantioselectivity (and consequently the diastereoselective outcome) for a kinetic resolution (Scheme 2). This has given rise to improved selectivity, and this approach has universally become known as a *Parallel Kinetic Resolution*.[3]

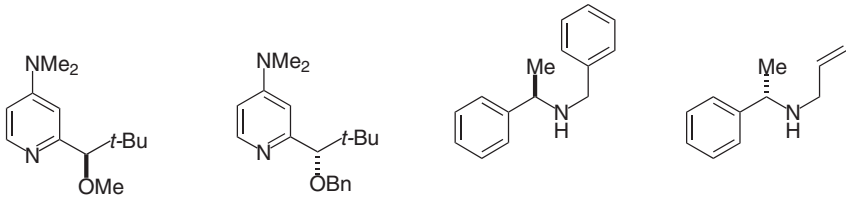
One of the first reports[5] that demonstrated the usefulness of this resolution approach utilized a substitution reaction to improve the levels of enantioselectivity for an enzyme-mediated resolution (Scheme 3). Faber[5] has shown that enantioselective hydrolysis of the racemic epoxide (*rac*)-**5** can occur using

*Correspondence to: J. Eames, Department of Chemistry, Queen Mary University of London, London E1 4NS, UK. E-mail: j.eames@qmul.ac.uk
[†]For a description see Glossary.

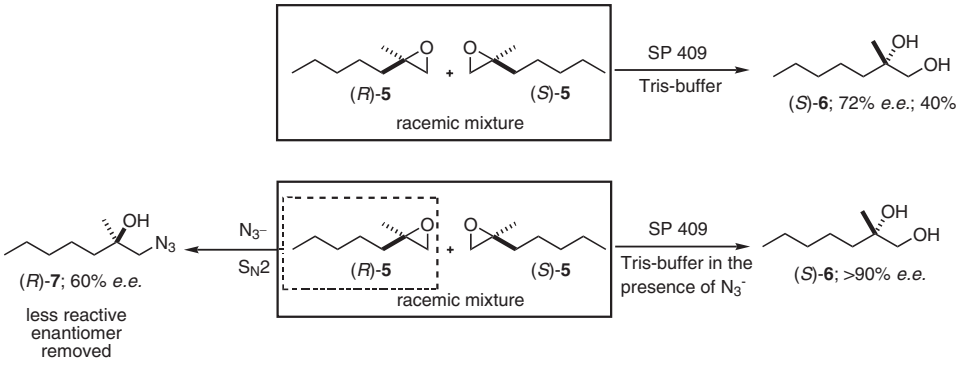
Received 14 May 2004
Revised 10 June 2004
Accepted 15 June 2004



Scheme 1.



Scheme 2.

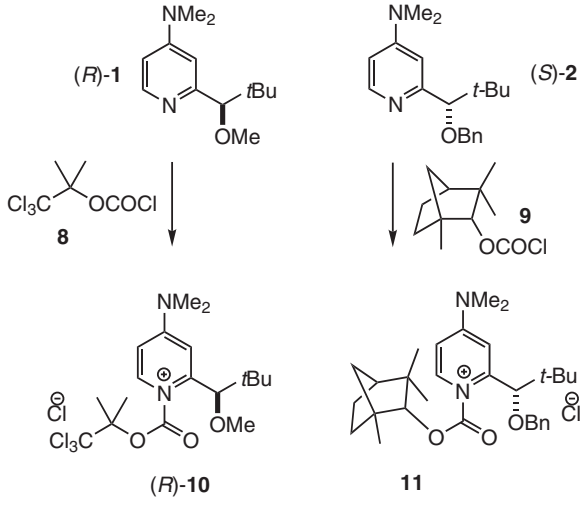


Scheme 3.

