Parallel kinetic resolution of racemic mixtures: a new strategy for the preparation of enantiopure compounds?

Juan R. Dehli and Vicente Gotor*

Departamento de Química Orgánica e Inorgánica, Universidad de Oviedo, c/ Julián Clavería 8, E-33006 Oviedo, Spain. E-mail: vgs@sauron.quimica.uniovi.es; Tel: +34 985 103448

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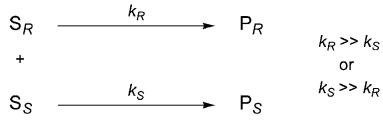
Kinetic resolution of racemic mixtures is a well-established methodology for the preparation of optically active compounds. However, excellent enantioselectivities are required to obtain them in enantiopure form, due to the decrease in *ee* when conversion values are close to 50%. To overcome this limitation, a parallel (asymmetric) reaction can remove the disfavored enantiomer. In this review, several examples of this strategy showing its wide range of applicability are described, as well as their mathematical treatment and some new applications in combinatorial chemistry.

1 Introduction

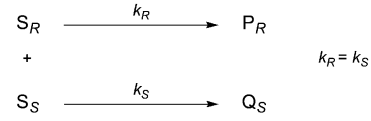
Enantiomerically pure chiral compounds are becoming more and more important in modern organic chemistry. To date, one of the major strategies for their preparation is still the kinetic resolution (KR) of racemic mixtures, by means of either chemical[1] or enzymatic[2] procedures: when one substrate enantiomer reacts much faster than the other one, substrate or product (or both) can be obtained in high enantiomeric excess (*ee*) at a certain conversion value (Scheme 1).

One of the major drawbacks of this methodology is the decrease in the *ee* of the product at conversion values close to 50%, due to the continuous increase of the relative concentration (and, therefore, the relative rate of reaction) of the less reactive substrate enantiomer.



Scheme 1

To avoid this limitation, the slower reacting enantiomer can be removed by a parallel reaction, ideally at an identical rate, thus maintaining the 1:1 ratio of the substrate enantiomers (Scheme 2).[3] These competing reactions would yield two different products (P and Q) with substantially improved *ee* and up to the 50% theoretical yield. This strategy was suggested and called parallel kinetic resolution (PKR) by Vedejs and Chen in 1997,[4] although there were some previous examples, as will be shown below.

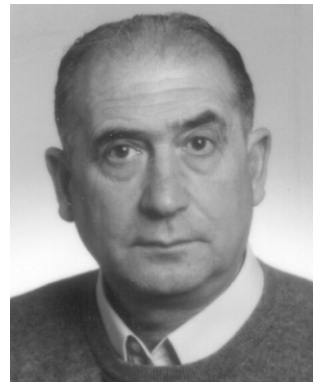


Scheme 2

In fact, the concept of simultaneous removal of both enantiomers of substrate can be dated back as far as 1979, when Cram designed his W resolving machine. It consisted of a central aqueous solution containing a racemic mixture of an amine salt, and in contact with two separate chloroform pools, each one containing a different enantiomer of a chiral crown ether host. The enantiomeric guests were finally delivered to separate aqueous solutions.[5]

As a consequence, very high *ee* values can be obtained in processes with relatively low selectivity factors (*s*). For

Juan R. Dehli, born in 1974, graduated in Chemistry in 1997 and obtained his MSc in 1999 at University of Oviedo. After a short stay at University of the Mediterranean, France, with Professor Furstoss, he returned to Oviedo, where he completed his PhD under the supervision of Professor Gotor in 2002. He is currently a Marie Curie postdoctoral fellow with Professor Bolm at RWTH Aachen, Germany.



Vicente Gotor, born in 1947, received his PhD from the University of Zaragoza in 1974 and carried out his postdoc at Max Planck Institut für Kohlenforschung (Mülheim/Ruhr, Germany). He joined the University of Oviedo as Assistant Professor in 1977, where he assumed his current position as Professor of Organic Chemistry in 1982, and where he has been Vice-chancellor of Research for four years. His current areas of research are enzymatic amidation reactions with hydrolases, enzymatic chemoselective transformations on natural products, biotransformations with oxynitrilases and oxidoreductases and supramolecular chemistry.

example, in a PKR experiment using two simultaneous reactions of complementary enantioselectivities with s = 49 (100% conversion) would be equivalent to a simple kinetic resolution with s = 200 at 50% conversion. Theoretically, both experiments would allow total recovery of each enantiomer with 96% *ee*.[6]

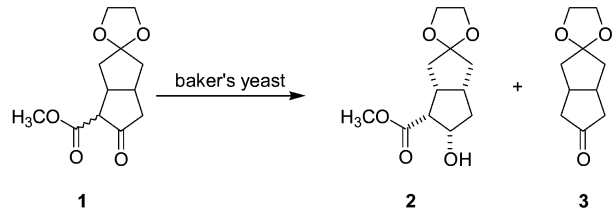
As has been pointed out,[4] all that is necessary is that both reactions (a) occur without mutual interference, (b) have similar rates, (c) have complementary enantiocontrol and (d) afford different and easily separable products.

