Parallel Kinetic Resolutions

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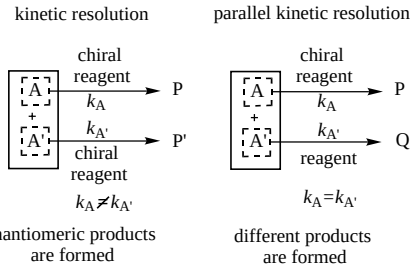
Kinetic resolution of a 50:50 mixture of two enantiomeric substrates (A and A′) with a single chiral reagent to give enantiomerically enriched compounds (P or P′) is well documented.[1] For resolution to occur the reaction rates must be unequal ($k_A \neq k_{A'}$), and for efficiency the reaction must be stopped at some stage before completion. At best, when only one enantiomer reacts, for example, reaction of A and A′ with a chiral reagent gives a maximum of 50% product P (derived from A) and 50% recovered A′, both of which are enantiomerically pure (Scheme 1). For this to occur, the



Scheme 1. Schematic representation of kinetic resolution and parallel kinetic resolution.

selectivity factor s ($k_A/k_{A'}$) needs to be greater than 200.[1] Selectivities such as these are above that for most chemical kinetic resolutions, and even above that of some enzymes, such as lipase esterase.[2] However, problems do arise depending on this inherent difference in selectivity and can have dramatic consequences on the yield and enantiomeric excess of the product P and the recovered substrate A′. This is in part due to the build-up of the less reactive enantiomer—its concentration is much greater than that of the more reactive enantiomer A owing to preferential removal of the latter. As the resolution approaches completion, the two enantiomers react equally due to the balance between this inherent rate and the available concentration.[1]

One way of preventing this concentration effect and the resulting dominance of enantiomer A′ near the end of the resolution is to remove it in parallel during the course of the resolution. Ideally, its rate of reaction is similar to that of the other enantiomer. This has lead to a new strategy termed parallel kinetic resolution[3] (PKR; Scheme 1).

The concept of such a strategy is not new, in fact, the theoretical data[4] have been available for many years. It has been shown that the selectivity factor s can be significantly lower for a parallel resolution than for a traditional kinetic resolution to acheive the same result. For example, an s factor of 49 for a parallel resolution corresponds to an s factor of 200 for traditional a kinetic resolution, where the products are isolated in 49% yield (out of a maximum 50%) and with 96% *ee*.

One of the first examples to illustrate the usefulness of this strategy surfaced in the intramolecular cyclopropanation of racemic secondary allylic diazoacetates (Scheme 2).[5] Treatment of (*rac*)-**1** with the catalyst tetrakis(4*S*-methoxycarbonyl-2-oxyoxazolidinyl)dirhodium(II) ([Rh_2(4*S*-MEOX)$_4$], (*S*)-**2**) gave the tricyclic ketone (1*S*,2*R*,6*S*)-**3** in 40% yield with an enantiomeric excess of 94%. Surprisingly, the fate of the other enantiomer (*R*)-**1** is accounted for by the by-product 2-cyclohexenone (**4**), which was formed by intramolecular hydride abstraction with subsequent ketene loss. Furthermore, it has been shown that the chiral catalyst selectively removes just one enantiomer in the resolution by converting it into the ketone, and consequently the concentration effect is removed. Both enantiomers of the catalyst are available, and thus either enantiomer of the tricyclic ketone **3** can be synthesized efficiently. It is also worthy of note that in the case of a mutual kinetic resolution, using [Rh_2(cap)$_4$] (dirhodium(II)-caprolactamate) as the catalyst, (*rac*)-**1** gives exclusively (1*SR*,2*RS*,6*SR*)-**3** in near perfect yield without formation of the by-product **4** (bottom of Scheme 2), which is due to the complementary recognition.

Another similar example involved the removal of the less reactive enantiomer by employing a stereorandom S_N2 substitution. Mischitz and Faber have shown that basic hydrolysis of the racemic epoxide (*rac*)-**5** occurs with the *Rhodococcus* sp immobilized enzyme (SP 409) to give the diol (*S*)-**6** in 40% yield with a modest enantiomeric excess of 72% (Scheme 3).[6] However, conducting the reaction in the presence of an additional nonnatural nucleophilic azide (N_3^-) increased the *ee* value of this diol to greater than 90%. It appears that this additional nucleophile removes the less reactive enantiomer (*R*)-**5** by a noncatalyzed S_N2 reaction.