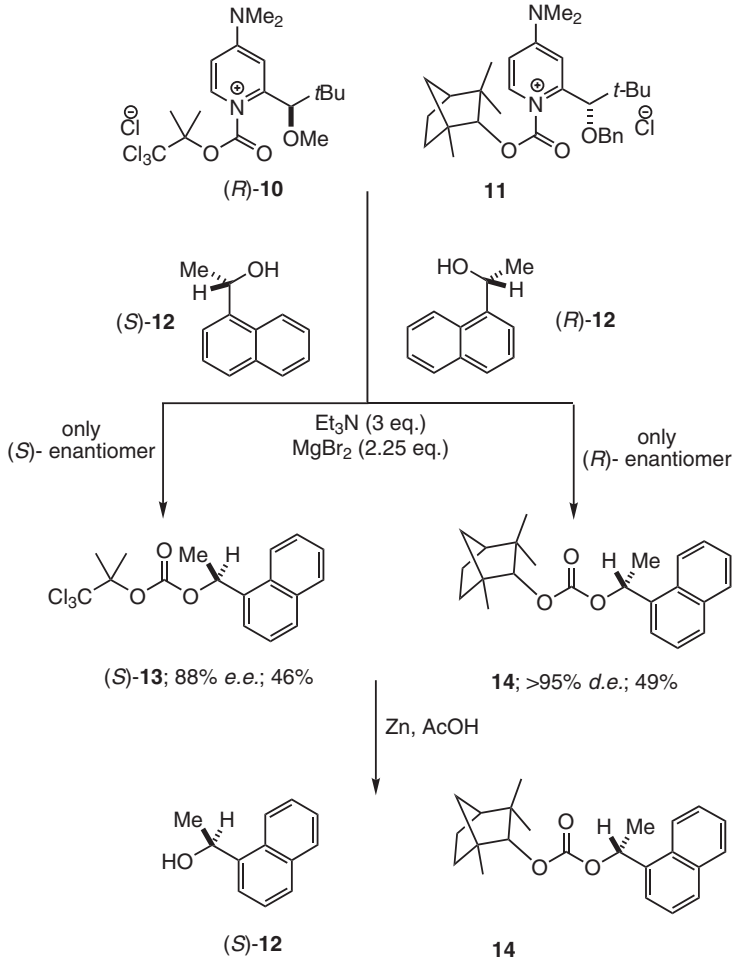
the *Rhodococcus* sp immobilized enzyme (SP 409) to give the diol (*S*)-**6** in 40% yield with a modest 72% enantiomeric excess (*e.e.*) (Scheme 3). However, by conducting this reaction in the presence of an additional non-natural nucleophilic azide (N_3^-), this increased the enantiomeric excess of the required diol (*S*)-**6** to over 90% *e.e.* It appears that this additional nucleophile (N_3^-)

simply removes the less reactive enantiomer of the epoxide (*R*)-**5** by a non-catalyzed S_N2 reaction to form the azide alcohol (*R*)-**7** in around 60% *e.e.* (Scheme 3).

This strategy has been further developed by Vedejs[6] by the use of two *quasi*-enantiomeric auxiliaries (*R*)-**1** and (*S*)-**2** within his chiral DMAP acyl transfer reaction (Scheme 4). These species were chosen due to the need for removal of both enantiomers of alcohol (*rac*)-**12** at an equal rate with complementary stereocontrol (Scheme 5). Activation of the *quasi*-enantiomeric pyridines (*R*)-**1** and (*S*)-**2** with a hindered chloroformate **8** and (+)-fenchyl chloroformate **9** gave the acyl transfer agents (*R*)-**10** and **11**, respectively. Both of these auxiliaries have previously been shown to give equal and opposite stereocontrol (Scheme 5). The structural nature of the alkyl substituent present in the complementary chloroformates is particular important since this is directly transferred during the resolution of the alcohol **12** and subsequently aids product separation. Addition of equimolar amounts of each separately formed pyridinium salts (*R*)-**10** and **11**, combined with an excess of $MgBr_2$ and Et_3N to a solution of racemic 1-(1-naphthyl)ethanol (*rac*)-**12** gave a mixture of carbonates (*S*)-**13** in 46% yield (>88% *e.e.*) and **14** in 49% yield (>95% *d.e.*), respectively. The levels of stereocontrol were impressive and this was as a direct consequence of removal of both enantiomers of **12** at an equal rate. These derivatives were easily separated by treatment with zinc in acetic acid to give the corresponding resolved alcohol (*S*)-**12** and the fenchyl carbonate **14** (Scheme 5).



Scheme 4.



Scheme 5.

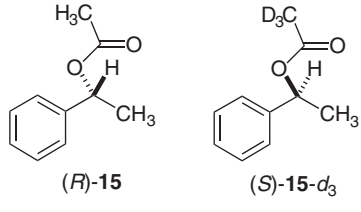
Use of chiral isotopomers for determining enantio- and diastereoisomeric purity

Reetz[7] has extended this idea towards the use of *quasi*-enantiomeric isotopomers, such as (*R*)-**15** and (*S*)-**15**-d_3, as a synthetic tool for determining the enantiomeric purity of a given reaction mixture (Scheme 6). The use of *quasi*-enantiomers is particularly important since they act stereochemically as separable enantiomers. However, due to their physical separability their relative composition can easily be measured using standard instrumentation (e.g. NMR spectroscopy, mass spectrometry (Mass spectrometry has additionally been used to measure enantiomeric excess by calibration. See Reference[8]) and HPLC). To test the reliability of this strategy, Reetz initially determined the accuracy of this approach by measuring a series of known *quasi*-enantiomeric compositions of (*R*)-**15** and (*S*)-**15**-d_3 independently by gas

chromatography (GC) and electrospray mass spectrometry (ESI-MS). He found that there was near perfect correlation between the measured *quasi*-enantiomeric excesses (*qe.e.*) by ESI-MS and GC. The use of mass spectrometry as a detection method is also important, as this method is capable of high throughput analysis of up to a thousand samples per day.[7]