This last requirement will be the basis of our classification of PKR processes, attending to the structural relationship between both products. Thus, the processes will be divided into chemodivergent, regiodivergent and stereodivergent.

2 Chemodivergent PKR

This first group of PKR includes those reactions that yield two non-isomeric compounds. In some cases, they are completely different, and one of them can even be useless, since it is non-chiral. However, in most examples described until now, the products of the chemodivergent PKR are pseudoenantiomers: two products possessing all the stereocenters with opposite configuration and differing at a position far from them.[7]

In 1987, Brooks *et al*. reported a dual kinetic resolution of the bicyclo[3.3.0] β-keto ester **1** by baker's yeast (Scheme 3): one

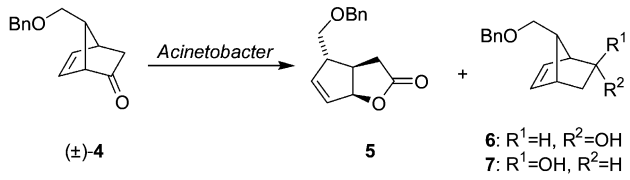


1 **2** **3**

Scheme 3

enantiomer was reduced to the corresponding hydroxy ester **2**, while the other was hydrolyzed and decarboxylated to the achiral half-ketal ketone **3**. This result is due to the presence in this microorganism of different enzymes (an alcohol dehydrogenase and an esterase) with opposite enantiodiscrimination.[8]

Another biocatalytic example was reported in 1991 by Königsberger *et al.* in the course of a Baeyer-Villiger reaction of a bridged bicyclic ketone (Scheme 4). Thus, the incubation of

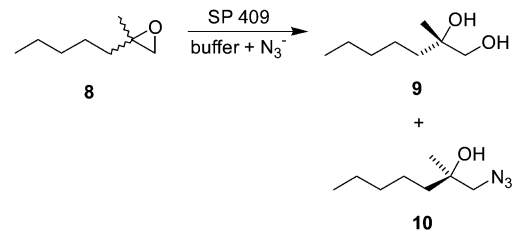


(±)-**4** **5** **6**: R^1=H, R^2=OH; **7**: R^1=OH, R^2=H

Scheme 4

racemic **4** with *Acinetobacter calcoaceticus* NCIB 9871 yielded the rearranged lactone **5** together with a mixture of the corresponding *endo* and *exo* alcohols, **6** and **7**. In this case, the strain performs oxidation and reduction concurrently, depending on the substrate enantiomer.[9]

An opposite enantiodiscrimination of two nucleophiles (water and azide) was observed by Mischitz and Faber in the biohydrolysis of (±)-2-methyl-2-pentyloxirane, **8**, catalyzed by an immobilized enzyme preparation from *Rhodococcus* sp (SP 409). Thus, after complete conversion, the (*S*)-diol, **9**, and (*R*)-azidoalcohol, **10**, were obtained in >90% and >60% *ee* respectively, as can be seen in Scheme 5.[10]

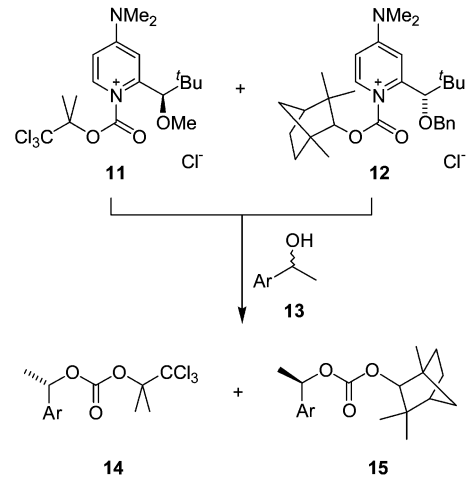


8 **9** + **10**

Scheme 5

Heijnen and coworkers performed the simultaneous hydrolysis and aminolysis of methyl 2-chloropropionate in the presence of *n*-butylamine in buffer saturated solvents (heptane or dichloromethane), catalyzed by *Candida cylindracea* lipase (CCL).[11] Again, the enzyme showed opposite enantiopreference for both reactions, yielding the corresponding (*S*)-2-chloropropanamide and the (*R*)-2-chloropropionic acid in higher *ee*, when compared with the reactions carried out independently.[12]

A very elegant application of this strategy is the use of quasi-enantiomeric resolution reagents and the concept of 'matched and mismatched pairs'.[13] The reaction of racemic 1-arylethanols, **13**, with two chiral DMAP-derived salts **11** and **12** yielded the corresponding trichloro-*tert*-butyl and fenchyl carbonates, **14** and **15**, respectively (Scheme 6). Although



