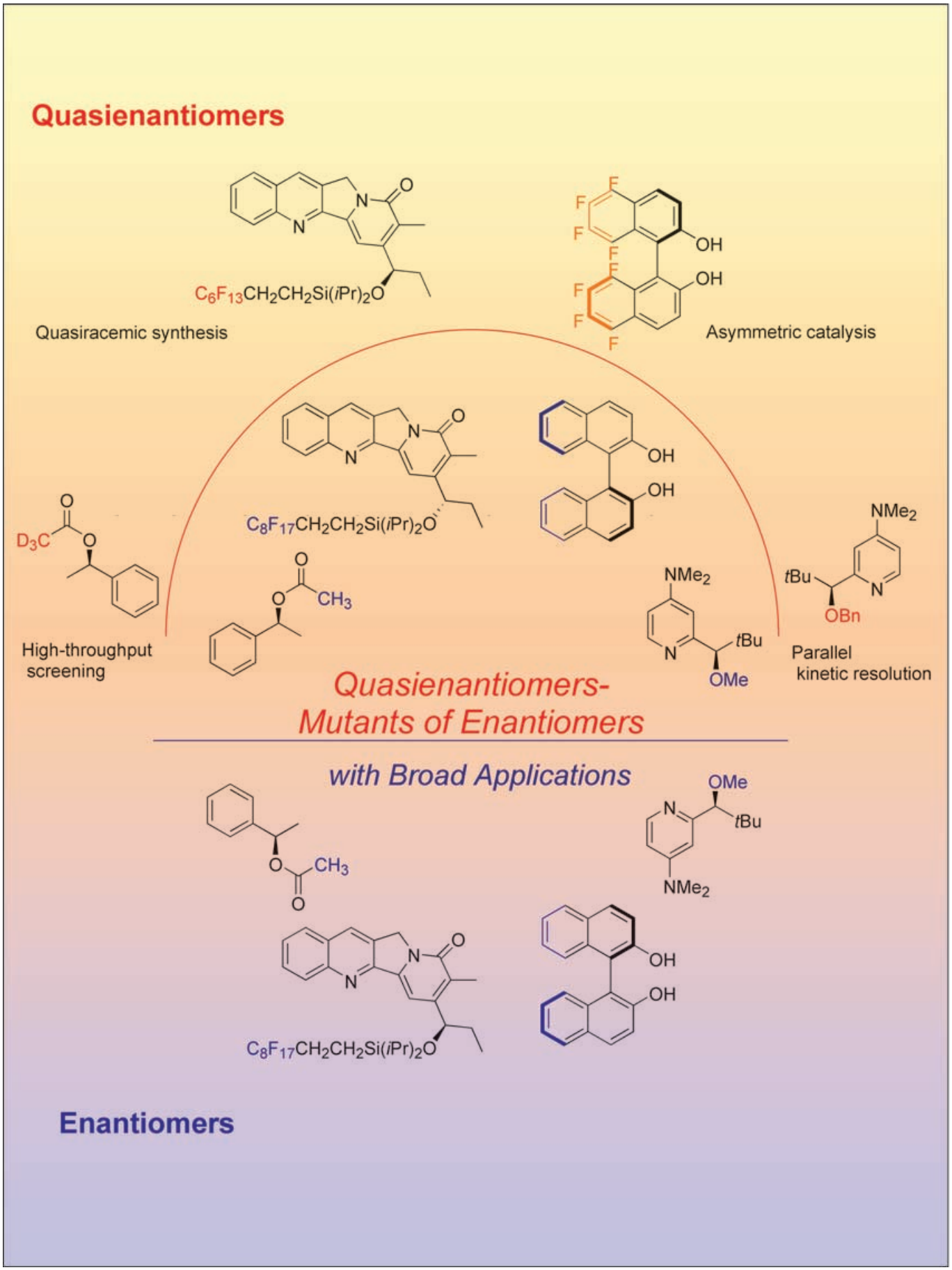

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Quasienantiomers and Quasiracemates: New Tools for Identification, Analysis, Separation, and Synthesis of Enantiomers

Qisheng Zhang[a] and Dennis P. Curran*[b]

Abstract: The old adage "never mix pure organic compounds" holds in spades for enantiomers. After going to all the trouble to make enantiopure molecules, who in their right mind would ever mix them to make a racemate? Quasienantiomers are almost enantiomers, but not quite. Yet unlike enantiomers, the interest is not so much in separating them but in mixing them to make quasiracemates. This backwards thinking opens new possibilities for identification, analysis, separation and synthesis of enantiomers. A short history is provided, the terms are defined and illustrated, and recent applications of quasienantiomers, quasiracemates and related species are reviewed.

Keywords: chemoselectivity · enantioselectivity · kinetic resolution · racemates

History and Definitions

In 1874, van't Hoff and Le Bel independently proposed that a tetravalent carbon is tetrahedral, thereby laying the molecular basis for chirality and stereoisomerism. All stereoisomers were later grouped into the now familiar classes of "enantiomers" or "diastereomers", and the basis for chirality was extended beyond tetrahedral atoms to include axial (helical) and planar chirality.

Eliel defines an enantiomer as "one of a pair of molecular species that are mirror images of each other and not superimposable".[1] All enantiomeric pairs must be stereoisomers since non-isomers can never reflect each other in a mirror. "A composite of equimolar quantities of two enantiomeric species" is the familiar "racemate". Diastereomers are "stereoisomers not related as mirror images". These definitions are unambiguous, though the definition of diastereomers based on exclusion rather than inclusion reflects the frequent conundrums in defining familiar concepts in organic chemistry.[2]

Enantiomers based on tetrahedral carbon have the general formula Cabcd where C is the stereogenic carbon bearing four different groups a–d. All molecules with a single stereocenter are chiral and therefore not superimposable on their mirror images. The generic case is exemplified by (+)- and (−)-chlorosuccinic acid **1a**, as shown in Figure 1.

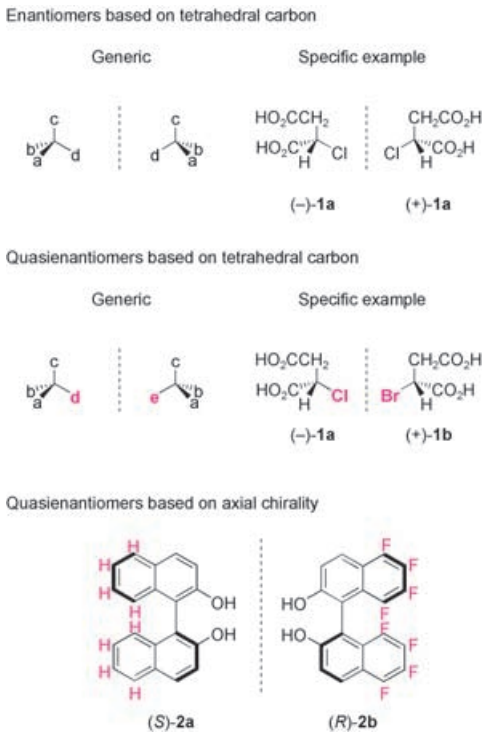

Figure 1. Enantiomers and quasienantiomers.

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In 1899, Centnerszwer discovered that the phase behavior of a 1:1 mixture of (+)-chlorosuccinic acid (+)-**1a** and (−)-bromosuccinic acid (−)-**1b** was very similar to that of the corresponding true racemic compounds.[3,4] The compounds are not isomers and cannot be enantiomers. But they have an obvious "almost mirror image" relationship. Such compounds later came to be called "quasienantiomers", and it follows that a 1:1 mixture of quasienantiomers is a "quasiracemate". Centnerszwer's observations laid the foundation for the "method of quasiracemates" discussed below.

Eliel defines quasienantiomers as "heterofacially substituted tetrahedral molecules Xabc*d* and Xabc*e*" with *e* taking the place of *d* but on the opposite face of the abc plane.[1] The definition nicely accommodates (+)-chlorosuccinic acid and (−)-bromosuccinic acid and many other related pairs of molecules. But it is at the same time too narrow and too broad. Too narrow because it does not encompass molecules like (*S*)-BINOL (*S*)-**2a** and (*R*)-F_8BINOL (*R*)-**2b** that do not have tetrahedral atoms. And too broad because d and e can be anything so long as they are not the same. The sense of quasienantiomers is that d and e should be similar but not the same.

We define quasienantiomers to be any pair of compounds that can be turned into true enantiomers by slightly changing the chemical composition of one or more substituents. So quasienantiomers are "almost enantiomers", but not quite. This definition is of necessity vague. The ersatz definition of quasienantiomers as "almost enantiomers" is readily extended with equal ambiguity to "quasidiastereomers", "quasi-isomers", "quasimeso compounds", and so on.