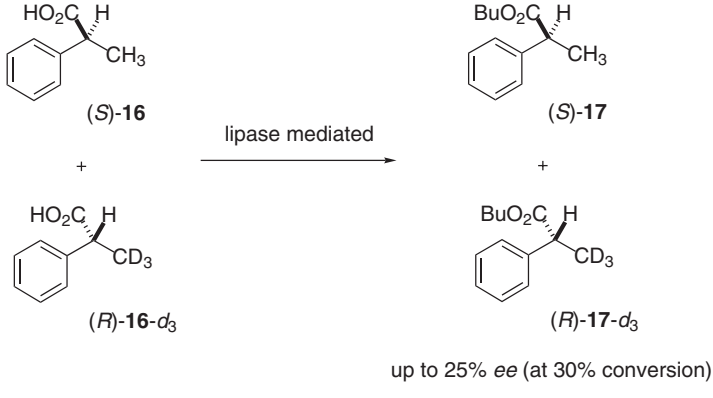
With this information in hand, Reetz initially screened the kinetic resolution of *quasi*-enantiomeric 2-phenylpropionic acids (*S*)-**16** and (*R*)-**16**-d_3 using a lipase-catalysed[7] esterification reaction (Scheme 7). In order to exclude the presence of a secondary kinetic isotope effect, the reaction was additionally monitored using a racemic sample of 2-phenylpropionic acid **16** which gave comparable stereoselectivity. This labelled kinetic resolution was efficiently monitored *in situ* by use of mass spectrometry because the starting precursors (*S*)-**16** and (*R*)-**16**-d_3, and products (*S*)-**17** and (*R*)-**17**-d_3 have different molecular masses. The *quasi*-enantiomeric excess of the product was found to increase nearly linearly with conversion; the highest level obtained was 25% *qe.e.* at approximately 30% conversion (Scheme 7).

This approach has been extended towards the *quasi*-desymmetrisation of a *quasi-meso* diester **18**-d_3 using a related lipase-catalysed hydrolysis reaction



(*R*)-**15** (*S*)-**15**-d_3

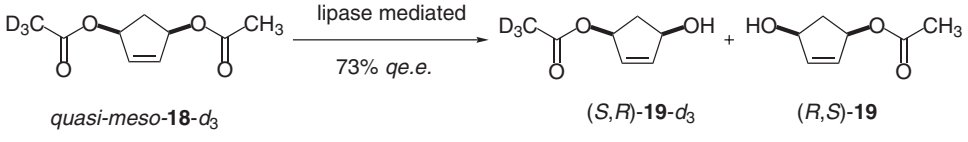
Scheme 6.



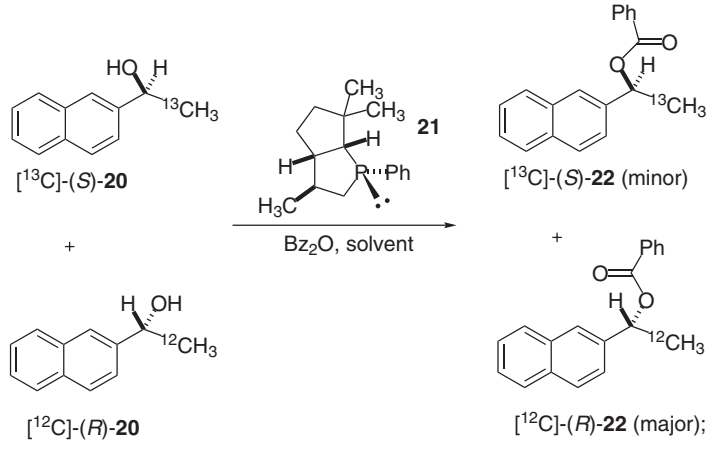
Scheme 7.

(Scheme 8). This strategy was particularly impressive since hydrolysis of the *quasi-meso* diester **18**-d_3 gave two detectable *quasi*-enantiomeric alcohols (*S*,*R*)-**19**-d_3 and (*R*,*S*)-**19**. Using the same detection approach outlined above, porcine liver esterase was found to give the best levels of *quasi*-enantiomeric excess (73% *qe.e.*) (Scheme 8).

Recently, Vedejs[9] has reported the kinetic resolution of *quasi*-enantiomeric 1-(2-naphthyl)ethanol [^{13}C]-(*S*)-**20** and [^{12}C]-(*R*)-**20** using his chiral phosphine benzoyl transfer catalyst **21** (Scheme 9). This approach is particularly interesting since the relative ratio of the *quasi*-enantiomers [^{13}C]-(*S*)-**20** and [^{12}C]-(*R*)-**20** were determined by ^{1}H NMR spectroscopy (due to the splitting



Scheme 8.