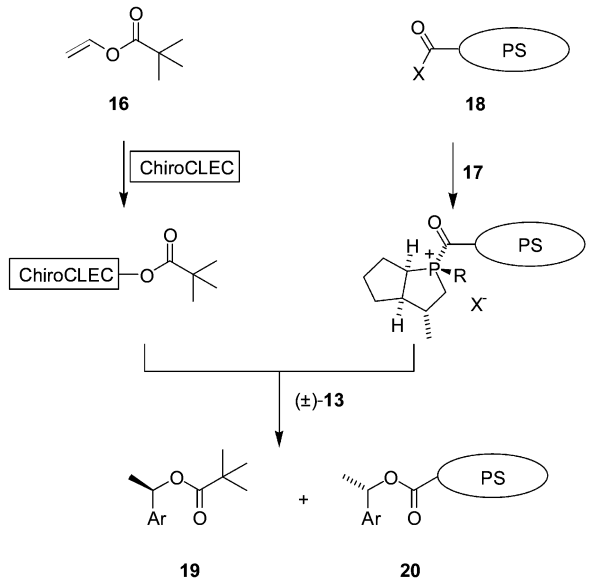
11 **12** **13** **14** **15**

Scheme 6

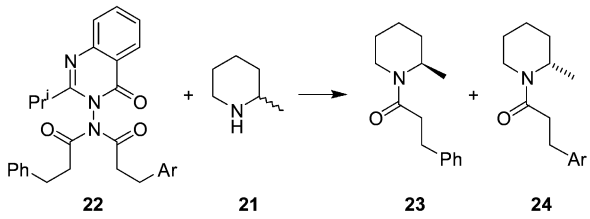
selectivity factors were around 40, *ee* values as high as 95% were obtained after complete conversion.[4]

Very recently, this kind of PKR has been further adapted to a catalytic version: a commercial cross-linked lipase acylation catalyst (ChiroCLEC-PC) together with a lipase-specific acyl donor, **16**, a complementary chiral phosphine acylation catalyst, **17**, and a phosphine-specific (PS) acyl donor, **18**, were simultaneously used to derivatize the enantiomeric alcohols **13** (Scheme 7). To avoid mutual interference between both acylation reactions, the catalytic PKR was performed in a three-phase system: (a) the enzyme (insoluble catalyst); (b) the insoluble acyl donor, **18**; and (c) the soluble catalyst, **17**, and soluble acyl donor, **16**. Furthermore, as the ester **20** is attached to the solid phase, it is easy to separate from the quasi-enantiomeric ester **19**, formed in solution.[14]

A similar approach was carried out for the PKR of amines, using enantiopure 3-*N*,*N*-diacylaminoquinazolin-4(3*H*)-ones, compounds that contain the N–N axis as the only chiral element. Thus, reaction of racemic 2-methylpiperidine, **21**, with **22** resulted in a 1:1 mixture of amides **23** and **24** in virtually enantiopure form and opposite configuration (Scheme 8). In this case, the two *N*-acyl groups were playing the rôle of the two pseudoenantiomeric reagents mentioned in the example above.[15]

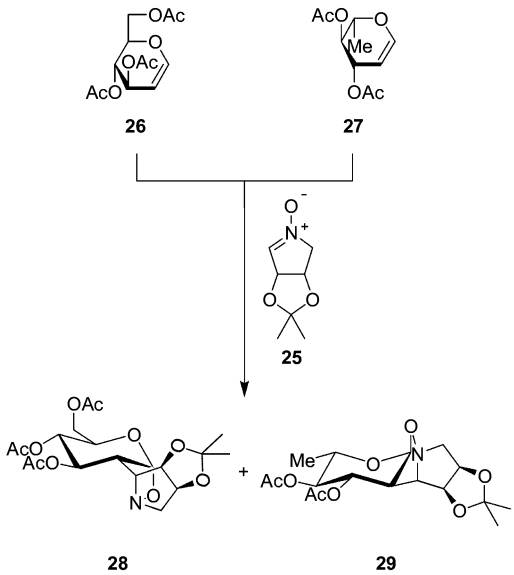


Scheme 7



Scheme 8

A chemodivergent PKR procedure was also applied to the synthesis of pseudo-imino-*C*-disaccharides through cycloaddition of racemic nitrones to 1,2-glycals by Cardona *et al.* (Scheme 9): the basis for this behavior is the different approach



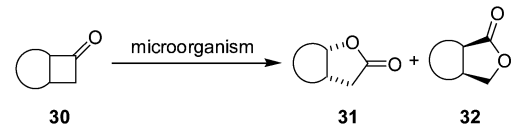
Scheme 9

of both enantiomers of the nitrone **25**, *syn* and *anti*, with respect to vicinal alkoxy protecting groups of the corresponding glycals: thus, one enantiomer of the pyrroline *N*-oxide **25** attacked preferably the bottom face of D-glucal, **26**, and the other one, the *top* face of L-rhamnal, **27**.[16]

3 Regiodivergent PKR

This second group of PKR includes either those in which the substrate has the same reacting functional group at different positions on the molecule, or those in which a single functional group leads to two regioisomeric compounds.