The terms "pseudoenantiomer" and "pseudoracemate" are often used interchangeably with quasienantiomer and quasiracemate. But we follow Eliel's lead[1] in discouraging the use of the "pseudo" prefix in this context because the word "pseudoracemate" has another well established meaning—it is one of the three possible crystalline forms of true racemates. The term "pseudoracemate" should be reserved for its use as a crystal form, and it follows that the term "pseudoenantiomer" should not be used at all. The words quasienantiomer and quasiracemate are sometimes hyphenated (quasi-enantiomer, quasi-racemate), but we recommend the spelling without hyphenation. "Quasi" is a prefix and prefixes are not customarily separated from their nouns by hyphenation.[5]

In short, nix the hyphen, quasi $\neq$ pseudo, and a precise definition of quasienantiomers is neither possible nor even desirable. Like beauty, quasienantiomerism is in the eye of the beholder. In this article, we behold the field of quasienantiomers and quasiracemates and strive to convince the reader that there is beauty here as well as practicality.

Properties of Quasienantiomers

Enantiomers must come in pairs that share the same physical and spectroscopic properties but differ in optical rotation. Likewise, they have the same chemical reactivity and chromatographic mobility under achiral conditions but can differ under chiral conditions. None of these considerations necessarily applies to quasienantiomers. A given chiral molecule has a virtually limitless number of possible quasienantiomers whose properties are subject to design and therefore limited only by imagination. So individual properties of members of pairs of quasienantiomers can range from being effectively identical to being as different as night and day.

Consider, for example, the quasienantiomer pair (*S*)-**3a** and (*R*)-**3b** shown in Figure 2. These differ only in the isotopic composition of the acetyl methyl group (CH_3 and CD_3). Such isotopomers will have similar—almost identical—chemical, physical, and chromatographic properties[6] in most aspects. Barring unusual isotope effects, a quasiracemate made of these two compounds should behave very much like either true racemate. Like true resolutions, the separation of this mixture into its quasienantiomeric components would probably require a chiral resolving agent. But the quasienantiomers differ in molecular weight by 3 amu. This difference is readily detected by mass spectrometry and forms the basis of a number of screening techniques for asymmetric reactions discussed below.

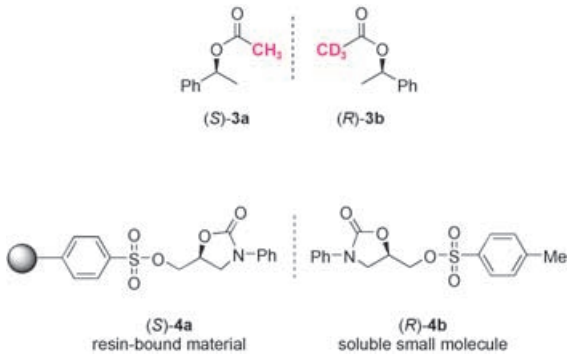


Figure 2. The variable properties of quasienantiomers.

In contrast, now consider the quasienantiomeric pair (*S*)-**4a** and (*R*)-**4b**; the former is a material by virtue of the linkage to polystyrene while that latter is a small molecule. The physical properties of (*S*)-**4a** are dominated by the polystyrene and are very different from (*R*)-**4b**. Separation of **4b** and **4a** by filtration, the equivalent of a resolution, is trivial.

So unlike enantiomers, which have fixed properties, the properties of quasienantiomers can be tuned to be similar in many respects but different in one or more key respects. The varying differences and similarities of quasienantiomers dictate their unique applications in identification, analysis, separation, and synthesis of enantiomers.

Diastereomers as Quasienantiomers

Certain pairs of diastereomers with near-mirror-image relationships are sometimes referred to as quasienantiomers.

Nature provides classic examples with cinchona alkaloids such as quinine **5a** and quinidine **5b** shown in Figure 3. These have opposite configurations at C8 and C9, but are not enantiomers because they have the same configuration of the vinyl group on the quinidine ring. These and related molecules tend to behave as if they were enantiomers in catalyzing assorted asymmetric transformations including conjugate additions, ketene cycloadditions, and dihydroxylations, among others.[7,8]

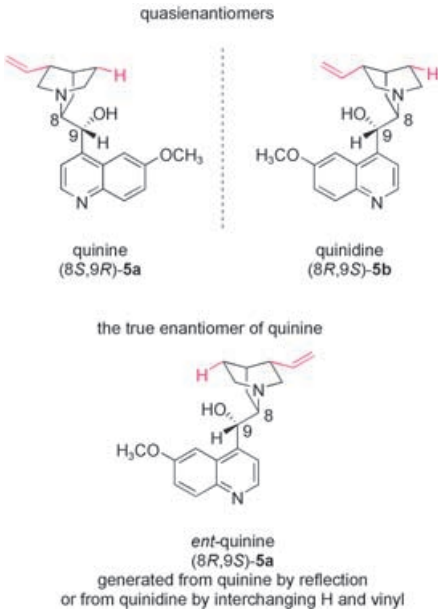


Figure 3. Diastereomeric alkaloids are sometimes called quasienantiomers.

Diastereomers are typically used as quasienantiomers as a convenience because the true enantiomers are not readily available. In other words, the same properties are sought and not different ones. This differs fundamentally from the use of non-isomers as quasienantiomers, where at least one key property is different. In the applications of quasienantiomers described below, it is typically the quasiracemate that is of interest. A quasiracemate formed by mixing equal quantities of quinine **5a** and quinidine **5b** (which, strictly speaking, is simply a mixture of diastereomers) is of little use for asymmetric catalysis because it is expected to behave more or less like a true racemate. However, because diastereomers are fundamentally different, essentially all of the applications of quasienantiomers described below in a "non-isomer" mode can also succeed in principle in a "diastereomer" mode.

Quasienantiomers as Tools for Enantiomer Identification: The Method of Quasiracemates

Although it has been eclipsed by more powerful spectroscopic and crystallographic methods, the "method of quasiracemates" was formerly an important method for assignment of absolute configurations of unknown compounds.[9] Briefly, when two very similar quasienantiomers (such as (+)-chloro- and (−)-bromosuccinic acid in Figure 1) are mixed, a "quasiracemate" that shows similar phase behavior to a true racemate may be formed. In contrast, the combination of the homofacial pair ((+)-chloro and (+)-bromosuccinic acid) shows a eutectic behavior of a typical conglomerate. More generally, the difference in ideality of phase behavior can often be used to assign absolute configuration of a molecule if a close analogue of known configuration is available because the heterofacial (quasienantiomeric) combination of molecules almost always deviates more from ideality than the homofacial combination.[10]

In a related method, cocrystallization of a pair of quasienantiomers, one of known absolute configuration and the other of unknown configuration, followed by X-ray crystallographic analysis of the quasiracemate can directly yield the absolute configuration of the unknown component. Again, the method is limited since the pair of compounds must yield suitable crystals. In an interesting application towards crystalline supramolecular architectures, Wheeler and co-workers conducted a series of experiments with quasienantiomers as building blocks for crystal design and growth.[11]

Quasienantiomers as Tools for Enantiomer Analysis

The coupling of a suitable mass spectrometric assay with a pair of quasienantiomers of differing mass is the key element featured in a number of simple yet powerful assays of enantiomer reactivity or composition. These methods share the feature that a mass code provides information about each of an individual pair of true enantiomers (which have the same molecular weight) from a pair of quasienantiomers (which have different molecular weights).

A key step in the development of most chiral drugs is the study of the ADME (absorption, distribution, metabolism and excretion) properties of both enantiomers of the drug. Because even very small structural differences can cause significant changes in complex organisms, the use of non-isomeric quasienantiomers is not suitable for such studies. Instead, pharmacologists often gain such information by using a quasiracemic mixture of isotopomers.[12] In a typical example, six healthy volunteers received doses of the calcium antagonist (*R*)-gallopamil (*R*)-**6** and its dideuterated (*S*) enantiomer [D_2]-(*S*)-**6** (Figure 4).[12c] Various fluids were collected and gallopamil and its metabolites were assayed by mass spectrometry to provide information about metabolism paths, clearance and serum protein binding as a function of configuration. Appreciable stereoselectivity was observed in a number of the processes.

Organic synthesis shares with pharmacology the common need to study the chemical behavior of pairs of enantiomers. But because reactions in flasks are both less precious and

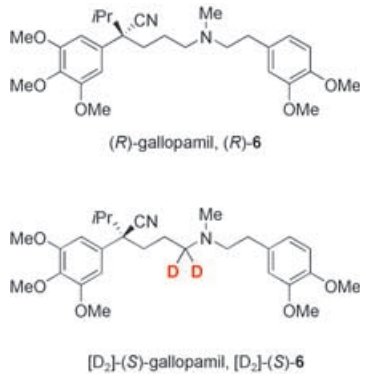
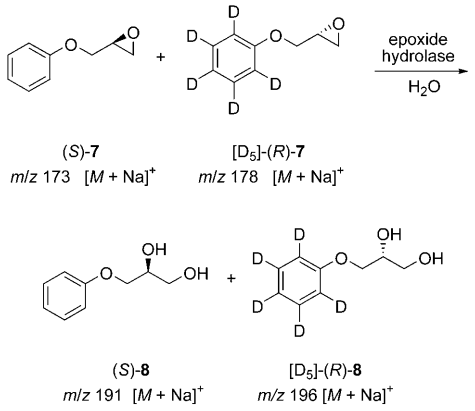


Figure 4. Structures of (*R*)-gallopamil and [D_2]-(*S*)-gallopamil.

less capricious than reactions in organisms, the synthetic community adopted the practice of separately reacting and analyzing each individual enantiomer. However, the advent of parallel screening of catalysts has stepped up the need for simple and rapid yet accurate analyses of enantiomer ratios, and an assortment of imaginative new assays have appeared.[13] Among these, the assays based on quasiracemates coupled with mass spectrometry[14] are of broad applicability and offer attractive features.

