Dutch Resolution: Separation of Enantiomers with Families of Resolving Agents. A Status Report

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Abstract: Dutch Resolution is the term given to the use of mixtures (families) of resolving agents in classical resolutions. In this status report an overview is given of the latest results and new (possible) families of resolving agents are introduced. The concept of families is discussed as well as the factors that come into play on use of families. Practical aspects of Dutch Resolution in particular and resolutions in general are discussed.

Key words: amino alcohols, asymmetric synthesis, chiral auxiliaries, chiral resolution, chirality, camphor, chalcones, sulfonic acids

Introduction

The market for pharmaceuticals vividly illustrates the need for reliable methods for obtaining enantiomerically pure compounds. A recent estimate of the position of single enantiomer drugs in the roughly $410 billion worldwide sale of pharmaceuticals in 2001 was 36% ($147 billion) of total sales. This was up from 34% in 2000 and 32% in 1999[1] and takes no account of the increasing market for applications of single enantiomers in areas such as materials.

If the chiral pool is not, or cannot, be employed, resolution is thought to be the most frequently used alternative industrial method for obtaining single enantiomers[2] although it is difficult to estimate exactly what the balance is between use of chiral pool, asymmetric synthesis, and resolution. Our rough impression based on current business trends is that some 30–50% of the single enantiomers required are obtained by classical resolution procedures. In our view the various approaches to obtaining single enantiomers should be seen as complementary tools in the arsenal of organic synthesis rather than as competitors for preeminence. Improvements in the trustworthiness, speed and predictability of all methods are highly desirable. In this article we will deal with some new developments with regard to resolutions by diastereomeric salt formation.

Improvements in optical resolution strategies are important not only for industrial applications but also for reasons of pure science; understanding the intricacies of transition from solution to solid phase with involvement of the most intricate stereochemical considerations forms a magnificent scientific challenge.

In 1998, an article 'The Family Approach to the Resolution of Racemates' was published.[3] This unusual title refers to the use of *mixtures* of resolving agents. The use of mixtures that were families was most effective. A family was defined as follows: 'The members of a family in general bear strong structural similarity and are stereochemically homogeneous (homochirality among family members and enantiomeric purity of the components)'. In general three (sometimes two) family members are used in a resolution. Such resolutions, chiefly of acids and bases, proceed rapidly and diastereomeric excesses in the precipitated salts are usually high. These salts almost always contain a mixture of the family of resolving agents. The ratios reflect to some extent the solubilities of the diastereomeric salts of the resolving agents used, although obvious relationships are absent. Success rates, defined for the moment as the chance of obtaining solid salts with significant diastereomeric excesses, were significantly higher, 90–95%, than the 20–30% estimated for classical resolutions.[4]

Although the method was first referred to as the 'Family Approach' this term has been more or less supplanted by the name 'Dutch Resolution', later introduced for marketing purposes. Although chemically less graphic, this name seems to have captured the imagination even more.

The idea of using mixtures runs contrary to chemical intuition and certainly makes the traditionalists among us uneasy. However, the deliberate use of mixtures is nowadays more palatable in view of both of the approaches used in combinatorial chemistry as well as the extensive work on non-linear effects in enantioselective reactions wherein enantiomerically non-pure compounds are deliberately employed.[5]

Dutch Resolution[3] certainly has something of combinatorial chemistry in it, except that in combinatorial chemistry a common presumption is that the chemical characteristics of reactants are not influenced seriously by companion reactants of similar structure. The influences that must occur between the family members in Dutch Resolution are also seemingly grounded in concepts different than those involved in non-linear effects.[5,6]

There are not that many families of resolving agents. Commonly used compounds such as quinine, brucine,

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camphor sulfonic acid and bromocamphor sulfonic acid tend to be one of a kind. Although small structural modifications might be introduced into such structures the difficulty thereof and attendant costs do not encourage this although there are exceptions (see later). Our own entry into the concept of families was via the cyclic phosphoric acids **1** developed by ten Hoeve and Wynberg.[7] Various substituted derivatives of **1** (Scheme 1) were available in the laboratory. The step to use of a mixture was therefore technically easy.

'P mix' in the nomenclature of reference 3 is a mixture of **1a**–**c**. A wide variety of substituted aldehydes can readily be used in the Cannizzaro reaction leading to the 1,3-diol precursors and then the phosphoric acids. The original P mix did not include the 2-nitro derivative **1d** shown in Scheme 1. This compound (see later) has subsequently been shown to be quite important. Many other derivatives obviously can be prepared. Resolution procedures for the cyclic phosphoric acids have been described.[7]

In this article we will go deeper into the concept of families. The definitions are in general heuristic although theoretical insight is increasing gradually. Attention will be paid to the new families of resolving agents. We will also go into practical aspects of Dutch Resolution. Finally we will discuss briefly a 'reverse' approach to Dutch Resolution, in which a 'family' of racemates is resolved. This phenomenon might have rather broad implications.

Biographical Sketches

Prof. Kellogg, who for many years was employed at the University of Groningen, is Chief Financial Officer of Syncom BV. He is an American citizen. He has been active in many different research areas including bio-organic chemistry and supramolecular chemistry.

Dr. Nieuwenhuijzen recently obtained her PhD under direction of Prof. Kellogg. She has contributed fundamentally to the practice and theory of Dutch Resolution.

Dr. Pouwer obtained his PhD degree with Prof. Wynberg at the University of Groningen and is a section leader at Syncom BV.