Another surprising and efficient outcome of the biocatalytic Baeyer–Villiger reaction was described by Furstoss and coworkers (Scheme 10). In this case, incubation of racemic

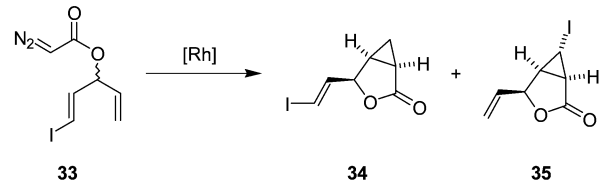


Scheme 10

bicyclic ketones, **30**, with *Acinetobacter* strains yielded the two regioisomeric lactones with almost total stereoselectivity: whereas one, **31**, arose from a 'normal' Baeyer–Villiger-type oxygen insertion between the more substituted carbon atom and the carbonyl group, the other, **32**, was formed with the chemically disfavored regiochemistry.[17] It was later shown that this result was also obtained when oxygenated heterocyclic substrates were used.[18]

A few years later, Bolm and Schlingloff carried out the asymmetric aerobic oxidation of several cyclobutanones using a copper catalyst, obtaining the corresponding lactones in optically active form. The higher *ee* of the 'abnormal' regioisomers (92–95%), compared to that of the 'normal' ones (59–76%) was attributed to the competition of uncatalysed pathways. Although these results in general fall short when compared with those obtained with microorganisms, it is expected that a more thorough understanding of the enantiodiscriminating event in these processes will result in the development of even more efficient catalysts.[19]

Martin and coworkers applied their methodology of enantioselective cyclization of diazoacetates of secondary allylic alcohols to the racemic divinyl diazoacetate **33** (Scheme 11). In

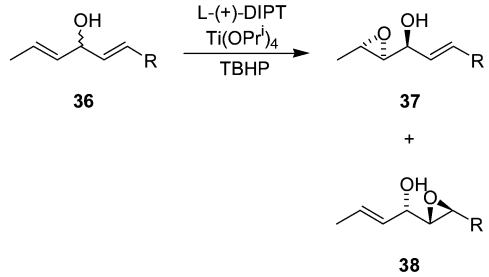


Scheme 11

this process, the use of the catalyst (a rhodium(II) complex) yielded the two products of intramolecular cyclopropanation *endo*, **34** and **35**, with high enantio- and diastereoselectivities (*ca.* 90%).[20]

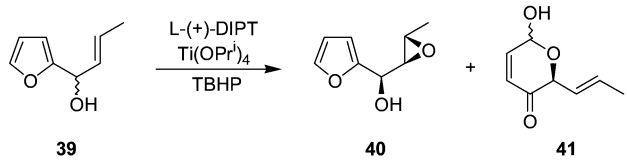
Another field where several examples of regiodivergent PKR have been described is the Sharpless epoxidation of secondary allylic alcohols. Zhou and coworkers carried out the resolution of unsymmetrical divinyl methanols, **36**, by this methodology (Scheme 12): the use of *tert*-butyl hydroperoxide (TBHP) in the presence of $Ti(OPr^i)_4$ and diisopropyl tartrate (DIPT) yielded a mixture of regioisomeric epoxides **37** and **38**, in enantiopure form in most cases.[21]

Independently, Honda and coworkers studied the Sharpless epoxidation of a 2-furylmethanol bearing an alkenyl moiety on the side chain, in the search for an enantioselective synthesis of an antibiotic, asperlin (Scheme 13). The titanium-L-(+)-DIPT



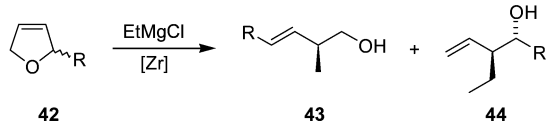
Scheme 12

complex formed matched pairs with the alkenyl double bond of (*R*)-**39** and with the furan double bond of (*S*)-**39**. Starting from racemic **39** resulted in the formation of epoxide **40** and (after rearrangement) pyranone **41** in excellent yields and *ee*.[22]



Scheme 13

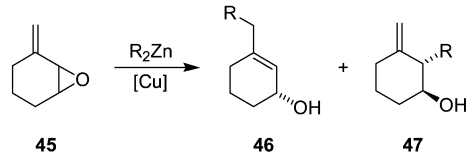
The zirconocene-catalyzed addition of the ethyl Grignard reagent EtMgCl to dihydrofurans **42** took place through a PKR, since both enantiomers found energetically acceptable divergent pathways through which they underwent reaction (Scheme 14). In the presence of a chiral zirconium complex (*S*)-