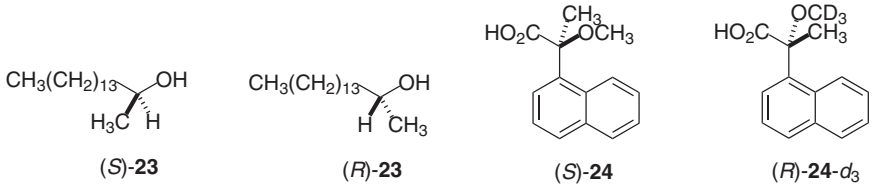
Entry	Solvent	Enantioselectivity
1	C_6F_6	s = 8-9[a]
2	C_6D_6	s = 8-9[a]
3	toluene-d_8	s = 8-9[a] (7)[b]
4	THF-d_8	s = 7-9[a]
5	CD_2Cl_2	s = 6-7[a] (5.5)[b]

[a] Value determined by ^{1}H NMR spectroscopy
[b] Value determined by HPLC

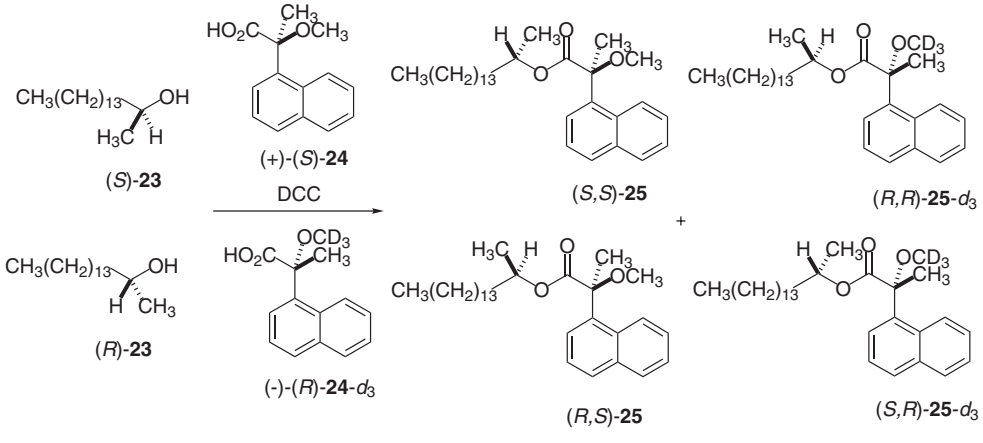
Scheme 9.

caused by the characteristically large $^{1}J_{C,C}$ coupling in [^{13}C]-(*S*)-**20**). The kinetic resolution of these *quasi*-enantiomeric alcohols favoured formation of benzoate [^{12}C]-(*R*)-**22**. The levels of stereocontrol were found to be solvent dependent; C_6F_6, C_6D_6 and toluene-d_8 gave better *quasi*-stereoselectivity than either THF-d_8 or CD_2Cl_2 (Scheme 9: Entries 1–3 versus 4–5). However, it does appear the relative levels of stereocontrol determined by ^{1}H NMR spectroscopy can sometimes be overestimated (*e.g.* toluene-d_8 and CD_2Cl_2) by comparison with HPLC methods (Scheme 9). The discrepancy was believed to be due to a combination of factors associated with accuracy (such as integration, alcohol *qe.e.* values and relative proportions of *quasi*-enantiomers), but the overall trend was evident.

Harada[10] has reported a related study towards the determination of enantiomeric purity of secondary alcohols (e.g. **23**) using *quasi*-enantiomeric carboxylic acids (*S*)-**24** and (*R*)-**24**-d_3 (Scheme 10). This approach was slightly different since the kinetic resolution parameters are now unimportant due to its similarity to a parallel kinetic resolution. Harada has shown by simple derivativisation of a scalemic alcohol **23** (of unknown composition) with an equimolar mixture of *quasi*-enantiomeric carboxylic acids (*S*)-**24** and (*R*)-**24**-d_3 by addition of DCC, gave a diastereoisomeric pair of *quasi*-enantiomers (*S*,*S*)-**25** and (*S*,*R*)-**25**-d_3, and (*R*,*S*)-**25** and (*R*,*R*)-**25**-d_3, respectively (Scheme 11).



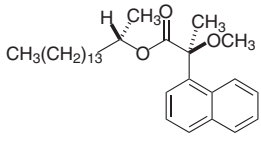
Scheme 10.



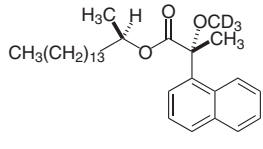
Scheme 11.

The enantiomeric excess of the scalemic alcohol **23** was determined by ^{1}H NMR spectroscopy by comparing the relative amounts of each *quasi*-enantiomer in each diastereoisomeric pair. For example, using an enantiomerically enriched sample of alcohol **23** (e.g. 60.9% *e.e.*) gave, after coupling with the *quasi*-enantiomeric carboxylic acids (*S*)-**24** and (*R*)-**24**-d_3, a separable mixture of the *quasi*-enantiomeric esters (*S*,*S*)-**25** and (*R*,*R*)-**25**-d_3 (ratio = 21.74:78.26) and (*R*,*S*)-**25** and (*S*,*R*)-**25**-d_3 (ratio 81.90:18.10). From these ratios, the enantiomeric excess of the starting alcohol **23** (60.9% *e.e.*) can be easily determined (Scheme 12). This method is particularly accurate (maximum error = 1.3% *e.e.* over 10 samples).