Dr. Broxterman is Senior Scientist at DSM Research and obtained his PhD degree with Prof. Hogeveen at the University of Groningen.

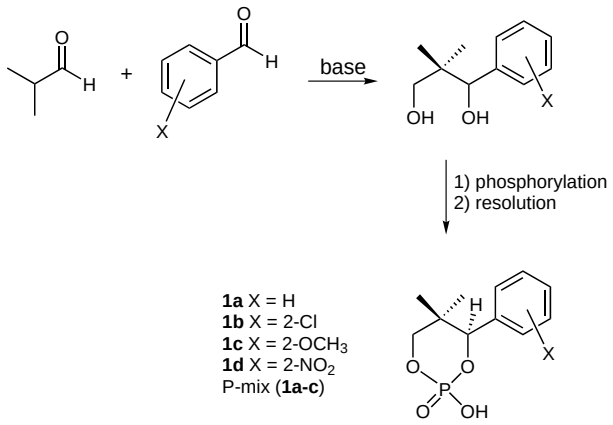
Dr. Kaptein is a scientist at DSM Research and obtained his PhD degree at the University of Groningen with Prof. Kellogg

Miss de Wever and **Miss Zwaagstra** are chemists at Syncom BV.

Dr. Vries is General Director of Syncom BV and is the discoverer of Dutch Resolution. He obtained his PhD degree at the University of Groningen under the direction of Prof. Wynberg.

Dr. Grimbergen is associated with the Centre for Particle Technology at DSM Research and obtained his PhD degree with Prof. Bennema in Nijmegen.

Dr. La Crois obtained his PhD degree with Prof. B. L. Feringa at the University of Groningen and **Dr. van der Laan** obtained his PhD with Prof. J. H. van Boom at the University of Leiden. Both are research chemists at Syncom BV.



Scheme 1 Synthesis of cyclic phosphoric acids

The methods leading to family **1a**–**d** are characteristic of what one desires, namely that the synthetic approach is not overly difficult and amenable to the preparation of derivatives, that starting materials are not exceptionally expensive and available and that the reactions can readily be run on a reasonable scale. We have carried out several of the syntheses described here on a kilogram scale. One should note, however, that in this procedure racemates are prepared and that each racemate must be resolved. A resolution procedure that works for one compound need not necessarily work for another of seemingly closely related structure, despite suggestions to the contrary.[8] In our experience, however, resolution is a fairly routine operation although each resolution has to be optimized.

Other families that have been used on a regular basis are, to use the abbreviations given in ref 3, M mix (**2a**–**c**), T mix (**3a**–**c**), PE-I mix (**4a**–**c**), PE-II mix (**5a**–**c**), PE-III mix (**6a**–**c**), PG mix (**7a**–**c**) and PGA mix (**8a**–**c**) as shown in Figure 1. In most cases the enantiomeric forms of the structures illustrated are also available.

The structural similarities of the members of the families are obvious. 'Cross mixing', for example a member of T-mix with M-mix, has not been successful in our experience. Except for PE-III in which alkyl groups are varied, family differences have been achieved by substitution on aromatic rings. The substituents chosen were based initially simply on what was available or could be readily synthesized. Recent insights (see later) suggest that, as luck would have it, more difficultly accessible substituents may be even more effective.[9]

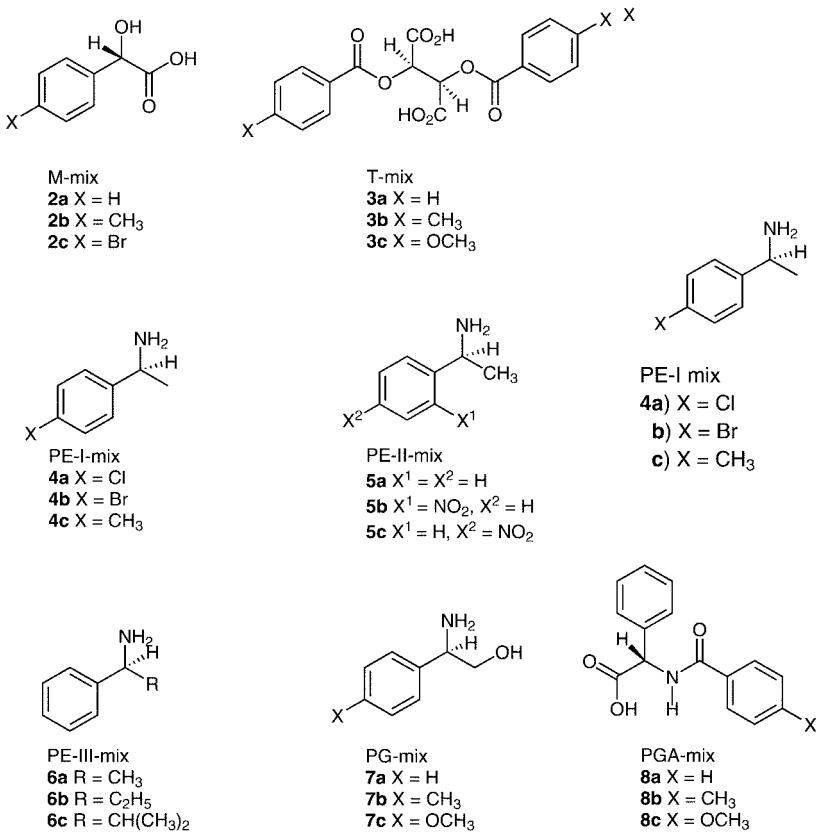


Figure 1 Families of resolving agents

There are essentially two approaches to the synthesis of families of resolving agents: either prepare each member of a family as the racemate and then resolve as described above for the cyclic phosphoric acids. It will be necessary to do this on the fairly large scale required for practical application. The other approach is to prepare each family member as a pure enantiomer by enantioselective synthesis. Combinations of these approaches might in certain cases be possible; certain members might be readily available via enantioselective synthesis and others not.