Scheme 14

42 afforded the primary alcohol **43**, whereas the *R* enantiomer yielded the secondary alcohol **44**.[23]

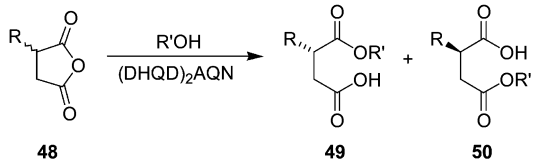
One of the few examples of PKR involving the formation of a C–C bond is the reaction of a vinyloxirane, **45**, with dialkylzinc reagents by using a copper complex of non-racemic phosphoramidite as chiral catalyst (Scheme 15), reported by



Scheme 15

Bertozzi *et al*. Although the use of 0.5 equivalents of the dialkylzinc reagent resulted in a kinetic resolution, treatment of **45** with an excess of this reagent led to complete conversion of the substrate, yielding two regioisomeric alcohols in *ee* as high as 99%: the alcohol (*R*)-**46** was formed *via* a S_N2'-regioselectivity, whereas its regioisomer (*S*)-**47** was formed through a S_N2 mechanism.[24]

A very efficient PKR of racemic monosubstituted succinic anhydrides has been recently accomplished by Chen and Deng using a modified cinchona alkaloid, $(DHQD)_2AQN$ (Scheme 16). A highly selective alcoholysis of several 2-alkyl and 2-aryl



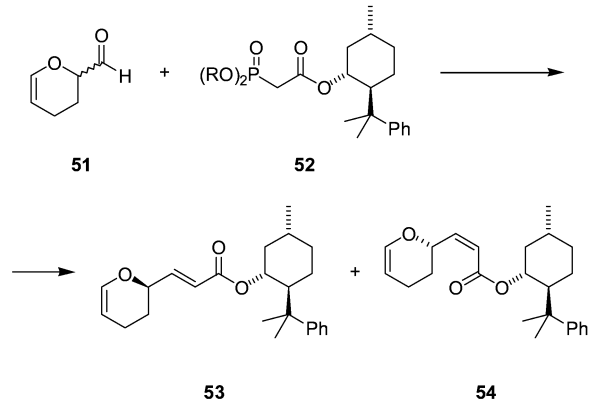
Scheme 16

derivatives, **48**, took place when 2,2,2-trifluoroethanol was used as nucleophile at −24 °C. Other primary alcohols were also tested as nucleophiles, but with more modest enantioselectivities. The hemiesters thus obtained, **49** and **50**, were further transformed into γ-butyrolactones, a versatile and pharmaceutically important class of chiral intermediates.[25]

4 Stereodivergent PKR

This last group of PKR processes will include those which yield geometric isomers (*E* and *Z*), due to the formation of a C–C double bond through an asymmetric Wittig-type reaction, and those in which a new chiral center (of one fixed configuration) is formed in both enantiomers of the molecule, thus generating two different diastereomers.

Rein *et al.* carried out the asymmetric Horner–Wadsworth–Emmons (HWE) reaction of the Diels–Alder acrolein dimer of acrolein, **51**, in an attempt to prepare it in optically active form, of great potential as a synthetic building block because of its aldehyde and enolether functionalities.[26] Although the results obtained using different chiral phosphonates, **52**, clearly show that each enantiomer of the substrate yields one different geometric isomer, **53** and **54**, it must be stated that partial racemization of the substrate must have taken place, allowing for the simultaneous relatively high chemical yield and excellent diastereomeric ratios of each isomer, whose proportion depends on the phosphonate **52** used. Therefore, a combination of dynamic kinetic resolution (DKR)[27] and PKR has very likely occurred (Scheme 17).

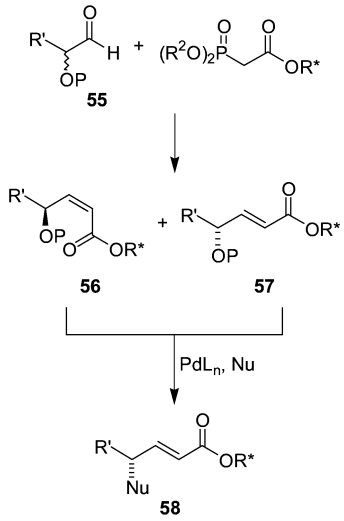


Scheme 17

These authors used a similar approach for the PKR of several α-oxygen-substituted racemic aldehydes, **55**, also transformed by asymmetric HWE reactions into mixtures of α,β-unsaturated esters, **56** and **57**, possessing opposite configurations at their allylic stereocenters, as well as opposite alkene geometry. Subsequently, these isomeric mixtures were subjected to palladium-catalyzed allylic substitution reaction with several nucleophiles in a stereoconvergent fashion: the (*E*)-alkene reacted with retention and the (*Z*)-alkene with inversion of stereochemistry with respect to both the allylic stereocenter and the alkene geometry, yielding a single γ-substituted ester, **58**, in high isomeric purity (Scheme 18).[28]

Another possibility to accomplish a stereodivergent PKR is a process in which a new chiral center is created in one molecule which already possesses a stereogenic centre. If this new stereocenter is created with high stereoselectivity, independently of the configuration of the preexistent one, and the substrate is used in its racemic form, the products thus obtained will be then diastereomers.