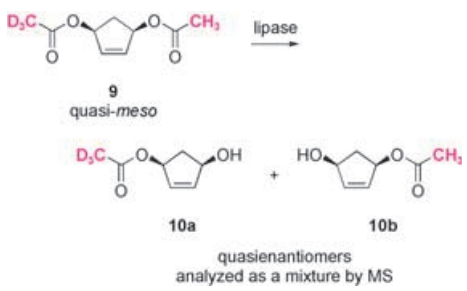
Reetz and co-workers launched the application of mass spectrometry in high-throughput detection of asymmetric catalysis and biotransformations by isotopically labeling one of the starting enantiomers of a racemic pair. In a demonstration example (Scheme 1), a quasiracemic mixture of (*S*)-**7** and [D_5]-(*R*)-**7** was used to mimic racemic glycidyl phenyl ether in a hydrolytic kinetic resolution by the enzyme epoxide hydrolase.[13a] To determine the *ee* of the products (*S*)-**8** and [D_5]-(*R*)-**8**, the crude reaction mixture was analyzed by ESI-MS. The areas below mass traces at *m*/*z* 191 and 196 (both as $[M+Na]^+$) for the nonlabeled and labeled quasienantiomers of diol **8** were integrated against a standard to provide the enantiomeric excess. Likewise, information on the efficiency of the epoxide hydrolase can also be obtained by integration of the peaks at *m*/*z* 173 and 178, which correspond to the remaining epoxides (*S*)-**7** and [D_5]-(*R*)-**7**.



Scheme 1. Mass coded analysis in enzymatic hydrolysis of quasiracemate **7**.

These techniques do not require the chromatographic separation of enantiomers or quasienantiomers of the products involved, and provide a fast and accurate way to determine the enantioselectivity and conversion for a library of ligands or catalysts in a given reaction. The reliability of the method is generally comparable to that of methods based on chromatographic analysis over chiral stationary phases. The principle is not limited to mass spectroscopic analysis, and NMR and IR spectroscopy have also been used.[13d–f]

This strategy can also be applied to the desymmetrization of quasimeso compounds. In this application, the quasienantiomers are generated during the reaction. The isotopically labeled quasimeso compounds must be enantiopure or highly enantioenriched. As demonstrated in Scheme 2, lipase-catalyzed hydrolysis of the quasimeso compound **9** provides a mixture of quasienantiomeric products **10a** and **10b**.[12b] Again, no separation is needed and the difference in the mass of the quasienantiomers reflects the selectivity of the desymmetrization process.



Scheme 2. Lipase-catalyzed hydrolysis of quasimeso compound **9** gives quasienantiomers **10a** and **10b**.

Analyses that require the preparation and mixing of quasienantiomeric substrates are convenient for screening one substrate against many catalysts, but not for screening many substrates against one catalyst. The attachment of mass coded tags to reaction products offers an attractive alternative for substrate screening since a single tag can be used for many different reaction products.

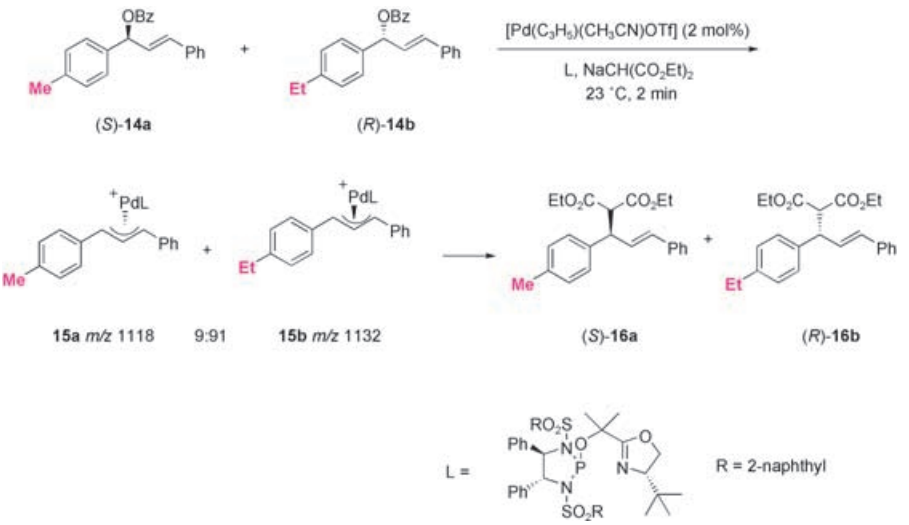
Siuzdak, Finn and co-workers measured the *ee* of samples of chiral secondary alcohols by coupling them with mass coded quasienantiomeric acids (*S*)-**12a** and (*R*)-**12b**.[15] An extension of the classic Horeau method for determination of configuration of secondary alcohols, the method is founded on the principle that reactions of the enantiomers of **11** with acids (*S*)-**12a** and (*R*)-**12b** provide diastereomeric products **13a**,**b** and should therefore occur at different rates. The *ee* values of the samples can be calculated simply from the intensities of the appropriate peaks in the mass spectrum and the selectivity factor (s) for the reactions involved. The method has suitable accuracy for high throughput screening and is convenient because no separation is involved.

This method is a parallel kinetic resolution, and such reactions are described in detail for enantiomer separation below. However, because the goal is analysis and not separa-

tion, a high selectivity factor is not needed; selectivity factors between 2–2.5 proved suitable for analysis with (*S*)-**12a** and (*R*)-**12b** (Scheme 3). Indeed, high selectivity factors are not desirable since there becomes a risk that the slower reacting enantiomer is not completely consumed (the analysis assumes 100% conversion and yield of both enantiomers).

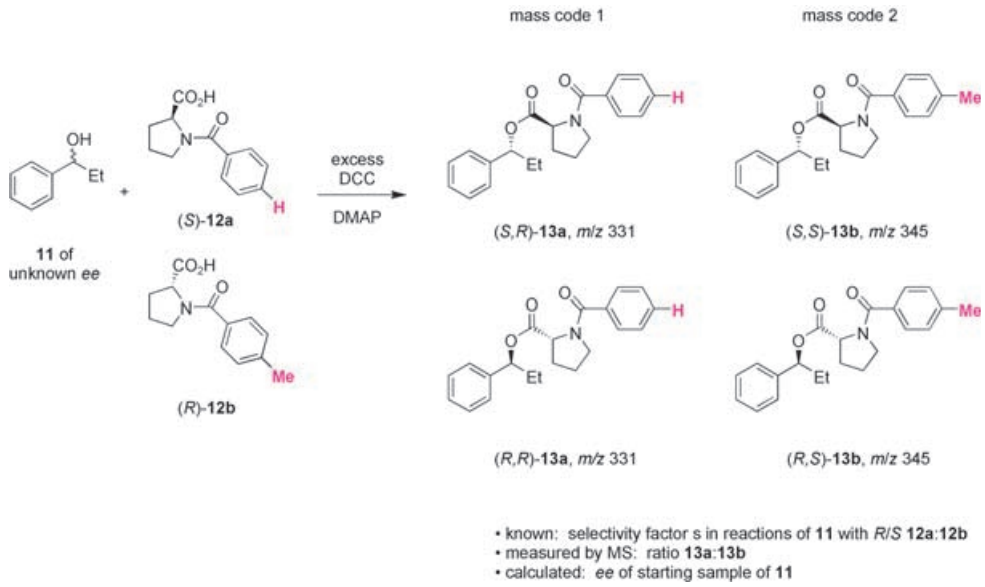
In a recent new direction, Markert and Pfaltz[16] pointed out that screening based on product analysis does not necessarily represent the inherent selectivity of a chiral catalyst due to potential unselective background reactions, catalytically active impurities and partial dissociation of a chiral ligand from a metal catalyst. They introduced a complementary approach that focuses on the detection of the catalytic intermediates instead of the precursors or products, and exemplified this in a setting of palladium-catalyzed allylic alkylation.

The kinetic resolution of allylic esters by palladium-catalyzed substitution is generally thought to occur via a cationic palladium–allyl complex, and is thus suitable for the examination of the catalyst-reactant complexes. Pfaltz and co-workers probed the relative rate of formation of complexes from quasienantiomer precursors as shown in Scheme 4. Quasienantiomers (*S*)-**14a** and (*R*)-**14b** were treated with *in situ* generated catalysts in the presence of the sodium salt of ethyl malonate. After 2 min at room temperature, the reaction mixtures were directly analyzed by ESI-MS. The peaks at *m*/*z* 1118 and 1132 correspond to the quasienantiomeric reactive intermediates **15a** and **15b**, and the ratio of their intensities (9:91 in this case) represents the selectivity imparted by the ligand in the reaction. By using this technique, Pfaltz and co-workers were able to identify several ligands from a library of 60 members with selectivity factors of >20.