It is easy to underestimate the amount of effort involved. In general the choice falls on fairly simple structures. On paper synthetic schemes often appear straightforward and not excessively challenging. One reason to desire simplicity is that in general reasonably large amounts are required if a resolving agent could ever be considered for an industrial application. Consideration of costs and labor, certainly in an industrial setting, is necessary. We do not claim that the approaches we describe in the following paragraphs are unique; the choices have usually been dictated by our own evaluation of practical considerations.

An example of the enantioselective approach is the condensation of camphor sulfonic acid **9**, a popular commercial resolving agent, with (substituted) benzaldehydes (Scheme 2). These condensation products **10** have been described in the patent literature[10] and are used as sunscreens. We are unaware of descriptions of the use of these materials as resolving agents.

The reader will immediately recognize a limitation, namely that in principle only a single enantiomer is available. The configuration around the benzylidene double bond is *E* as established by 2D-NMR. The pure materials are highly crystalline. Resolutions of amines can be carried out with these materials although the high crystallinity sometimes complicates obtaining the salts.

Hydrogenation of the double bonds in **10** leads to benzyl substituted camphor sulfonates. These in our experience unfortunately do not readily provide crystalline salts with amines.

Bromocamphor-10-sulfonic acid **11** is also used commercially but lends itself less readily to functionalization. The prototype chiral sulfonic acid is probably 1-phenylethanesulfonic acid **12** and derivatives thereof (Figure 2).

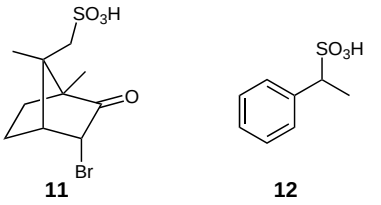
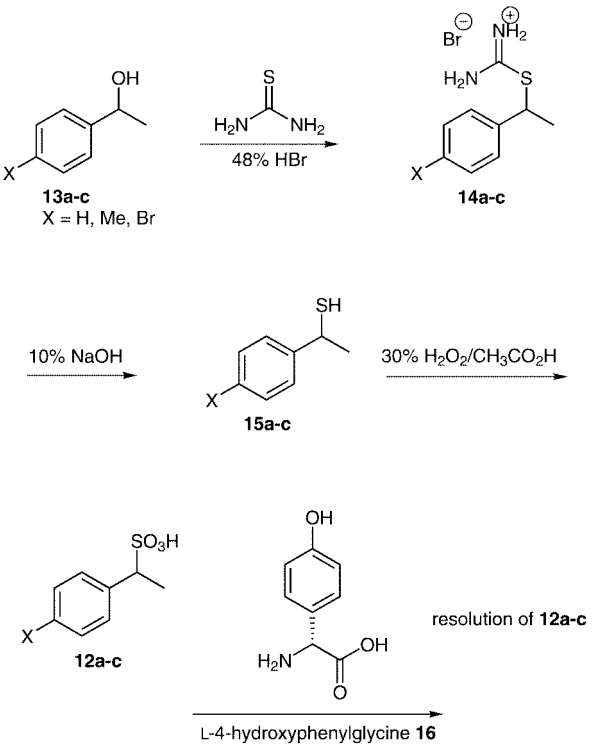


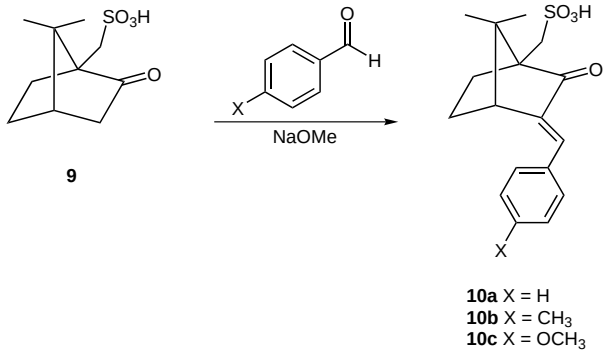
Figure 2 Bromo camphor sulfonic acid **11** and 1-phenylethane sulfonic acid **12**

The synthesis of the racemic sodium salt of 1-phenylethanesulfonic acid **12a** from the reaction of sodium sulfite with 1-phenylethyl chloride was described more than 100 years ago.[11] In our hands this reaction is not readily reproducible although others[11b–d] describe the successful use of the procedure. An enantioselective synthesis of **12a** has been described.[12] Although this approach is elegant we did not consider it for the preparation of a family because of the costs of the procedure as well as doubts about whether it would be reliable for the preparation of derivatives (we have not examined whether this is so) or could be used on a larger scale.

The simple cost-effective alternative we use for the preparation of racemic **12** and derivatives thereof is shown in Scheme 3.