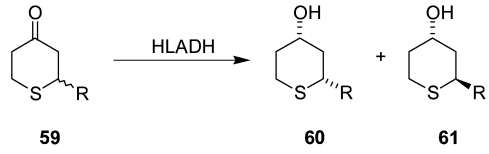
A process that, *a priori*, fulfils these requirements is the reduction of ketones catalyzed by alcohol dehydrogenases. In fact, the empirical rule that predicts the stereochemical outcome



Scheme 18

of this reaction (known as Prelog's rule), takes into account only the size of the two substituents attached to the carbonyl group. It should be emphasized that the ketones must be configurationally stable, otherwise they will be reduced through DKR, as are α-monosubstitued β-keto acid derivatives.[27]

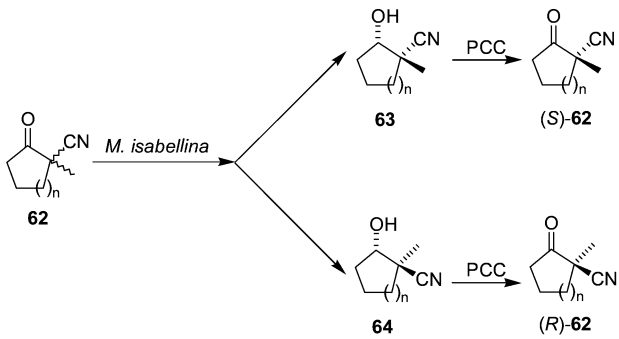
In 1979, Davies and Jones described one of the oldest examples of PKR: reduction of racemic 2-substituted tetrahydrothiopyran-4-ones, **59**, by horse liver alcohol dehydrogenase (HLADH), took place in the same absolute configuration sense to give the corresponding *cis* and *trans* alcohols, **60** and **61** (Scheme 19). Quite surprisingly, reductions were



Scheme 19

only carried out until 50% conversion, thus resulting in low chemical yields of the diastereomeric alcohols (11–29%).[29]

We have recently shown that this methodology can be an efficient approach for the preparation of enantiopure alcohols and ketones containing a quaternary stereocenter. Racemic 1-methyl-2-oxocycloalkanecarbonitriles, **62**, were subjected to bioreduction by the fungus *Mortierella isabellina*, yielding the corresponding hydroxy nitriles as a mixture of diastereomers **63** and **64** (Scheme 20). An interesting feature of this process is the

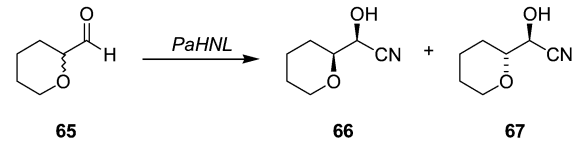


Scheme 20

possibility of recycling, by mild oxidation of the alcohols to the optically active ketone, that can be submitted to a second reduction. This allows an increase of the *ee* of both enantiomers of the ketone (96–>99%). The diastereodivergent PKR was confirmed by independent bioreduction of each enantiomer of the ketone.[30]

Another organic reaction whose stereochemical outcome is well-known is the synthesis of cyanohydrins from aldehydes or ketones catalyzed by hydroxynitrile lyases (HNL). Several of these enzymes have been deeply studied, and depending on the configuration of the product they are classified as (*R*)- and (*S*)-HNL.

Bianchi *et al.* have developed a method for the enzymatic cyanation of racemic oxygenated aldehydes, such as **65** (Scheme 21). Although this reaction proceeds with moderate



Scheme 21

diastereoselectivity, the *ee* of the cyanohydrins formed, **66** and **67**, could be easily increased using the recycling strategy explained above, hydrolysing the cyanohydrins to the optically active aldehydes. An interesting point in this report is the opposite diastereoselectivity shown by two enzymes, from *Prunus amigdalus* (*PaHNL*) and *Hevea brasiliensis* (*HbHNL*), respectively, that would allow the preparation of the four possible stereoisomers.[31]

Independently, Roos and Effenberger studied a similar reaction of racemic aldehydes, also obtaining modest results, as far as stereoselectivity is concerned.[32] Due to the possibility of recycling, together with the extraordinary importance of cyanohydrins as chiral building blocks, new research in this area is expected in the near future.