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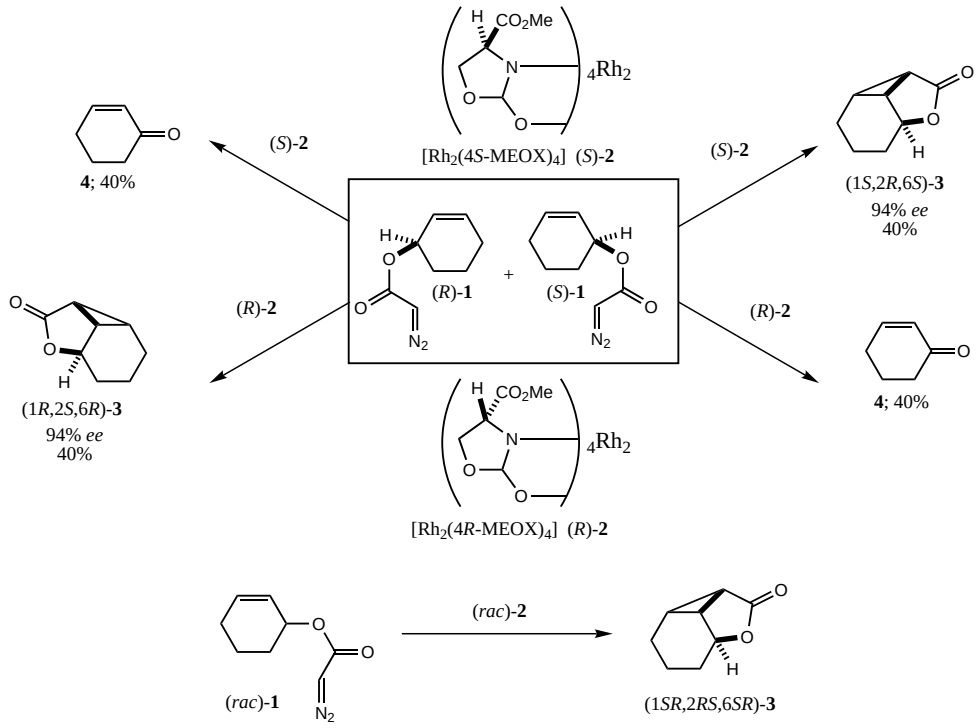
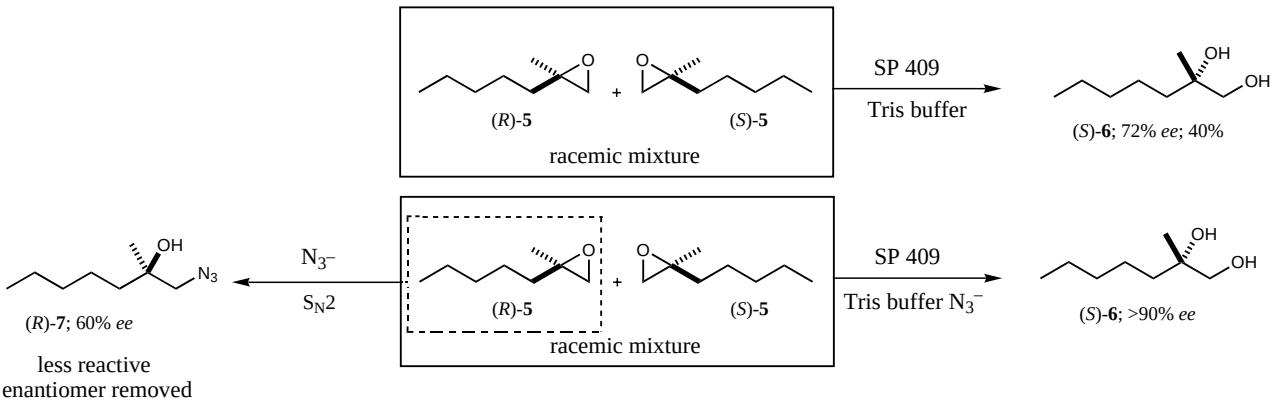


Scheme 2. Intramolecular cyclopropanation of (*rac*)-**1**.

The azide alcohol (*R*)-**7** was isolated with over 60% *ee*. The lower *ee* value for this alcohol is not unusual as the reaction was uncatalyzed and clearly the azide reacts equally with both enantiomers of epoxide **5**, but preferentially with the one present in larger concentration.