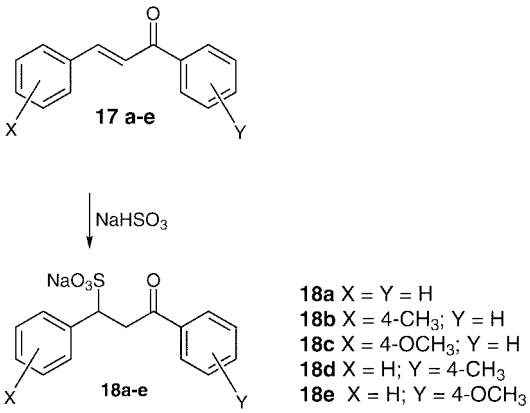
Scheme 3 Synthesis of 1-phenylethanesulfonic acid **12**



Scheme 2 Condensation of benzaldehydes with camphor sulfonic acid **9**

Overall yields starting from the appropriate acetophenone, which is reduced with $NaBH_4$ to the alcohol **13**, on a 0.1 mol scale are 56–85%. The alcohol **13** is subsequently converted to the thiourea salt **14**, which is hydrolyzed with NaOH to the corresponding thiol **15**. Although the oxidations with H_2O_2 need to be done with care, in our experience this procedure for the conversion of thiol **15** to sulfonic acid **12** is trustworthy and better than oxidation with heavy metals. The preparation of **12a** has been carried out in 61% yield on an 8.6 mol scale. Resolutions of **12a**–**c** can be carried out with L-4-hydroxyphenyl glycine **16** as described for **12a** itself.[13] This resolution provides the (*S*)-enantiomer of **12a**.

The addition products **18** of $NaHSO_3$ to α,β-unsaturated ketones **17** represent another, extremely easy to obtain, class of racemic sulfonic acids (Scheme 4). These sulfonic acids were first described by Knoevenagel[14] and later in detail by Pfoertner[15,16] although there have been to our knowledge no reports of the resolution of these materials.



Scheme 4 Addition of sodium bisulfite to chalcones **17a**–**e**

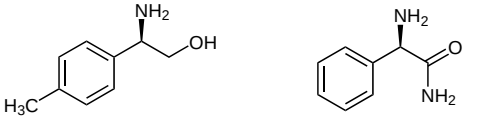
The procedure as described by Pfoertner[15] allows use of substituted benzaldehydes and substituted acetophenones for the syntheses of the required chalcones **17**. The reactions are performed in general at high concentration (roughly 1.4 M) and the products (**17a**–**e**) crystallize from the reaction mixture. Several other substituents were used (not shown here) and the reaction proceeds equally well. For cases where ortho- or meta-substituents are present the products do not crystallize from the reaction mixture, but can be obtained via normal extraction procedures.

These chalcones react smoothly with $NaHSO_3$ at reflux temperatures in EtOH–H_2O. Again the products (**18a**–**e**) crystallize from the reaction mixture as sodium salts except for cases where ortho- or meta-substituents are present in which case the solutions must be concentrated to induce crystallization. These reactions have been carried out without problems on a 1 kg scale.

Resolution of sulfonic acid **18a** was first investigated. Frustration grew rapidly as we found that the use of resolving agents and families of resolving agents were not effective and that ephedrine, dehydroabiethylamine, quinidine, quinine, D-4-hydroxyphenylglycine **16**, and L-cysteine were also ineffective as resolving agents. Salts were readily formed but these in all cases had virtually no diastereomeric excess (although the yields were <50%). We discovered, however, that (*R*)-4-methylphenylglycinol **19** (Figure 3), derived from reduction of (*R*)-4-methylphenylglycine, was an effective resolving agent for **18b** and **18c**. An interesting observation is that **18a**–**c** can be resolved simultaneously as a mixture. After recrystallization the enantiomeric excesses are, respectively 90%, 98%, and 96% in a 1:10:4 mixture obtained on resolution with **19** as is shown in Table 1.

Table 1 Resolution of Mixtures of Sulfonates **18**

Entry	Racemate	ee H/Me/OMe	Ratio H/Me/OMe	ee H/Me/OMe after rec.	Ratio H/Me/OMe after rec.
1	**18b**	67	–	99	–
2	**18a**:**18b**, 1:1	79/86	1:1.3	99+/99+	1:2.7
3	**18a**:**18b**:**18c**, 1:1:1	19/79/27	1:5:5	90/98/96	1:10:4



19 **20**

Figure 3 (*R*)-4-methylphenylglycinol **19** and D-phenylglycinamide **20**

Resolutions are best carried out in a 1:1 mixture of *i*-propanol and 10% HCl. The resolution of mixtures of racemates is an obvious extension of Dutch Resolution itself.

Compound **18a** under basic conditions undergoes a retro-Michael reaction with concomitant decomposition/racemization. However, **18a** and other sulfonic acids are entirely stable under neutral or acidic conditions. The salts formed with amines under resolution conditions are also stable and we have never observed racemization of **18a** or other sulfonic acids.

Crystals of **18a** and **18b** with **19** were suitable for X-ray crystallography. In the unit cell three components are present: the sulfonate (**18a** or **18b**), compound **19** and one molecule of water. A crystal structure is shown (Figure 4) which contains 17% **18a** and 83% **18b**. A layered structure is formed (Figure 5), in which the phenyl rings of **18** and **19** are nicely stacked. Several hydrogen bonds are formed; some of them with a water crystal.