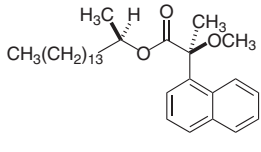
The approach is also very versatile since the enantiomeric excess can also be determined using mass spectrometry by comparing the peaks heights of both *quasi*-enantiomers present in each diastereoisomeric mixture. The relative abundance of each *quasi*-enantiomer of (*S*,*S*)-**25** and (*R*,*R*)-**25**-d_3 can be



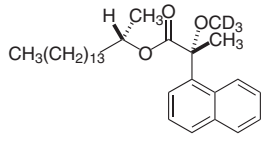
(*S*,*S*)-**25**



(*R*,*R*)-**25**-d_3



(*R*,*S*)-**25**



(*S*,*R*)-**25**-d_3

(*S*,*S*)-**25** and (*R*,*R*)-**25**-d_3, and (*R*,*S*)-**25** and (*S*,*R*)-**25**-d_3 are *quasi*-enantiomeric.
Whereas, (*S*,*S*)-**25** and (*S*,*R*)-**25**-d_3, and (*R*,*S*)-**25** and (*R*,*R*)-**25**-d_3 are *quasi*-diastereoisomeric.

$$x(S)\text{-}\mathbf{23} + y(R)\text{-}\mathbf{23} \xrightarrow[(-)\text{-}(R)\text{-}\mathbf{24}\text{-}d_3]{(+)\text{-}(S)\text{-}\mathbf{24}} xk_1(S)\text{-}\mathbf{23}\text{-}(S)\text{-}\mathbf{24} + xk_2(S)\text{-}\mathbf{23}\text{-}(R)\text{-}\mathbf{24}\text{-}d_3 + yk_2(R)\text{-}\mathbf{23}\text{-}(S)\text{-}\mathbf{24} + yk_1(R)\text{-}\mathbf{23}\text{-}(R)\text{-}\mathbf{24}\text{-}d_3$$

(*S*)-**23**-(*S*)-**24** = (*S*,*S*)-**25**; (*S*)-**23**-(*R*)-**24**-d_3 = (*S*,*R*)-**25**-d_3; (*R*)-**23**-(*S*)-**24** = (*R*,*S*)-**25**; (*R*)-**23**-(*R*)-**24**-d_3 = (*R*,*R*)-**25**-d_3

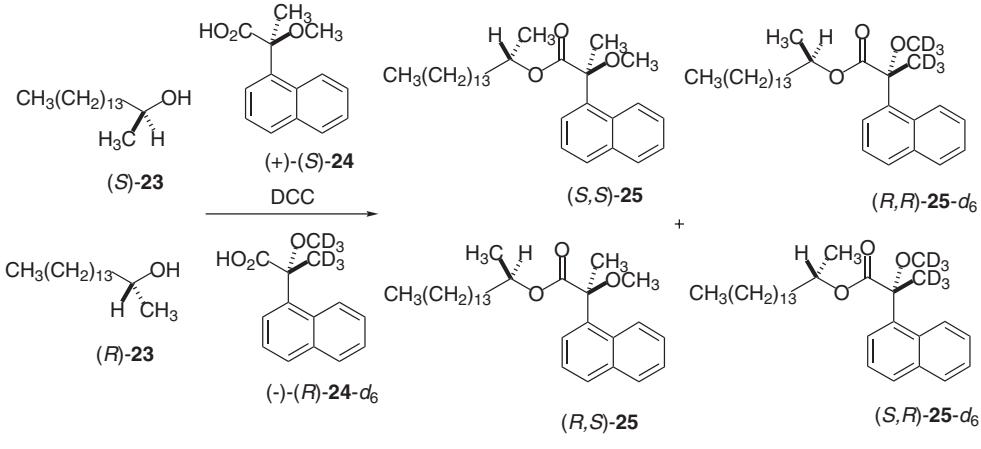
$$xk_1(S,S)\text{-}\mathbf{25} + xk_2(S,R)\text{-}\mathbf{25}\text{-}d_3 + yk_2(R,S)\text{-}\mathbf{25} + yk_1(R,R)\text{-}\mathbf{25}\text{-}d_3 = 1$$

$$[xk_1(S,S)\text{-}\mathbf{25} + yk_1(R,R)\text{-}\mathbf{25}\text{-}d_3] + [xk_2(S,R)\text{-}\mathbf{25}\text{-}d_3 + yk_2(R,S)\text{-}\mathbf{25}] = 1$$

The relative ratio of;
(a) $xk_1(S,S)$-**25** + $yk_1(R,R)$-**25**-d_3, and
(b) $xk_2(S,R)$-**25**-d_3 + $yk_2(R,S)$-**25** can easily be determined by ^{1}H NMR spectroscopy and mass spectrometry.

Scheme 12.