5 Mathematical treatments of PKR

Apart from the theoretical interest in developing equations that relate the different variables involved in a chemical process, sometimes they are useful for the evaluation of 'how good' such a process is. In enantioselective reactions, most significant ones are chemical yield and enantiomeric purity (usually quantified by *ee*). In PKR the relationship between both is even more important since, as will be shown below, they are inversely dependent: the higher the yield, the lower the *ee*.

In 1966 Guetté and Horeau developed some simple and useful equations that relate the proportion of diastereomers and their optical purity (*ee*) in a transformation of a racemic substrate containing an asymmetric center and a prochiral one.[33] After complete conversion, the following expression can be deduced:

$$ee_x \cdot [x] = ee_y \cdot [y] \quad (1)$$

where *x* and *y* are the diastereomers formed, and [*x*] and [*y*], their concentrations.

It can be easily seen that the diastereomer that is obtained in higher proportion will have the lower *ee*.

If the substrate used is enriched in one enantiomer, eq. 2 can be obtained.

$$ee_x \cdot [x] - ee_y \cdot [y] = ee_o \quad (2)$$

where ee_o is the initial *ee* of the substrate. As expected, it can be simplified to eq. 1 when the initial substrate is racemic (ee_o = 0).

Some years later, Kagan and coworkers extended this study to the case in which only partial conversion is reached. As

suggested by the authors, these new equations can also help to detect inconsistences in experimental data.[34]

Within our ongoing interest in the bioreduction of ketones by microorganisms, we have recently developed some equations that relate the *ee* of the diastereomers of the alcohols obtained with the diastereoselectivity of the reduction of each enantiomer of the ketone. We extended it also to the case in which an enantioenriched ketone is used as substrate. These equations can be easily applied to the cyclic strategy explained above, since the enantioenriched ketone can be obtained by non-selective oxidation of the alcohol obtained in the previous reduction step. Therefore, a prediction of the viability of the iterative process can be made.[35]

6 New applications of PKR

As has been stated in the introduction, by PKR it is possible to obtain much higher *ee* than by classical KR, in processes with similar enantioselectivities. Apart from this initial interest in PKR, in the last years some other applications have appeared in the field of combinatorial chemistry and high-throughput-screening.

Guo *et al.* developed a technique that employs an equimolar mixture of pseudo-enantiomeric 'mass-tagged' chiral acylating agents (*N*-acyl prolines) that differ in a substituent remote from the chiral center, so that the mass of the molecule is correlated to its absolute configuration. The relative amounts of the product esters, measured in this case by ESI-MS, can be used to determine the enantiomeric composition of the starting alcohol.[36]

This method has shown some distinctive features, such as: (a) since only a low level of kinetic resolution is necessary, it is likely that readily available chiral acids can be used; (b) it can be reversed: mass tagged chiral nucleophiles can be used to measure *ee* of acylating agents; (c) no chromatographic separation is needed; (d) it requires little or no purification; and (e) it is rapid, amenable to automation and usable for small amounts of substrate (10 nmol or less).

More recently, Shair and coworkers have adapted the DNA microarray technology to what they have called reaction microarrays: in this case, immobilized amino acids (attached to amine-functionalized glass slides) are subjected to PKR with two pseudo-enantiomeric fluorophores. Upon excitation by an automated laser scanner, the ratio between fluorescent intensities can be converted into *ee* information. Since spot diameters can be smaller than 140 μm, 75000 samples can be arrayed onto a 25 mm × 75 mm slide. Pronounced differences in color enabled also both rapid identification and determination of absolute configuration of samples with high *ee*.[37]

7 Summary and outlook

In this review, we have tried to highlight the diversity of reactions that have undergone PKR to date. The fact must attract the reader's attention that, although the term was coined just five years ago, examples of PKR have appeared in almost all general areas in modern enantioselective synthesis, like oxidation, reduction, acylation, addition and C–C bond formation. It can be presumed that in the future many more examples will be described, in which divergent behaviour of both enantiomers of a racemic mixtures is observed. Finally, some new applications, different from the original attempt to increase the *ee*, have been presented.