Sulfonic acids **18d** and **18e** substituted at the Y position in our experience can be resolved with a somewhat unusual resolving agent, D-phenylglycinamide **20**, which recently became available in large quantities (Figure 3). Simultaneous resolution of a mixture of sulfonic acids was often

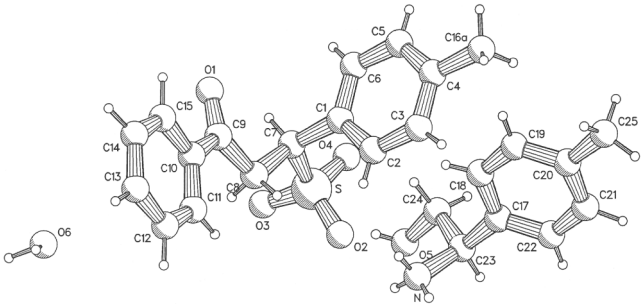


Figure 4 Crystal structure of **18a**+**18b**/**19** with **18a**:**18b**, 17:83

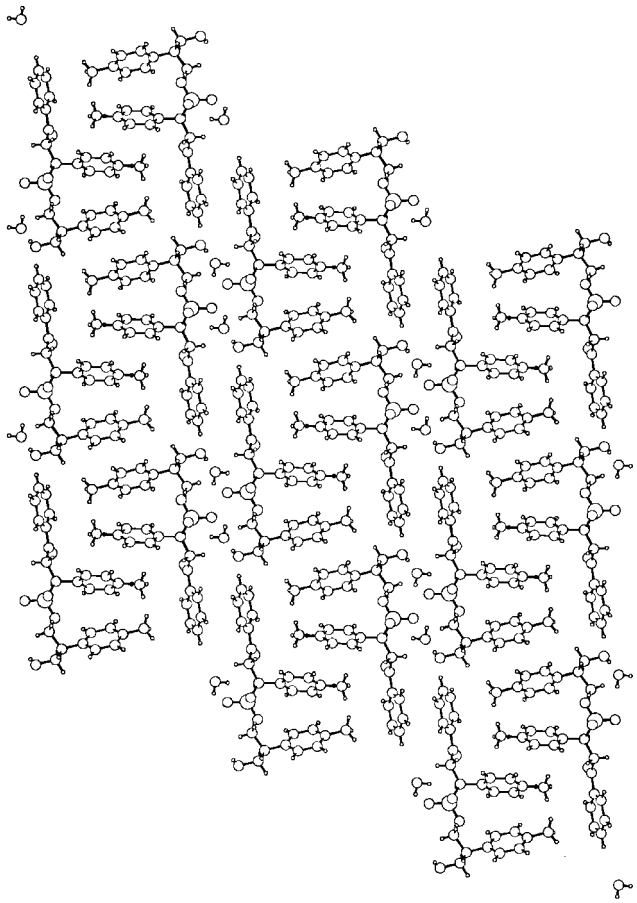
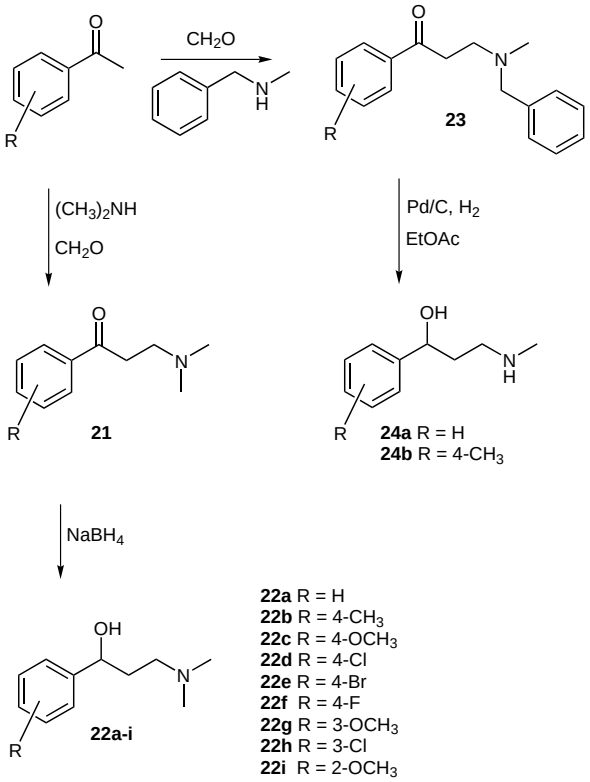


Figure 5 Stacking plot of **18a**+**18b**/**19** with **18a**:**18b**, 17:83

very effective whereas resolution of the racemates separately proceeded poorly. In a Dutch Resolution approach mixtures of resolving agents are used hence a separation of the individual enantiomers is not necessary.

A number of derivatives of **18** were prepared in which *tert*-butyl, cyclohexyl of naphthyl groups replaced the aromatic rings. It was observed that for the aliphatic groups, no salts could be formed with a number of resolving agents that were tested including **19** and **20**. Only the compounds with one naphthyl group were able to form salts. This supports the idea that π-stacking is important, as was also shown in the crystal structures.

The Mannich reaction is well suited for the preparation of racemic families of amino alcohols as shown in Scheme 5.