Scheme 4. ESI-MS Screening of ligands for the kinetic resolution of quasiracemate **14**.

Since the ligand is still bound to the metal center in the intermediates detected, Pfaltz's method makes the evaluation of several chiral ligands in one reaction possible. Indeed, by lowering the reaction temperature from +23 to −78 °C to minimize ligand exchange, the catalytic efficien-



Scheme 3. Determining *ee* by mass coded tagging with parallel kinetic resolution.

cies (stereoselectivities and relative rates) of five different chiral ligands were evaluated in a single reaction.

Although it could be potentially highly attractive, Pfaltz's strategy has to be used with scrutiny. Detailed knowledge of the reactive intermediates of the reaction has to be available for the experiment planning so that the mass readout is relevant to the goal. Nonetheless, the use of a pair of quasienantiomers instead of a racemic compound for catalyst screening opens a creative new avenue to identifying better catalytic systems for suitably well understood reactions.

Quasienantiomers as Tools for Enantiomer Separation

Enantiomers can be separated by combining them with chiral resolving agents in reactions that are under either thermodynamic control or kinetic control.[17] Reactions under thermodynamic control include the formation of salts from chiral acids and bases, while reactions under kinetic control include familiar kinetic resolutions with enzymes and other chiral catalysts or reagents.

It is, of course, not possible to resolve a racemic substrate with a racemic resolving agent. However, if the resolving agent is instead a quasiracemate, then both enantiomers of the substrate can in principle be simultaneously resolved in processes called parallel thermodynamic or parallel kinetic resolutions. The quasienantiomers of the resolving reagent or catalyst must be designed to react selectively with one of the enantiomers of the substrate. They can also be designed to have different chromatographic or physical properties for easy separation of the products through chromatography or filtration.

Consider the general case of resolution of a racemic acid (*R*/*S*)-**A** with a racemic base (*R*/*S*)-**B** in Figure 5. Salts (*R*,*R*)-**AB**/(*S*,*S*)-**AB** and (*R*,*S*)-**AB**/(*S*,*R*)-**AB** are diastereomers and therefore do not have to be formed in a 1:1 ratio. Presumably, the thermodynamic ratio is generally obtained. However, even if these diastereomeric salts are readily separable, each is racemic so no resolution has occurred. Now consider the case where one of the components, here base **B**, is a pair of quasienantiomers with one of the enantiomers, here (*S*)-**B***, bearing a phase tag.[18] After salt formation, the product is readily bifurcated into two fractions based on the presence or absence of the tag. Now, the diastereoselectivity of the tagged and untagged products equals the diastereoselectivity of the original salt forming reaction. Breaking the salts by neutralization then provides enantioenriched substrates (*R*)-**A** and (*S*)-**A** in *ee* values that equal the diastereoselectivity of the salt forming reaction along with the recovered quasienantiomers of the resolving agent **B** and **B***. We call this process "parallel thermodynamic resolution".

In 1993,[19] Bergbreiter and Zhang resolved racemic 10-camphorsulfonic acid (CSA) with a pair of quasienantiomeric amines (Scheme 5) (*R*)-**17a** (with a polyethylene phase tag) and (*S*)-**17b** (with no phase tag). These amines form diastereomeric salts with CSA in an 82:18 ratio. In the resolution experiment, a 1:1 mixture of (*R*)-**17a** and (*S*)-**17b** was heated with racemic CSA (2 equiv) in toluene at 110 °C for 20 min to achieve the complete salt formation. Salts derived from the polymeric amine (*R*)-**17a** are not soluble in cold toluene while those from (*S*)-**17b** are, so cooling the reaction mixture to room temperature and filtration provided the polyethylene solid fraction enriched in (*R*,*S*)-**18a**. The ratio of the salts of (*S*,*S*)-**18b** to (*S*,*R*)-**18b** in the soluble fraction was measured by polarimetry to be 18:82. Neutralization of the soluble fraction then provided (+)-CSA in 64% *ee*, which corresponds to the original diastereoselectivity of the salt forming reaction (82 − 18 = 64). While the analysis of the polymeric salt was not reported, it presumably also has an 82:18 ratio of diastereomeric salts and would provide (−)-CSA in 64% *ee* after neutralization.

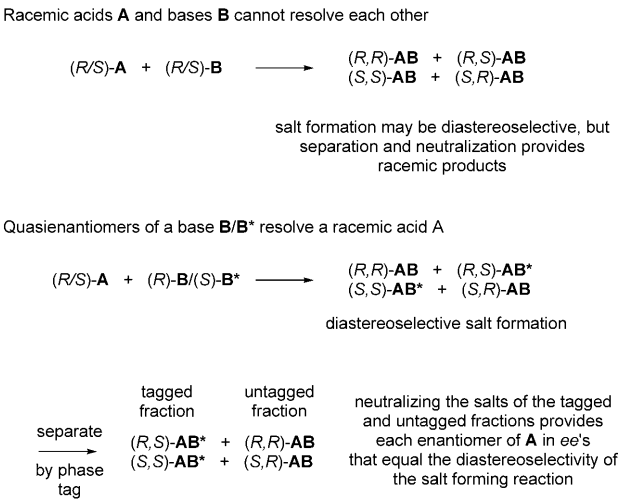
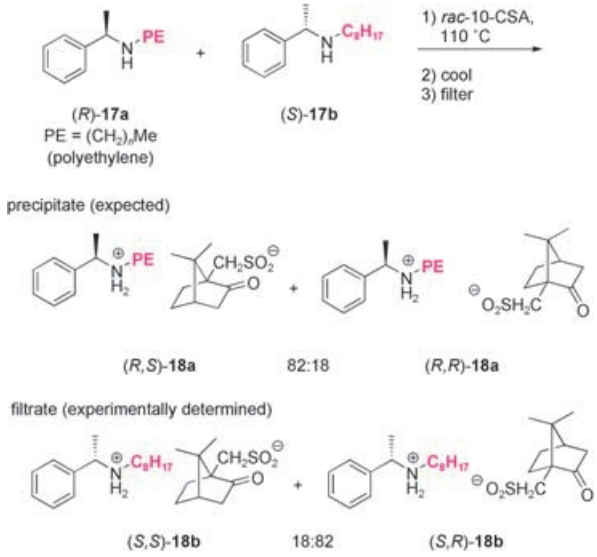


Figure 5. Parallel thermodynamic resolution of enantiomeric acids A with quasienantiomeric bases B/B*.



Scheme 5. Resolution of (*rac*)-10-camphorsulfonic acid with quasienantiomeric amines **17**.

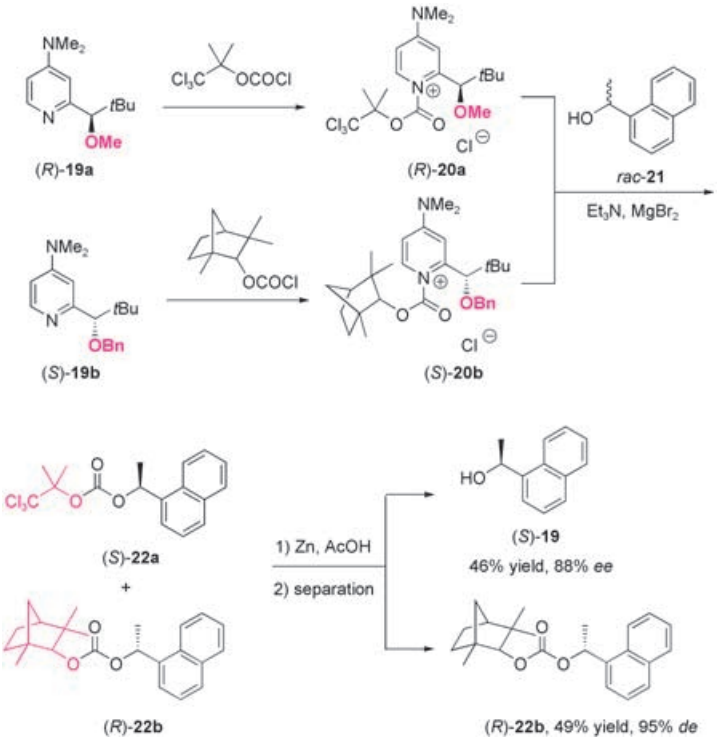
While the *ee* of Bergbreiter's resolution is modest, the concept is clear and readily extendable to many types of quasiracemic acids and bases and other resolving agents. In principle, both enantiomers of a substrate can be obtained in a single parallel thermodynamic resolution in an *ee* that is determined by the reaction under thermodynamic control. Reactions with sufficiently high equilibrium free energies, say 3 kcal mol^{-1} or so, have the potential to provide both enantiomers in quantitative yield in effectively enantiopure form.