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9 References

1 H. B. Kagan and J. C. Fiaud, *Top. Stereochem.*, 1988, **18**, 249–330.
2 C. J. Sih and S.-H. Wu, *Top. Stereochem.*, 1989, **19**, 63–125.
3 J. Eames, *Angew. Chem., Int. Ed.*, 2000, **39**, 885–888.
4 E. Vedejs and X. Chen, *J. Am. Chem. Soc.*, 1997, **119**, 2584–2585.
5 M. Newcomb, J. L. Toner, R. C. Helgeson and D. J. Cram, *J. Am. Chem. Soc.*, 1979, **101**, 4941–4947.
6 The selectivity factor *s* (introduced by Kagan) and the enantiomeric ratio *E* (introduced by Sih) stand for the ratio of pseudo-first order reaction rates of enantiomers. See references 1 and 2.
7 For a definition, see: E. L. Eliel, S. H. Wilen and L. N. Mander, in *Stereochemistry of Organic Compounds*, John Wiley & Sons, New York, 1994, ch. 7, pp. 1205–1206.
8 D. W. Brooks, M. Wilson and M. Webb, *J. Org. Chem.*, 1987, **52**, 2244–2248.
9 K. Königsberger, V. Alphand, R. Furstoss and H. Griengl, *Tetrahedron Lett.*, 1991, **32**, 499–500.
10 M. Mischitz and K. Faber, *Tetrahedron Lett.*, 1994, **35**, 81–84.
11 J. L. L. Rakels, A. G. M. Schneiders, A. J. J. Straathof and J. J. Heijnen, *Biocatalysis Biotransf.*, 1996, **13**, 179–188.
12 V. Gotor, R. Brieva, C. González and F. Rebolledo, *Tetrahedron*, 1991, **47**, 9207–9214.
13 S. Masamune, W. Choy, J. S. Petersen and L. R. Sita, *Angew. Chem., Int. Ed.*, 1985, **24**, 1–30.
14 E. Vedejs and E. Rozners, *J. Am. Chem. Soc.*, 2001, **123**, 2428–2429.
15 A. G. Al-Sehemi, R. S. Atkinson and C. K. Meades, *Chem. Commun.*, 2001, 2684–2685.
16 F. Cardona, S. Valenza, A. Goti and A. Brandi, *Eur. J. Org. Chem.*, 1999, 1319–1323.
17 V. Alphand and R. Furstoss, *J. Org. Chem.*, 1992, **57**, 1306–1309 and references therein.
18 F. Petit and R. Furstoss, *Tetrahedron: Asymmetry*, 1993, **4**, 1341–1352.
19 C. Bolm and G. Schlingloff, *J. Chem. Soc., Chem. Commun.*, 1995, 1247–1248.
20 S. F. Martin, M. R. Spaller, S. Liras and B. Hartmann, *J. Am. Chem. Soc.*, 1994, **116**, 4493–4494.
21 Z.-C. Yang, X.-B. Jiang, Z.-M. Wang and W.-S. Zhou, *J. Chem. Soc., Chem. Commun.*, 1995, 2389–2390.
22 T. Honda, N. Sano and K. Kanai, *Heterocycles*, 1995, **41**, 425–429.
23 M. S. Visser and A. H. Hoveyda, *Tetrahedron*, 1995, **51**, 4383–4394.
24 F. Bertozzi, P. Crotti, F. Macchia, M. Pineschi and B. L. Feringa, *Angew. Chem., Int. Ed.*, 2001, **40**, 930–932.
25 Y. Chen and L. Deng, *J. Am. Chem. Soc.*, 2001, **123**, 11302–11303.
26 T. Rein, N. Kann, R. Kreuder, B. Gangloff and O. Reiser, *Angew. Chem., Int. Ed. Engl.*, 1994, **33**, 556–558.
27 (*a*) F. F. Huerta, A. B. E. Minidis and J.-E. Bäckvall, *Chem. Soc. Rev.*, 2001, **30**, 321–331; (*b*) S. Caddick and K. Jenkins, *Chem. Soc. Rev.*, 1996, **25**, 447–456.
28 T. M. Pedersen, E. L. Hansen, J. Kane, T. Rein, P. Helquist, P.-O. Norrby and D. Tanner, *J. Am. Chem. Soc.*, 2001, **123**, 9738–9742.
29 J. Davies and J. B. Jones, *J. Am. Chem. Soc.*, 1979, **101**, 5405–5410.
30 J. R. Dehli and V. Gotor, *J. Org. Chem.*, 2002, **67**, 1716–1718.
31 P. Bianchi, G. Roda, S. Riva, B. Danieli, A. Zabelinskaja-Mackova and H. Griengl, *Tetrahedron*, 2001, **57**, 2213–2220, and references therein.
32 J. Roos and F. Effenberger, *Tetrahedron: Asymmetry*, 1999, **10**, 2817–2828.
33 J.-P. Guetté and A. Horeau, *Bull. Soc. Chim. Fr.*, 1967, 1747–1752.
34 S. El-Baba, J.-C. Poulin and H. B. Kagan, *Tetrahedron*, 1984, **40**, 4275–4284.
35 J. R. Dehli and V. Gotor, *Arkivoc*, 2002 (V) 196-202 (http://www.arkat-usa.org/ark/journal/2002/MManas/MM-369C/369C.pdf).
36 J. Guo, J. Wu, G. Siuzdak and M. G. Finn, *Angew. Chem., Int. Ed.*, 1999, **38**, 1755–1758.
37 G. A. Korbel, G. Lalic and M. D. Shair, *J. Am. Chem. Soc.*, 2001, **123**, 361–362.