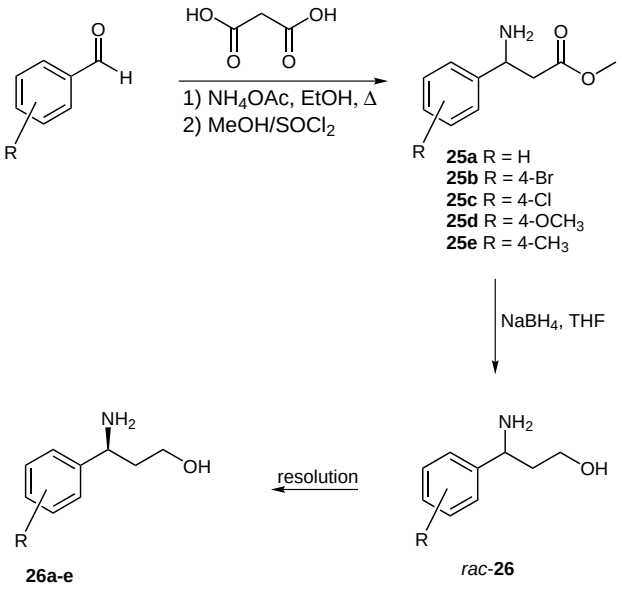


Scheme 5 Mannich approach to amino alcohols **22** and **24**

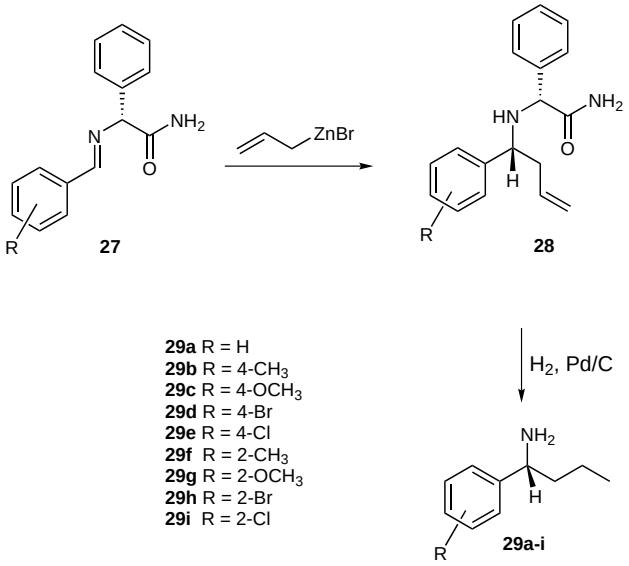
Reaction of (substituted) acetophenones with dimethylamine and formaldehyde furnishes ketoamines **21**, which can be reduced to the dimethylamino alcohols **22** with sodium borohydride. Alternatively, the Mannich reaction can be performed with methylbenzylamine, followed by a reduction giving in one step the monomethyl alcohols **24**. Individual members of family **22** can be readily resolved with mandelic acid. Compound **24a** and **24b** can be resolved with phosphoric acid **1a** in high resolution efficiencies. Asymmetric (transfer) hydrogenation might be used to prepare some of these derivatives.[17]

Another very simple approach to new racemic amines is shown in Scheme 6. Condensation of malonic acid with substituted benzaldehydes in the presence of an ammonia source gives β-amino acids, which are converted to the esters **25**. These esters are readily resolved with, for example, **1c** or tartaric acid. As example the first crystals of **25b** and **1c** are obtained in 89% diastereomeric excess (S = 0.88) on use of isopropanol as solvent. Reduction delivers 1,3-amino alcohols **26**. One can resolve the racemic alcohols; for example **26d** can be resolved with M-mix (Figure 1) and the first salt is obtained in a diastereomeric excess of 92% (S = 0.40) in isopropanol. The ability of **25** and **26** to act as families remains to be examined.

A highly promising diastereoselective route to chiral amines is shown in Scheme 7.



Scheme 6 Synthesis of amino esters **25** and amino alcohols **26**



Scheme 7 Diastereoselective allylzinc additions to imines of (*R*)-phenylglycinamide **27**

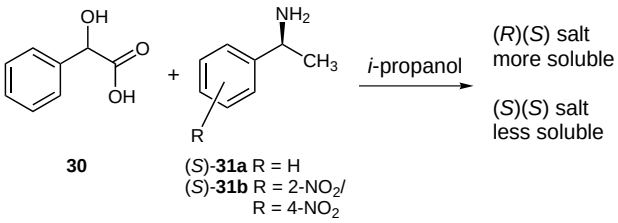
The route shown in Scheme 7 begins with the highly diastereoselective addition of allylzinc bromide to imines **27** of (*R*)-phenylglycine amide **20**.[18] Removal of the chiral auxiliary from addition product **28** to provide enantiomerically pure amines **29** may be performed without complications on a multigram scale. Resolutions of acids with these materials are under investigation and initial results are promising.[19]

What Constitutes a Family?

The families that have been used so far differ in general only in the nature of substituent on an aryl ring. All components of families that we use are enantiomerically pure. Little success has been achieved with the use of enantiomerically enriched materials although this point has not been investigated in exhaustive detail.

On the use of a family – normally three family members are used in a 1:1:1 molar ratio – the first salt obtained nearly always contains a mixture of resolving agents. The ratio is usually skewed in non-stoichiometric fashion in favor of one of the resolving agents. In a number of cases one of the three resolving agents was not, or only barely, incorporated although it was clear to us that the resolutions proceeded better in the presence of this non (or poorly) incorporated material. Nitro substituents seem to be particularly effective although not unique in their effects: halo and alkyl substituents can also be active. However, the number of examples is limited and at this stage general conclusions are risky.

Further investigation has led to the discovery that the poorly incorporated resolving agents can be effective nucleation inhibitors.[9] The case studied in most detail so far is the resolution of mandelic acid **30** with phenylethylamine **31a**. A 1:1 mixture **31b** of the 2- and 4-nitro derivatives (this easy to prepare mixture is also used for commercial purposes) was used as an additive (Scheme 8).