The separation of two enantiomers with the aid of an irreversible asymmetric reaction is the standard technique called kinetic resolution.[20] However, a major drawback of classical kinetic resolutions is that enantioselectivity decreases as the conversion increases due to the negative effects of mass action as reaction progresses. For a practical kinetic resolution, a selectivity factor (s) must be >100 to achieve a very high *ee* of both possible products at about 50% conversion. Of course, attempting a kinetic resolution of a racemic substrate with a racemic resolving agent is pointless. But the use of a quasiracemate as a resolving agent again offers fundamentally new options.

In 1977, Ugi and co-workers described a general theory of independent parallel reactions that encompasses what today is called parallel kinetic resolution.[21,22] But they focused on situations of partial conversion where at least one of the reacting components was partially enantiomerically enriched and did not explicitly suggest that reactions of racemates and quasiracemates might be useful. In closing their short but thought-provoking paper, Bergbreiter and Zhang suggested that parallel thermodynamic resolution could be extended to irreversible reactions.[18]

In 1997, Vedejs and Chen[23] clearly articulated the features of parallel kinetic resolution (PKR) of racemates by quasiracemates[24] and exemplified these with the acyl transfer reaction shown in Scheme 6. In this PKR, two quasienantiomeric acyl transfer reagents (*R*)-**20a** and (*S*)-**20b** simultaneously derivatize each enantiomer of a racemic mixture of alcohols to give quasienantiomeric esters. Pyridine (*R*)-**19a** was activated by reaction with trichloro-*tert*-butyl chloroformate to generate acyl transfer reagent (*R*)-**20a**. Similarly, the quasienantiomeric pyridine (*S*)-**19b** was activated as (*S*)-**20b** by reacting with fenchyl chloroformate. (In this reaction, the use of the chiral fenchyl substituent is inconsequential; any ester substituent with suitable chemical and physical properties should suffice.) The quasienantiomeric DMAP-derived salts (*R*)-**20a** and (*S*)-**20b** show excellent selectivities in the acyl transfer reaction with enantiomers of 1-(1-naphthyl)ethanol **21**: (*R*)-**20a** preferentially reacts with the (*S*)-alcohol (s = 42) while (*S*)-**20b** prefers to react with the (*R*)-alcohol (s = 41).

In a parallel kinetic resolution, the two salts **20a**,**b** were mixed and treated with racemic 1-(1-naphthyl)ethanol (*rac*)-**21**. The reaction was allowed to proceed to completion to provide a mixture of quasienantiomers (*S*)-**22a** and (*R*)-**22b**. This mixture was then treated with Zn in acetic acid to selectively cleave the trichloro-*tert*-butyl carbamate of (*S*)-**22a**, and the resulting (*S*)-1-(1-naphthyl)ethanol (*S*)-**19** and the fenchyl carbonate (*R*)-**22b** were separated by column chromatography for enantiomeric excess analysis. In this process, the alcohol (*S*)-**21** was obtained in 46% isolated yield with 88% *ee*, while ester (*R*)-**22b** was obtained in 49% yield with 95% *ee*. The quasienantiomeric pyridines **19a**,**b** could also be recycled with about 90% recovery.



Scheme 6. Parallel kinetic resolution of *rac*-1-(1-naphthyl)ethanol with quasienantiomeric acylating reagents.

This implementation of PKR with selective cleavage of one of the quasienantiomeric products back to the starting alcohol resembles a standard kinetic resolution. However, in a standard resolution, the selectivity of formation of the reaction product can never exceed the *s* factor and decreases continuously with increasing conversion. In contrast, the selectivity of an ideal PKR does not depend on the conversion and is equal to *s* at all times for both products. Further, the selective ester cleavage reaction in Scheme 6 is not an essential design component since the quasienantiomeric products **22** are already directly separable in principle.

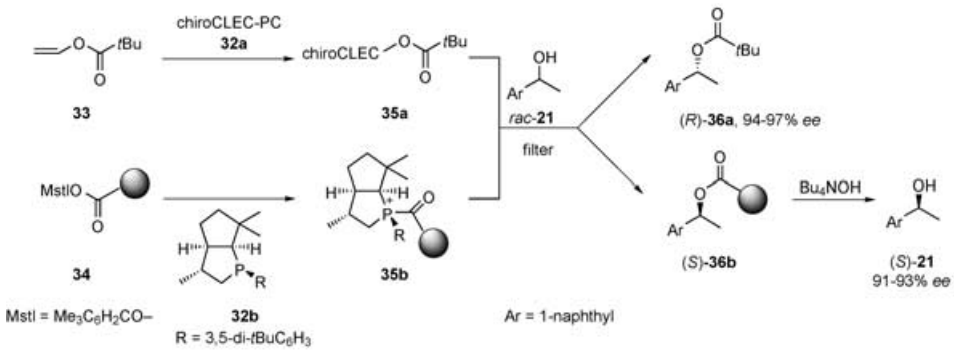
Practically useful parallel kinetic resolutions with quasienantiomers will result when the two parallel reactions: 1) occur with little or no mutual interference, 2) have identical or very similar rates, 3) have opposite enantioselectivity, and 4) provide readily separable products.[21,22]

The ease of designing PKR reactions of quasienantiomers depends on whether the reactions are stoichiometric or catalytic in the quasienantiomeric resolving agent. For stoichiometric reactions, essentially any traditional kinetic resolution serves as starting point; one simply converts one enantiomer of the resolving agent into a quasienantiomer by suit-

ably altering one or more remote substituents. Three recent examples of parallel kinetic resolutions of racemates with stoichiometric quantities of quasiracemates are summarized in Figure 6. Brandi and co-workers used triacetyl-D-glucal (*S*)-**24a** and triacetyl-L-rhamnal (*R*)-**24b** as quasiracemates to resolve nitrones **23** with modest selectivities.[25] In contrast, high selectivities were observed by Fox and co-workers in resolution of cyclopropene carboxylic acid chlorides **26** with quasienantiomeric oxazolidinones derived from D-phenylalanine (*S*)-**27a** and L-tyrosine (*R*)-**27b**.[26] Davies and co-workers resolved 3-alkylcyclopentene-1-carboxylate esters **29** by 1,4-addition reactions with quasienantiomeric derivatives (*S*)-**30a** and (*R*)-**30b** of phenethyl amine (Figure 6).[27]

Many classical kinetic resolutions use catalytic amounts of the resolving agent, and it is possible in principle to conduct parallel kinetic resolutions with a chiral quasiracemic catalyst. However, the implementation is much more challenging because each quasienantiomer of the catalyst must be charged with a different stoichiometric reagent in order to provide quasienantiomeric products. To the extent that cross-charging occurs, the selectivity of the PKR decreases below the theoretically attainable level.

Vedejs and Rosner[28] met the challenge of catalytic version of parallel kinetic resolution by designing and implementing a three-phase system that allows selective reagent activation by using two different charging reactions with two catalysts—one soluble and one insoluble—and two tagging reagents—one soluble and insoluble. As shown in Scheme 7, the reaction system consists of a commercial cross-linked



Scheme 7. A three-phase system allows parallel kinetic resolution under catalytic conditions.

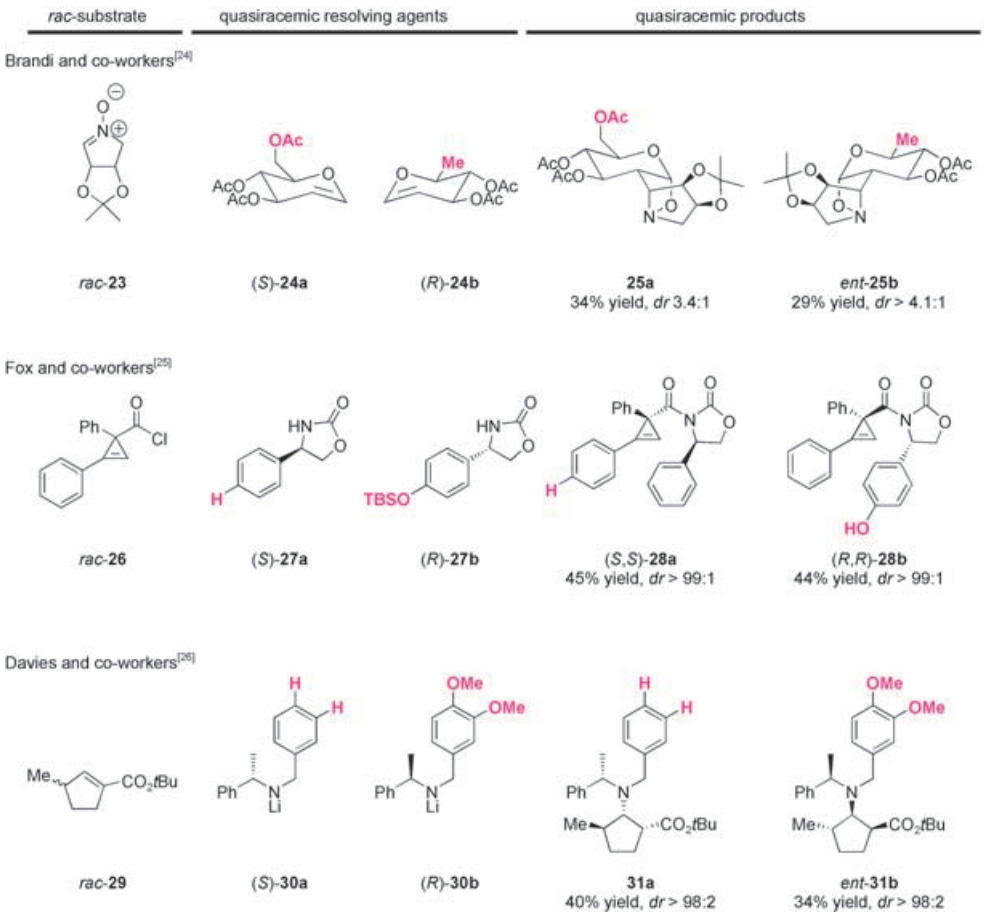
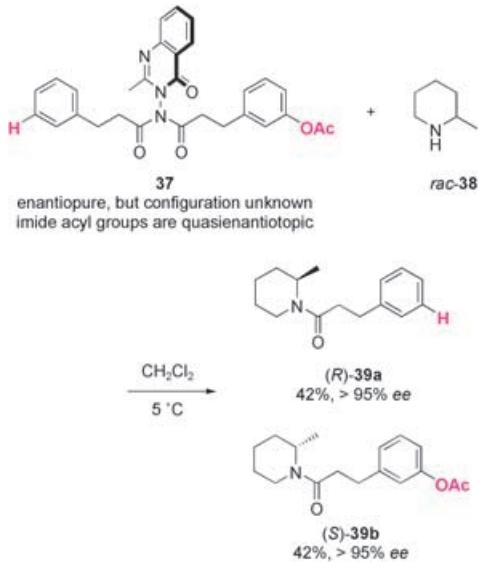