In an extension of this strategy Goti, Brandi et al. used the two quasi-enantiomeric dihydropyrans **8** and **9** as complementary reagents to selectively remove both enantiomers simultaneously (Scheme 4).[7] They have shown that with a traditional kinetic resolution procedure the racemic *syn*-dihydroxypyrroline *N*-oxide **10** can be partially resolved by 1,3-dipolar cycloaddition to recover **10** as an enantiomer in either configuration with a modest enantiomeric excess (37–43% *ee*) depending on which dihydropyran is used. In the parallel kinetic resolution, racemic nitrone **10** was treated with a slight excess of **8** and **9**, both of which displayed complementary selectivity and thus afforded two distinct and separable adducts **11** and **13**. Since the two competing reactions have similar rates, the optimum 50:50 substrate ratio was maintained, and therefore the maximum inherent selectivity was preserved throughout. The *exo* adducts **11** and **13** were formed exclusively in the expected 50:50 ratio by "matched" interactions as a result of 1,3-dipolar cycloaddition on the more electon rich bottom face of the dihydropyran. No minor diastereoisomeric adducts were observed, indicating that a near perfect match in relative rates was achieved. These adducts were further converted into quasi-enantiomeric imino-C-diasaccharides.[7]

By far, the most elegant application of this strategy has been developed by Vedejs and Chen with a chiral DMAP acyl transfer reaction.[3] Activation of the quasi-enantiomeric pyridines (*R*)-**15** and (*S*)-**16** with the hindered chloroformates **17** and (+)-fenchyl chloroformate (**18**) gave the acyl transfer agents **19** and **20** (Scheme 5), which have previously been shown to have opposite enantioselectivity. The alkyl substituent of these chloroformates (trichlorobutyl and fenchyl) is very important since it is transferred to the resolved alcohol, and because the substituents are obviously different the chloroformates can be used to enable product separation. The fact that the fenchyl group in **23** is chiral is probably irrelevant to the selectivity. Addition of equimolar amounts (1.1 mol equiv) of the separately formed pyridinium salts **19** and **20**, combined with an excess of $MgBr_2$ and Et_3N, to a solution of racemic 1-(1-naphthyl)ethanol (**21**, 1 mol equiv) gave the mixed carbonates **22** (46% yield, >88% *ee*) and **23** (near



Scheme 3. Basic hydrolysis of (*rac*)-**5** with (bottom) and without (top) additional nonnatural nucleophilic azide (N_3^-). Tris = tris(hydroxymethyl)-aminomethane.