Scheme 8 Resolution of **30** with **31a** in the presence of **31b**

With the aid of turbidity measurements it was established that this mixture of nitro derivatives functioned as an effective nucleation inhibitor. For both diastereomers nucleation inhibition is observed, whereas the dissolution temperatures remain more or less identical.

In passing we note that in order to compare resolution efficiencies, resolutions need to be carried out under comparable conditions. In practice this requires identical starting concentrations and resolution under temperature-controlled conditions. For small scale and scouting work this is achieved in a programmable bath fitted with a thermostat. Our procedure is as follows: once a clear solution is obtained in a Kimble test tube with a diameter of 25 mm and height of 150 mm this is covered and placed in the programmable bath. The stirring speed is 900 rpm using a 1 cm magnetic stirring bar. The temperature program is started at, for example, 65 °C with a cooling rate of 0.1 °C per min to 20 °C. These details are given as an example of

the care that must be taken, in our experience, to achieve reproducibility.

At 0.25M in isopropanol, compound **30** with an equivalent amount of **31a** provides salt with a diastereomeric excess (de) of 14% and S factor 0.19, where S = 2 × ee × yield.[20] The S factor for a perfect resolution (50% yield based on racemate, 100% enantiomeric excess) is thus 1. When the resolution is carried out at the same concentration and under the same temperature conditions with 0.9 equivalents of **31a** and 0.1 equivalents of **31b** the first salt is obtained with a *de* of 55% and an S factor of 0.41. No detectable amount of **31b**, which is visible to the naked eye owing to its yellow color, is incorporated into the salt.[9]

This improvement may seem marginal. Numerous cases have been studied, however, and effects are sometimes spectacular. For example, in an experiment carried out under controlled conditions as described above, resolution of 1-(2-chlorophenyl)ethyl amine (not shown) with **1a** gave salt with 22% de (S factor 0.26). Addition of **1d** as nucleation inhibitor to **1a** led to 86% de (S factor 0.62). In some cases, particularly with 2-nitro substituted resolving agents, the nucleation inhibitor is not even incorporated in detectable amounts in the first salt. An ideal resolution would be based on two resolving agents, one in great excess, and the other only present in small amounts. If the minor component acts as nucleation inhibitor and is not incorporated one obtains a pure salt, which on neutralization affords only a single resolving agent. This is particularly attractive when recycling is desired.

Practical Aspects of Dutch Resolution in Particular and Resolutions in General

We will concentrate here only on those aspects that in our experience have been essential for practical success.

Since the initial discovery of Dutch Resolution in 1996 around 1000 resolutions of racemic acids and bases have been carried out for clients. Obviously most of these 1000 different structures fall under client confidentiality. Dutch Resolution has been used on a regular basis in the screening of these resolutions. The overall success rate for achieving resolution is greater than 95%. The technique of Dutch Resolution has obviously played a large role in this success. In addition, however, another factor deserves to be mentioned, namely the human component, 'Fingerspitzengefühl', to express it in German, is important.

From the technical side chiral HPLC facilities are essential to aid in the rapid determination of enantiomeric excesses of new racemates submitted for resolution. To work effectively one must be able to evaluate quickly the effectiveness of a resolving agent. Each compound requires its own HPLC conditions and this continual challenge must be taken seriously. HPLC is for us by far the most general and accurate method with which to determine enantiomeric excesses. Chiral GC is, of course, entirely suitable for compounds of sufficient volatility. Salts are in general better handled by chiral HPLC. Further backup is given by differential scanning calorimetry (DSC), which is indispensable for analysis of melting behavior.

Although it may seem a trivial aspect, the presence in the laboratory of all common resolving agents as well as the common mixes for Dutch Resolution together with familiarity with their solubility and crystallization behavior are indispensable for the achievement of speedy and secure resolutions.

In our experience, for the first screening of a new resolution, a stoichiometry of 1:1 is convenient, in other words 1 molar equivalent of resolving agent, which is a mixture in the case of Dutch Resolution, and 1 molar equivalent of racemate. We prefer in general to use reasonably polar solvents, which can be readily removed by a rotary evaporator. Acetone, methyl ethyl ketone, isopropanol, ethanol, and methanol, sometimes as mixtures with H_2O, are popular solvents. Toluene is used on occasion. If quantitative or semi-quantitative comparisons are required, we find it convenient to carry out the resolutions in tubes, which are placed in a temperature programmable bath. The temperature is then lowered at a set rate. The temperature at which crystallization occurs can be carefully monitored. This technique has been very useful for determination of the effectiveness of new families of resolving agents.

For the optimization of resolutions in principle 0.5 equivalents of resolving agent should suffice if only the less soluble combination of resolving agent and enantiomer of the racemate crystallize A concomitant advantage of the use of less than one molar equivalent of resolving agent is the fact that also the more soluble diastereomer is less supersaturated, and thus less likely to crystallize. Resolutions including Dutch Resolution can be optimized with respect to the amount of resolving agent used. The resolution efficiency is readily followed by calculation of the S-factor.[20]

In the Peachey and Pope variant, 0.5 equivalent of the resolving agent is supplemented with an achiral acid or base (depending on whether the resolving agent is acidic or basic).[21] In this way, a neutral system is obtained.