Figure 6. Examples of PKRs with quasiracemic resolving agents.

lipase acylation catalyst chiroCLEC-PC **32a**, a chiral phosphine catalyst **32b**,[29] stoichiometric amounts of vinyl pivalate **33** and polymer-supported mixed anhydride **34**. Soluble vinyl pivalate can be activated by insoluble ChiroCLEC-PC **32a** but not by phosphine **32b**. On the other hand, the reaction between mixed anhydride **34** and chiroCLEC-PC **32a** is negligible because both are in the solid phase. The mixed anhydride **34** is therefore only activated by phosphine **32b**. Sterically differentiated vinyl ester **33** also enables selective carbonyl activation. Furthermore, activated chiroCLEC-PC **35a** is selective for the formation of (*R*)-**36a** while the activated chiral phosphine **35b** selectively forms (*S*)-**36b**. In typical reactions with racemic 1-(1-naphthyl)ethanol **21** with conversions in the range of 85–90%, (*S*)-**21** was recovered with 91–93% *ee* after cleavage of the polymer support, while the soluble pivalate (*R*)-**36a** was obtained with 94–97% *ee*.

In an interesting twist on the concept, Al-Sehemi and coworkers[30] used a single reagent with two quasienantiotopic groups in place of two quasienantiomeric reagents. The two enantiomers of a racemic substrate can then react selectively and at about the same rate with the two enantiomeric functional groups to generate two quasienantiomers.

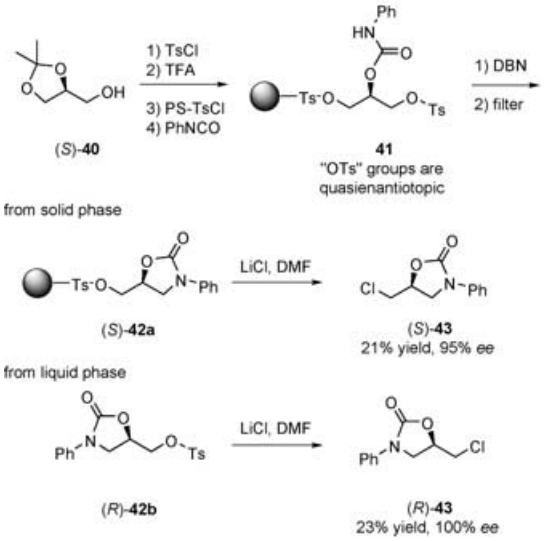
The parallel kinetic resolution of racemic 2-methylpiperidine **38** by using this strategy is shown in Scheme 8. The resolving agent is imide **37**, which resembles biaryls such as BINOL and BINAP and is accordingly axially chiral and has a relatively high rotation barrier about the N–N bond. We call the two N-acyl groups of this imide "quasienantiotopic" because they would be truly enantiotopic if they were the same. In other words, **37** is only chiral because these two groups are different. The reactions of either quasienantiotopic group with a racemic reagent pass through diastereomeric transitions states, so selectivity can be observed according to the usual kinetic principles.



Scheme 8. Selective reactions of quasienantiotopic groups can resolve a racemic substrate to provide quasienantiomeric products in high *ee*.

Reaction of enantiopure **37** (but with unknown absolute configuration) with one equivalent of racemic amine (*rac*)-**38** was carried out at 5 °C for 48 h and provided quasienantiomeric amides (*R*)-**39a** and (*S*)-**39b**, which were easily separated by column chromatography over silica gel. Both (*R*)-**39a** and the (*S*)-**39b** were obtained in 42% yield and >95% *ee*. Thus, the reaction has occurred with exceptionally high group selectivity. Compared with other resolution methods, this approach combines the advantage of traditional kinetic resolution (only one resolving reagent used) with that of parallel kinetic resolution (complete conversion, high enantiopurity of the product).

Zwanenburg and co-workers applied a conceptually similar strategy in a different way for synthesis of both enantiomers of oxazolidinones from a common chiral precursor.[31] The reaction involves the unselective cyclization of compound with quasienantiotopic leaving groups to generate two readily separable quasienantiomers. As shown in Scheme 9, the enantiomerically pure **41** (made from (*S*)-**40**



Scheme 9. Polymer-aided stereodivergent synthesis of both enantiomers of **43**.

was treated with 1,5-diazobicyclo[4.3.0]non-5-ene (DBN) to induce unselective cyclization to the quasienantiotopic tosylates (one is resin bound, the other not). The so-formed quasienantiomers (*S*)-**42a** and (*R*)-**42b** were separated by a simple filtration. An intermolecular substitution with LiCl then generates two true enantiomers (*S*)-**43** and (*R*)-**43** with 95% and 100% *ee*, respectively.

Al-Sehemi's and Zwanenburg's reactions of quasienantiotopic groups share the feature that a single chiral reagent is converted into both quasienantiomers of a product in about equal quantities and *ee* values. However, they differ in that Al-Sehemi's reaction (Scheme 8) is a resolution (a racemic substrate is separated into its enantiomer components), whereas Zwanenberg's (Scheme 9) is a "reverse resolution". In other words, a single chiral reagent (*S*)-**40** ultimately

gives rise to two enantiomeric products **43** in equal quantities. A true reverse resolution—the conversion of an enantiopure starting material to a racemic product—is of little interest. However, a reverse resolution to form quasienantiomers is potentially very useful when both enantiomers of a product are desired and one enantiomer of the appropriate chiral precursor is much more readily available than the other.

Quasienantiomers as Tools for Enantiomer Synthesis

The two standard ways to make enantiopure compounds are racemic synthesis followed by resolution and asymmetric synthesis. Racemic synthesis[32] has the advantage of making both enantiomers of a target compound in a single process, but the separation of the final racemate and the identification of the individual enantiomers can be difficult. While racemic synthesis still plays an important role in production of drugs and fine chemicals, it has largely been supplanted by asymmetric synthesis in an academic research setting. This provides single enantiomers, bypassing the need for separation and identification, but two separate syntheses are needed if both enantiomers are desired.

In 2001, we and our co-workers introduced the technique of "quasiracemic synthesis" as a complement to racemic synthesis and asymmetric synthesis.[33] As Figure 7 illustrates, each enantiomer of a starting material (SM) is differentially tagged with related but non-identical tags (T) to give a pair of quasienantiomers. These are mixed to form a quasiracemic mixture [(*R*/*S*)-SM-T^1/T^2], which is taken through a series of synthetic steps. At the end of the synthetic sequence, the quasienantiomers are separated based upon a property of their tags. This type of tag-based separation is called "demixing". Removal of the tags (detagging) then provides both enantiomers of the chiral product. Quasiracemic synthesis simultaneously captures the efficiency of racemic synthesis (two products made in one synthesis) while retaining the key advantages of asymmetric synthesis (enantiomerically pure products can be obtained without resolution).