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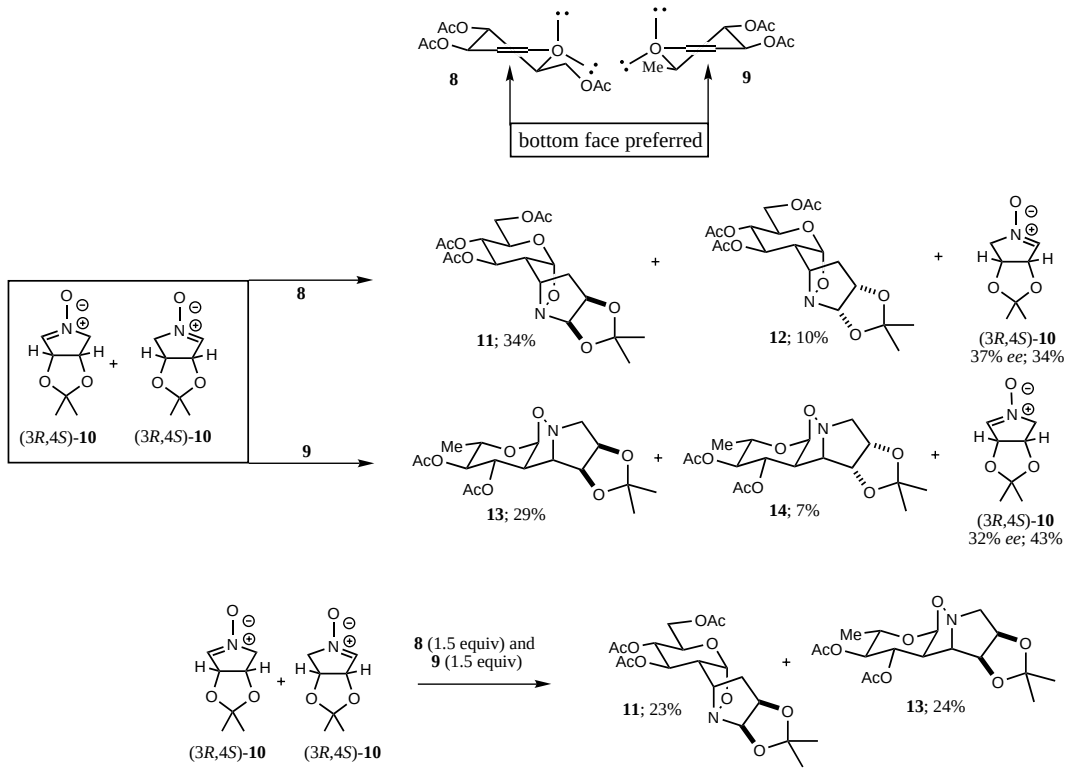
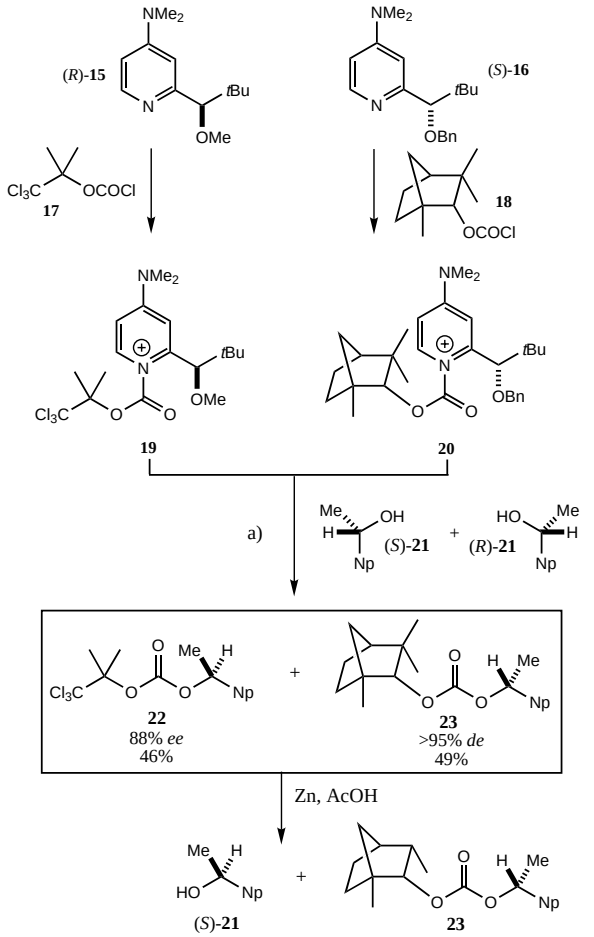


Scheme 4. Use of complementary reagents **8** and **9** for the resolution of **10**.



Scheme 5. a) Et_3N (3 equiv), $MgBr_2$ (2.25 equiv). In the case of **19** only the S enantiomer reacts, and for **20** only the R enantiomer. Np = 1-naphthyl.

perfect 49% yield, 95% *ee*). The separation of the products was made much simpler by treatment of the mixture with Zn in acetic acid (which chemoselectively removed the trichlorobutyl protecting group) to give the more readily separable, resolved alcohol (*S*)-**21** and the fenchyl carbonate **23**. The stereoselectivity was exceptional, and the two mixed carbonates were isolated in near perfect yield and with high enantiomeric excess. These quasi-enantiomeric chiral DMAP equivalents **15** and **16** have furthermore been shown to be fully recyclable.

It is unsurprising that such examples of efficient parallel kinetic resolution are rare—this is primarily due to the infancy of this strategy. It is clear that this resolution procedure is far more efficient than traditional methods at improving the enantiomeric excess of the required product. As a disadvantage, both types of resolutions can only give a maximum yield of 50% for a minimum of two possible products. As an alternative, the overall yield can be improved to 100% by conducting a dynamic kinetic resolution (DKP).[8] This strategy also relies on removal of the less reactive enantiomer—in this case by recycling through racemization—rather than direct derivatization with an additional complementary chiral reagent, as in a parallel kinetic resolution.

From these studies it has been shown that for a successful and efficient parallel kinetic resolution the following guidelines need to be adhered to: 1) derivatization with both complementary chiral reagents has to occur without mutual interference, 2) the two reactions need to occur at a similar rate and have complementary stereocontrol, and 3) the reactions must afford distinct and easily separable products.