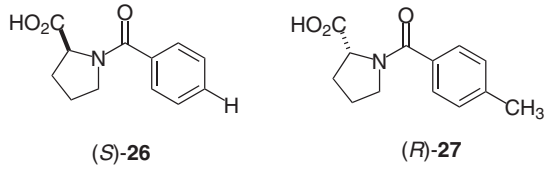
determined by comparison of the peak intensity for M and M + 3, respectively in the mass spectrum. The approach can be repeated for the remaining combination of *quasi*-enantiomers (*R*,*S*)-**25** and (*S*,*R*)-**25**-d_3. The average error was found to be approximately 0.7% *e.e.* (and the maximum error was determined to be 1.9% *e.e.*). However, in order to calculate these values accurately the initial values were corrected to remove the minor overlap of isotope peaks due to natural abundance. This is necessary due to the small difference in intensity of the parent ions between the parent ions of the *quasi*-enantiomers of three m/z units (M + 3 versus M). In an attempt to extend this methodology, Harada has developed a second generation of *quasi*-enantiomeric carboxylic acids based on (*S*)-**24** and (*R*)-**24**-d_3 (Schemes 10 and 13). Using these substrates, the amount of isotopic overlap was negligible over the six m/z unit difference between M + 6 and M, and no isotopic correction was required. By using the same alcohol **23** with a known enantiomeric purity (of 69.77% *e.e.*) gave a separable mixture of the *quasi*-enantiomeric esters (*S*,*S*)-**25** and (*R*,*R*)-**25**-d_6 (ratio = 86.53:13.47) and (*R*,*S*)-**25** and (*S*,*R*)-**25**-d_6 (ratio 17.66:82.34). From these values, the enantiomeric excess of the original starting alcohol **23** could easily be re-determined (69.09% *e.e.*).



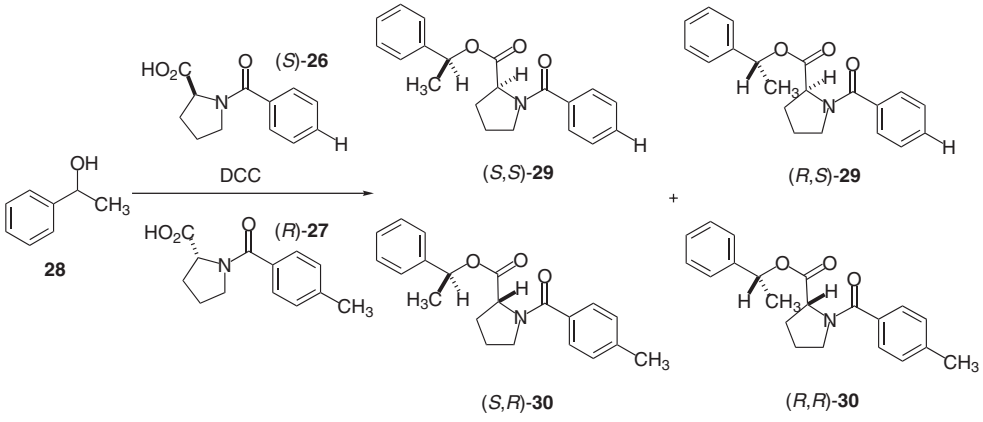
Scheme 13.

Finn[11] has additionally used mass spectrometry to determine the level of enantiomeric excess. However, instead of using a *quasi*-enantiomeric isotopomer[‡] to distinguish between the enantiomers of the alcohol **28**, he chose to use two *quasi*-enantiomeric auxiliaries (*S*)-**26** and (*R*)-**27** and relied on their large fourteen m/z unit difference (Schemes 14 and 15). Simple DCC

[‡] For a description see Glossary.



Scheme 14.



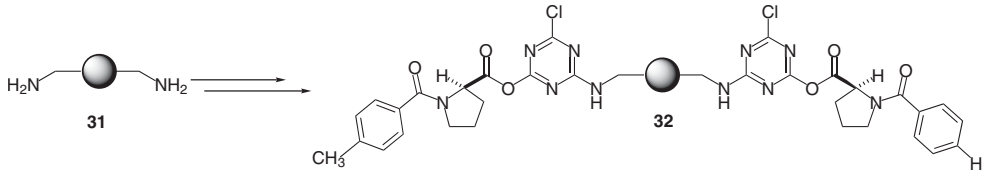
Scheme 15.

coupling of the alcohol **28** to the *quasi*-enantiomeric auxiliaries (*S*)-**26** and (*R*)-**27** gave the required diastereoisomeric pairs of *quasi*-enantiomers (*S*,*S*)-**29** and (*R*,*S*)-**29**, and (*S*,*R*)-**30** and (*R*,*R*)-**30**, respectively (Scheme 15). These samples were analysed by HPLC-EMS and LC-MS using similar methodology outlined above (Scheme 12). To ensure greater accuracy, the instrument was calibrated using a racemic and scalemic sample of known enantiomeric purity to account for the subtle differences in electrospray ionisation of these *quasi*-enantiomeric components (*S*)-**26** and (*R*)-**27** (which differ by a single CH_2 unit). This approach was very successful, but the accuracy was a limiting factor and the enantiomeric excess was determined to be within 10% *e.e.* of the known purity.