The tags are the key to successful quasiracemic synthesis. In most respects, they should be similar to each other so that the tagged enantiomers have nearly identical physical and spectroscopic properties and chemical reactivities towards achiral reagents. They should also be different from each other in at least one key feature so that the quasienantiomers can be separated based on the tag in a reliable way. The use of fluorous tags to achieve easy separations of the tagged molecules from non-tagged ones and from each other on fluorous silica gel has developed rapidly.[34,35] Fluorous silica gel has been found to separate molecules primarily by their fluorine content.[36] To demonstrate the concept of quasiracemic synthesis, we selected fluorous protecting groups with slightly different perfluorinated fragments as tags for the synthesis of both enantiomers of natural product mappicine (Scheme 10).

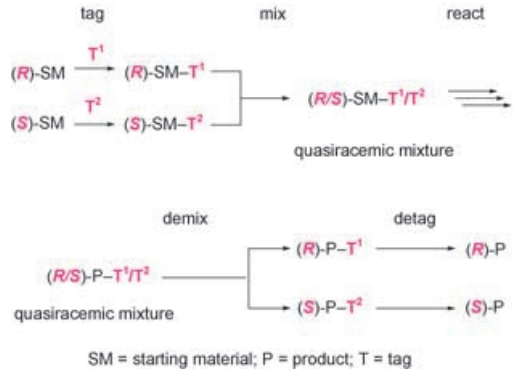
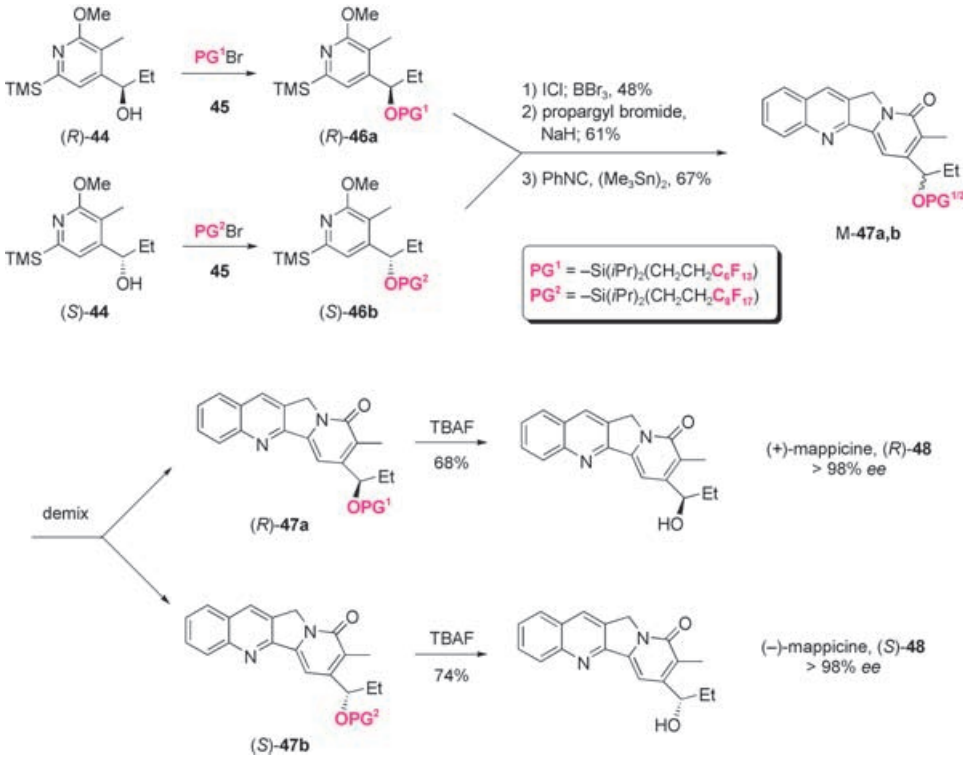


Figure 7. Quasiracemic synthesis with separation tags (T).



Scheme 10. Quasiracemic synthesis of both enantiomers of mappicine.

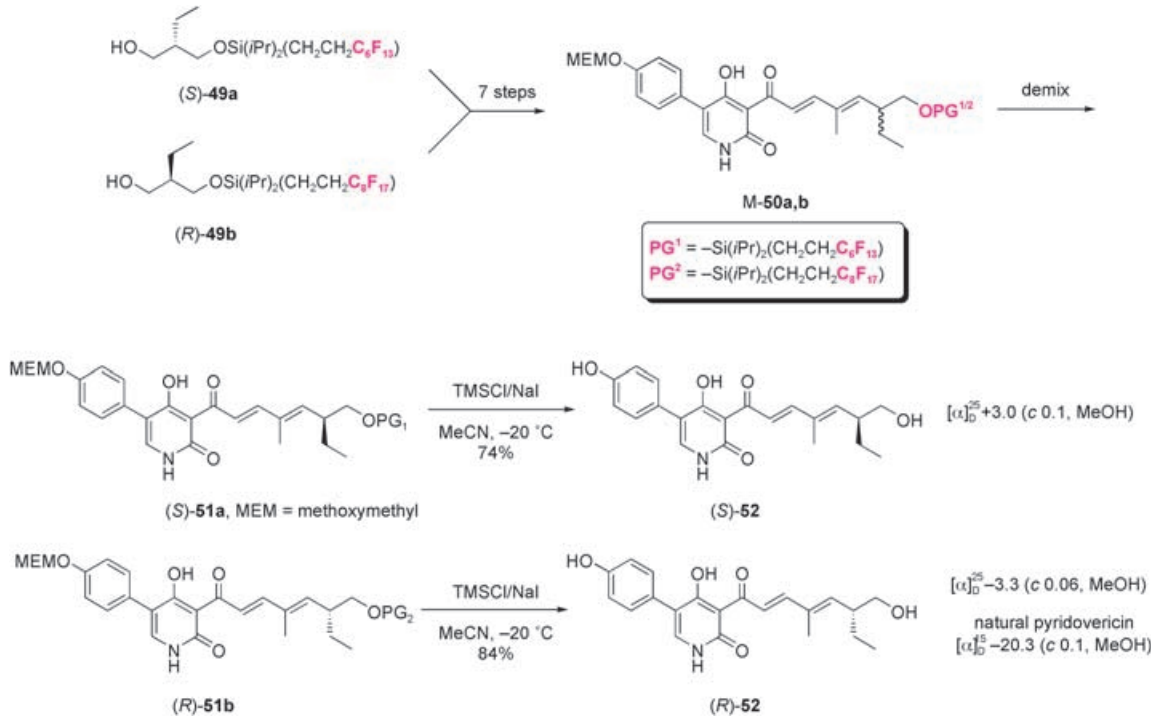
True enantiomers (*R*)- and (*S*)-**44** were prepared in 79% *ee* by asymmetric reduction, and then tagged with homologous silyl protecting reagent **45**. The resulting quasienantiomers (*R*)-**46a** and (*S*)-**46b** were mixed in 1:1 molar ratio to form a quasiracemate. Exchange of trimethylsilyl group for iodine with ICl and demethylation with BBr_3 followed by N-propargylation and subsequent radical cyclization with phenyl isonitrile provided quasiracemic mixture M-**47a**,**b**. The separation of this mixture over fluorous silica gel yielded two quasienantiomers (*R*)-**47a** and (*S*)-**47b**. Both (+)- and (−)-mappicine **48** were then obtained in enantiopure forms after deprotection with TBAF in THF in 68 and 74% yields, respectively.

All the traditional chromatographic and spectroscopic techniques (including flash chromatography, LCMS, ^{1}H NMR, ^{19}F NMR and ^{13}C NMR spectroscopy) that have been used in solution-phase synthesis are also used in quasiracemic synthesis. Due to the inert nature of the fluorous tags, all the quasiracemic mixtures in Scheme 10 behaved like racemic mixtures as judged from R_f values on silica gel TLC (all single spots) and ^{1}H NMR spectra.[37] However, unlike racemic synthesis, the mixtures can be resolved at any time into their quasienantiomeric components by fluorous chromatography.

Quasiracemic synthesis should be considered whenever both enantiomers of the target are needed. The assignment of the absolute configuration of a natural product is one such application. As a demonstration, both enantiomers of natural product pyridovericin were synthesized by using a quasiracemic synthesis approach.[31] As summarized in Scheme 11, equimolar amounts of quasienantiomers (*S*)-**49a** and (*R*)-**49b** were mixed to start the quasiracemic synthesis. The mixture M-**50a**,**b** was obtained after seven synthetic steps and separated over fluorous silica gel into two pure quasienantiomers (*S*)-**51a** and (*R*)-**51b**. Both enantiomers of pyridovericin (*S*)- and (*R*)-**52** were obtained after deprotection and detagging by treatment with TMSCl/NaI in acetonitrile. By comparing the optical rotations of the synthetic samples with that of the natural one, we assigned the absolute configuration of pyridovericin as (*R*).