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Selective Oxidations of Linear Alkanes with Molecular Oxygen on Molecular Sieve Catalysts—A Breakthrough?

Martin Hartmann* and Stefan Ernst

Hydrocarbons that are oxidized at the terminal, that is, in the α- or 1-, position are important feedstocks for the chemical and pharmaceutical industry. Nevertheless, the selective oxidation of alkanes at their terminal methyl groups is still a challenge in modern catalysis research. It is well known that some enzymes are capable of performing selective terminal oxidations, however, without the necessary stability for use in the conditions employed for pure inorganic catalysts. In principle, selective partial oxidations are easier to control when hydrogen peroxide or organic hydroperoxides (for example, *tert*-butylhydroperoxide) are used as oxygen donors, although from an economic point of view, the use of molecular oxygen, that is, air or O_2, is preferred.

Recently, Thomas and co-workers [1, 2] succeeded in the preparation of a pure inorganic catalyst that allows for the oxidation of *n*-alkanes at the terminal carbon atoms with high selectivity using molecular oxygen in a liquid-phase reaction. These catalysts belong to the group of zeolite-like, crystalline and microporous aluminophosphates, in which small amounts of manganese or cobalt ions are introduced as redox centers into the zeolite framework.[3, 4] Essential for this group of catalysts is the fine tuning of the pore diameter, which enables the terminal C atom of the *n*-alkane to approach the catalytically active site. The especially selective catalysts have the $AlPO_4$-18 (AEI) topology. These are eight-ring molecular sieves with pore openings formed by eight TO_4 tetrahedra (T = Al, P, Co, Mn) and a pore diameter of about 0.38 nm. With such catalysts it seems feasible that the terminal carbon atom of the reactants approach the active site (that is, the transition metal ions in tetrahedral positions) and are oxidized at the end of the hydrocarbon chain to give the respective alcohols, ketones, and carboxylic acids. The catalytic results are explained by an oxidation mechanism involving radical intermediates, whose selectivities are superimposed by shape selectivity, that is, certain products or intermediates are not formed as a result of the restricted space in the zeolite channels or cages.

From mechanistic considerations, oxidation reactions can be divided into three categories: 1) autoxidation via a free-radical chain reaction; 2) oxidation of the substrate coordinated to the metal ion followed by reoxidation of the reduced metal, and 3) catalytic oxygen transfer.[5] The dominance of one of these mechanisms depends on the reaction conditions (gas or liquid phase, reaction temperature, pressure) and especially on the nature of the metal and the oxidizing agent used. Cobalt- and manganese-containing compounds are known to be highly efficient catalysts for the liquid-phase autoxidation via free radicals (mechanism 1) with oxygen as the oxidizing agent. Intermediates along this reaction path are alkoxy and alkylperoxy radicals [Eq. (1 – 6)]:

$$RH + O_2 \longrightarrow R^{\cdot} + HOO^{\cdot} \quad (1)$$

$$R^{\cdot} + O_2 \longrightarrow ROO^{\cdot} \quad (2)$$

$$ROO^{\cdot} + RH \longrightarrow R^{\cdot} + ROOH \quad (3)$$

$$ROOH + Me^{II} \longrightarrow RO^{\cdot} + Me^{III}OH \quad (4)$$

$$ROOH + Me^{III}OH \longrightarrow ROO^{\cdot} + Me^{II} + H_2O \quad (5)$$

$$RO^{\cdot} + RH \longrightarrow R^{\cdot} + ROH \quad (6)$$

The initiation reaction [Eq. (1)] is typically very slow; once formed, the radicals quickly react with dissolved oxygen to form peroxy radicals ($ROO^{\cdot}$) [Eq. (2)]. Such peroxy radicals are stabilized in different ways, for example, by formation of a hydroperoxide [Eq. (3)]. The main role of the metal ions is to catalyze the homolytic decomposition of the intermediate hydroperoxide (ROOH) according to Equations (4) and (5). As a result of this decomposition, metal ions generate chain-initiating radicals, which form alcohols as oxidation products according to Equation (6). Only those metals that exist in two oxidation states with comparable stability are active catalysts for the hydroperoxide decomposition. Besides Cu^{+}/Cu^{2+} and Fe^{2+}/Fe^{3+}, Co^{2+}/Co^{3+} and Mn^{2+}/Mn^{3+} are suitable. Until now,

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