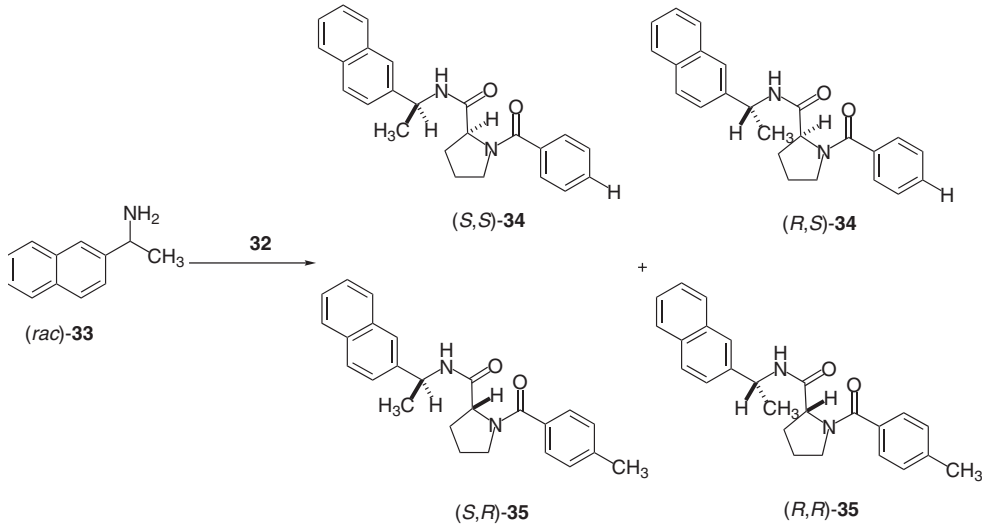
Finn[12] has additionally used these *quasi*-enantiomeric components (*S*)-**26** and (*R*)-**27** to determine the stereoselectivity of kinetic resolution processes involving a series of amino alcohols. He chose to use a *quasi-meso*-adduct **32** – formed by coupling the auxiliaries (*S*)-**26** and (*R*)-**27** onto a diamino polymer **31** – as the activated coupling agent (Scheme 16). Addition of a series of racemic amines [e.g. (*rac*)-**33**] to the activated bis-ester **32** gave a diastereoisomeric pair of *quasi*-enantiomers (*S*,*S*)-**34** and (*R*,*S*)-**34**, and (*S*,*R*)-**35** and (*R*,*R*)-**35**, respectively (Scheme 17). The relative stereoselectivity was easily determined by HPLC (in order to separate each *quasi*-enantiomeric combination) and mass spectrometry (to determine the relative composition). This

process was screened for an array of racemic amines **33, 36, 37, 38, 39** and **40**. These racemic amines gave virtually the same level of stereocontrol ($s = 1.1-1.4$), the highest being $s = 1.8$ for the 1-(1-napthylethyl) amine **33** (Scheme 18).

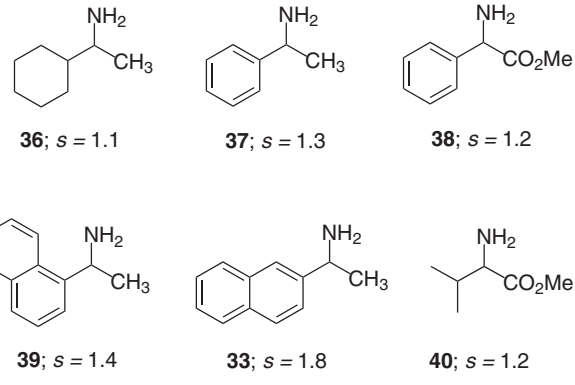
This approach has not been limited to the use of distinguishable *quasi*-enantiomeric components. Morken[13] has elegantly shown the use of an



Scheme 16.



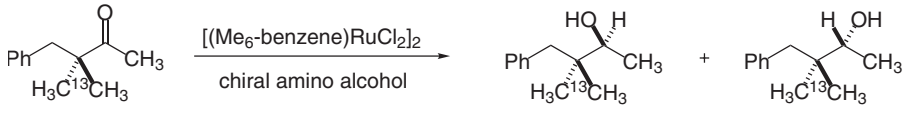
Scheme 17.