The technique of fluorous quasiracemic synthesis is the simplest in a larger suite of tagged-based mixture synthesis techniques that go under the rubric of fluorous mixture synthesis. Diastereomers and even non-isomeric sets of analogues can be tagged. In each case, the theme is the same; stereochemical or substituent information is coded to a fluorous tag, which also serves as a protecting group and orchestrates the final demixing.[38,39]

The syntheses of 16-member stereoisomer libraries of the natural products murisolin[40] and the pine sawfly sex pheromone[41] by using fluorous mixture synthesis leveraged by splitting have recently been reported. Scheme 12 summarizes the synthesis of four diastereomers of murisolin in one reaction sequence. Two pairs of quasienantiomers (*R*,*S*)-**53a**/(*S*,*R*)-**53b** and (*S*,*S*)-**54c**/(*R*,*R*)-**54d** were synthesized individually in enantiopure form and mixed. The acetate mixture M-**55a**–**d** obtained after five steps of mixture synthesis was epoxidized with chiral ketone **56** and Oxone to generate two new stereocenters in M-**57a**–**d**. Another eight steps of mixture synthesis provided mixture M-**58a**–**d**, which was demixed into its four underlying components by fluorous HPLC. Deprotection and detagging of each component then gener-



Scheme 11. Quasiracemic synthesis of both enantiomers of pyridovericin.

ated four murisolin isomers **59** shown in Scheme 12. The use of diastereomeric pairs of quasienantiomers as starting materials with subsequent splitting and generation of new stereocenters greatly extends the scope of this mixture synthesis method to make stereoisomers of natural products.

Tagged-based mixture synthesis is not limited to fluorous tags, and recently Wilcox and Turkylimaz have introduced a series of oligoethylene glycol reagents as suitable tags.[42] These reagents have varying numbers of $(OCH_2CH_2)_n$ units, and this variation imparts huge differences in polarity. Molecules with larger tags are more polar, and demixing is accomplished by standard silica gel chromatography. In the first example of OEG-mixture synthesis,[43] a quasidiastereomeric mixture of four hydroxy lactones M-**60** suitable for use in synthesis of murisolin isomers has been made (Figure 8). Strategically, the exercise is similar to that in Scheme 12. Two pairs of quasienantiomers are made as quasiracemates and then combined to make the quasidiastereomer mixture that is taken forward to M-**60a–d**. Though conceptually similar, fluorous and OEG tagging methods have significant practical differences that make them complementary techniques.

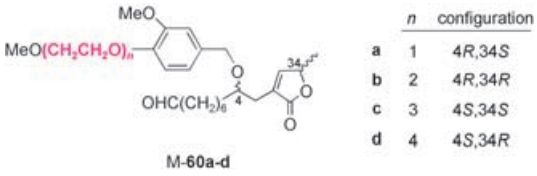
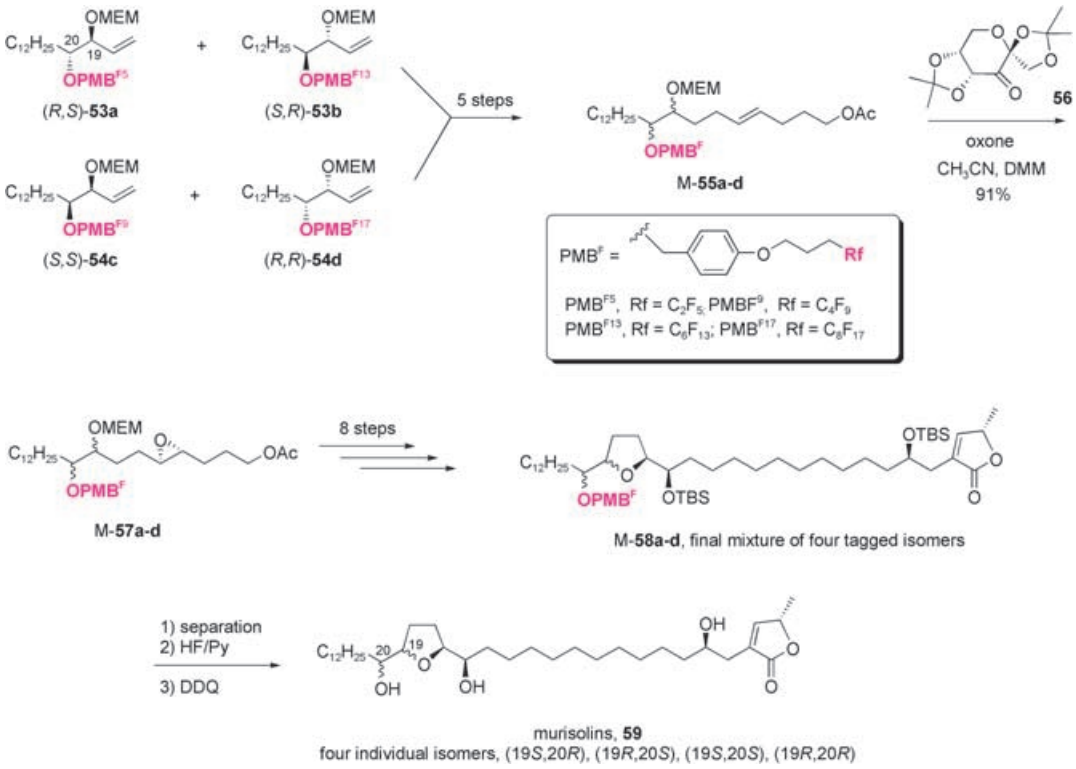


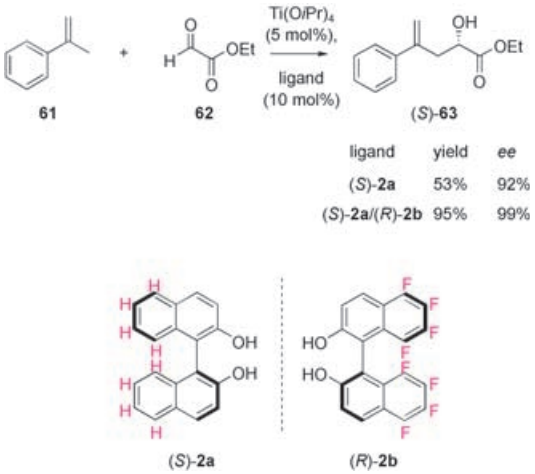
Figure 8. Oligoethylene glycol (OEG) encoded mixture of hydroxy butenolide intermediates **60** for murisolin synthesis.

All these applications feature quasienantiomers as synthetic intermediates, but they have also been used as asymmetric catalysts. A racemic mixture of ligands naturally cannot provide asymmetric induction, and likewise quasiracemates might, at first glance, appear to have no use as catalysts. However, quasienantiomers are not isomers, and Yudin and co-workers have recently reported remarkable asymmetric induction in the ene reaction shown in Scheme 13.[44]

When a 1:1 mixture of (*S*)-BINOL **2a** and (*R*)-F_8BINOL **2b** was used as the ligand for Ti(OP*i*r)$_4$-catalyzed ene reaction of ethyl glycolate **62** with α-methyl styrene **61**, the hydroxy ester (*S*)-**63** was formed in 95% yield and with 99% *ee* (Scheme 13). In contrast, the racemic product **63** was obtained as expected when a racemic mixture of BINOL was used as the ligand. Moreover, significant yield enhancement was observed when the pair of quasienantiomers was used instead of enantiopure BINOL or F_8BINOL alone. While some structural evidence is available and electronic effects are presumably important, it is still not clear how the changes in the ligands lead to these dramatic differences. Nonetheless, this interesting observation is likely to stimulate new directions in the field of asymmetric catalysis.



Scheme 12. Synthesis of four isomers of murisolin from two quasidiastereomeric pairs of quasienantiomers.



Scheme 13. Quasienantiomeric BINOL ligands in a Ti(O*i*Pr)$_4$-catalyzed ene reaction.

Conclusions and Outlook

We suggest that these recent applications of quasienantiomers and quasiracemates in the identification, analysis, separation and synthesis of enantiomers only begin to scratch the surface. Organic chemists are predisposed to thinking that racemates are of little use until they are separated into their individual enantiomers. Accordingly, mixing pure enantiomers is an anathema because it violates the long held adage to "never mix pure organic compounds". Quasienantiomers are, by definition, similar to enantiomers. But using them effectively requires a reversal of the logical mindset—quasienantiomers typically become interesting after you mix them. This backwards thinking opens many new possibilities for uses of quasienantiomers, quasidiastereomers and related quasisymmetric molecules.

Acknowledgements

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[2] A definition should preferentially say what something is, rather than what something is not. Trying to write a definition for what diastereomers "are" that includes all diastereomers and nothing else quickly shows why the exclusive definition is needed.
[3] M. Centnerszwer, *Z. Phys. Chem. (Leipzig)* **1899**, *29*, 715.
[4] Throughout the paper, true isomers are labeled as (*R*), (*S*) and (*rac*) as usual. Suffixes "a" and "b" are added to numbers to denote non-isotopic quasienantiomers, while a prefix "M" denotes a mixture of quasienantiomers or quasi-isomers. The differing groups of quasienantiomers are highlighted in red in the Figure and Schemes.
[5] A good case can be made for an exception with "quasi-isomers" to interrupt the awkward double "i" in "quasiisomers". Related exceptions are made. Compare the spelling of "anti-infective" with "antiinfective". The hyphenated spelling is recommended by the ACS Style Guide.
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