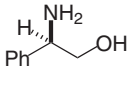
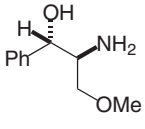
Scheme 18.

enantiomerically pure ketone [^{13}C]-**41** as a *quasi*-prochiral substrate (Scheme 19). This approach is only made possible since all reagents present in the reaction mixture are unable to detect the difference between the CH_3 and $^{13}CH_3$ groupings in the ketone [^{13}C]-**41** thus rendering the substrate prochiral. This ketone was subsequently used as a chiral probe for determining the efficiency of a stereoselective reduction. Morken has discovered that the use of a combination of [(Me_6-benzene)$RuCl_2$]$_2$ catalyst in the presence of a suitable amino alcohol gave good to excellent levels of facial reduction. In particular, the use of the amino alcohols **43** and **44** gave complementary stereocontrol; the amino alcohol **43** favoured formation of one *pseudo*-enantiomer in 81% *d.e.*, whereas, **44** gave the other *pseudo*-enantiomer with slightly lower facial control (76% *d.e.*). Both reactions proceeded in near quantitative yield; however, the absolute configuration of each *pseudo*-enantiomer is unknown. The most interesting aspect of this study was the determination of the diastereoisomeric excess. This was achieved by measuring the relative ratio of these diastereoisomerically labelled products [^{13}C]-(*R*,*S*)-**42** and [^{13}C]-(*R*,*R*)-**42** by ^{13}C NMR spectroscopy at their associated chemical shift.

In conclusion, the use of enantiomeric isotopomers as chiral probes for determination of enantiomeric and diastereoisomeric purity has been shown to significantly aid the development and improvement of stereoselective processes. This is a direct consequence of these chiral isotopomeric probes enabling rapid and efficient determination of the levels of associated stereocontrol within a given reaction which can easily be achieved using



[^{13}C]-**41** [^{13}C]-(*R*,*S*)-**42** [^{13}C]-(*R*,*R*)-**42**

Entry	Chiral amino alcohol		Configuration at *C*(1) of **42**	*D.e.*	Yield
1		**43**	**A**[a]	81%	98%
2		**44**	**B**[b]	76%	98%

[a]unspecified configuration at *C*(1); major diastereoisomer in this reaction is the minor diastereoisomer in entry 2
[b]unspecified configuration at *C*(1); major diastereoisomer in this reaction is the minor diastereoisomer in entry 1

Scheme 19.

standard instrumentation such as ^{1}H and ^{13}C NMR spectroscopy and mass spectrometry. This methodology appears to be particularly well suited towards the development of novel combinatorial approaches for the discovery of novel stereoselective synthetic processes.

Glossary

For the purpose of this review the following terms have been defined;

Quasi-enantiomers are a pair of molecules that have a non-superimposable non-mirror image but have opposite relative configuration(s) at all stereogenic centre(s).

Quasi-diastereoisomers are a pair of molecules that have a non-superimposable non-mirror image but have at least one common stereocentre.

Quasi-enantiomeric isotopomers are a pair of stereoisotopomers that have a non-superimposable mirror image.

Quasi-diastereoisomeric isotopomers are a pair of stereoisotopomers that have a non-superimposable non-mirror image.

Pseudo-enantiomers are a pair of molecules that physically act like enantiomers but contain two (or more) stereocentres, where one (or more) stereocentres play little or no role.

References

1. (a) Eames J. *Angew Chem Int Ed* 2000; **39**: 885.
   (b) Eames J. *Angew Chem* 2000; **112**: 913.
2. Eames J. Parallel kinetic resolutions. *In Organic Synthesis Highlights*, vol. V, Chapter 17. VCH-Wiley: Weinheim, 2003; pp. 151 (ISBN 3-527-30611-0 Wiley-VCH, Weinheim).
3. Vedejs E, Daugulis O, Mackay JA, Rozners E. *Synlett* 2001; 1499.
4. Davies SG, Diez D, El Hammouni MM, Garner AC, Garrido NM, Long MJ, Morrison RM, Smith AD, Sweet MJ, Withey JM. *Chem Commum* 2003; 2410.
5. Mischitz M, Faber K. *Tetrahedron Lett* 1994; **35**: 81.
6. (a) Vedejs E, Chen X. *J Am Chem Soc* 1997; **119**: 2584.
   (b) Vedejs E, Rozners, E. *J Am Chem Soc* 2001; **123**: 2428.
7. Reetz MT, Becker MH, Klein HW, Stockigt D. *Angew Chem Int Ed* 1999; **38**: 1758.
8. (a) Grigorean G, Ramirez J, Ahn AH, Lebrilla CB. *Anal Chem* 2002; **72**: 4275.
   (b) Botta B, Botta M, Fillippi AF, Tafi A, Monache GD, Speranza M. *J Am Chem Soc* 2002; **124**: 7658.
9. Vedejs E, Daugulis O. *J Am Chem Soc* 2003; **125**: 4166.
10. Taji H, Watanabe M, Harada N, Naoki H, Ueda Y. *Org Lett* 2002; **4**: 2699.
11. Guo J, Wu J, Siuzdak G, Flinn MG. *Angew Chem Int Ed* 1999; **38**: 1755.
12. Diaz DD, Yao S, Finn MG. *Tetrahedron Lett* 2001; **42**: 2617.
13. Evans MA, Morken JP. *J Am Chem Soc* 2002; **124**: 9020.