An integral part of optimization experiments is exploration of the effects of concentration and temperature. In general the lower the concentration the higher the enantiomeric excess. Unfortunately this boon is often swiftly negated by lower yields. For larger scale commercial applications the construction of phase diagrams is essential for analysis and optimization of crystallization behavior. Excellent discussions of phase diagrams are available.[6b,d] Since the solubility of a diastereomer is in general dependent on the temperature, it is possible that the resolution efficiency could also be temperature dependent. In principle, it would be best to screen a resolution at different temperatures, especially when a low resolution efficiency is obtained after filtration at room temperature.

The effects of nucleation inhibition have already been discussed. We anticipate that the discovery and use of 'designer nucleation inhibitors' will in the future lead in many cases to improved resolutions. A rough strategy for the discovery of such inhibitors based on extrapolation of the principles of Dutch Resolution has been presented.

Reverse Resolution

In addition to the resolution of a racemate with a family of resolving agents also a family of racemates might be resolved with a (family of) resolving agent(s). An illustrative example is the resolution of alaninol in methyl ethyl ketone (MEK) as solvent. This resolution is very difficult with mandelic acid (or any other resolving agent). Aminobutanol on the other hand is resolved very effectively with mandelic acid. We were pleased to observe that a *mixture* of both amino alcohols is readily resolved with mandelic acid. Amino butanol as well as alaninol is obtained in high ee. In this case, however, a mixture of both amino alcohols is obtained.

Pure alaninol can be obtained when using optically pure aminobutanol (forming the more-soluble salt with mandelic acid) as additive, instead of racemic aminobutanol or optically pure aminobutanol forming the less-soluble mandelic acid salt (normal Dutch Resolution addition strategy).

From a clear mixture of (+)-2-amino-1-butanol (1 equiv), racemic alaninol (2 equiv) and *R*(–)-mandelic acid in 2-butanone, (–)-alaninol/(*R*)-(–)-mandelic acid crystals with an ee of 99% and an aminobutanol content <2% in a recovery yield of 73% is obtained (after 1 recrystallization) (Table 2).

We refer to this approach as reverse Dutch Resolution. Most likely nucleation inhibition also plays a role here. More details of this system will be described in a separate publication.[22]

Table 2 Reverse Resolution

Aminobutanol	Alaninol	Mandelic acid	Solvent	Yield	Alaninol content	ee (of alaninol)
(+) 33.3 mmol	rac 66.6 mmol	*R*(-)100 mmol	MEK 1000 ml	23.7%	>98%	94%
recrystallization			MEK 180 ml	86.4%	>98%	98.9% (–)

Starting materials were commercially available and were used without further purification. Melting points were determined on a Mettler Toledo DSC-822[e] apparatus with a heating rate of 10 °C/min in standard aluminum crucibles. ^{1}H NMR spectra were recorded on a Varian Gemini-200 spectrometer (at 200 MHz) at ambient temperature. ^{13}C NMR spectra were recorded on a varian Gemini-200 (at 50.3 MHz). Chemical shifts are denoted in δ (ppm) referenced to the residual protic solvent peaks. Coupling constants *J*, are denoted in Hz. High resolution mass spectra were recorded on an AEI-MS-902 mass spectrometer. To ensure accurate ee determination, racemic mixtures were always measured first. Optical rotations were recorded on a Perkin Elmer 241 polarimeter.

Phosphoric Acids 1a–d

The synthesis of these cyclic phosphoric acids is fully described in the literature.[7a]

Synthesis of Benzylidene Camphorsulfonates 10a–c[10a–c]

A mixture of camphor sulfonic acid (**9**) (0.08 mol) and NaOMe (0.8 mol, 10 equiv) was refluxed in toluene (400 mL) for 1 h. After cooling somewhat, benzaldehyde was added (0.08 mol) and the reaction mixture was heated to reflux for 3 h. The mixture was allowed to cool to r.t overnight. H_2O (100 mL) was added and after stirring for 30 min the precipitate, which formed, was removed by filtration. The crude product was recrystallized from H_2O.

Sodium 3-Benzylidene Camphorsulfonate (10a)

Yield: 35% after recrystallization from H_2O; mp 173.3–176.9°C.

^{1}H NMR (DMSO-d_6): δ = 0.72 (s, 3 H), 1.12 (s, 3 H), 1.43 (m, 2 H), 2.17 (m, 1 H), 2.51 (m, 1 H), 2.80 (m, 1 H), 3.00 (m, 2 H), 3.35 (s, 3 H), 7.00 (s, 1 H), 7.39 (m, 3 H), 7.55 (d, 2 H).

^{13}C NMR (DMSO-d_6): δ = 21.5 (q), 22.7 (q), 27.6 (t), 33.0 (s), 49.2 (t), 50.8 (d), 52.5 (s), 60.0 (t), 129.2 (d), 130.8 (d), 131.4 (d), 131.5 (d), 132.2 (d), 137.5 (s), 144.2 (s), 208.2 (s).

Sodium 3-(4-Methylbenzylidene) Camphorsulfonate (10b)

Yield: 73% after recrystallization from water; mp 171.2–173.3 °C.

^{1}H NMR (DMSO-d_6): δ = 0.67 (s, 3 H), 1.08 (s, 3 H), 1.36 (m, 2 H), 2.18 (m, 2 H), 2.30 (s, 3 H), 2.97 (m, 1 H), 3.11 (m, 2 H), 7.03 (s, 1 H), 7.21 (d, 2 H), 7.40 (d, 2 H).

^{13}C NMR (DMSO-d_6): δ = 19.6 (q), 20.9 (q), 21.6 (q), 25.8 (t), 26.1 (t), 47.5 (s), 47.8 (t), 49.1 (s), 58.2 (d), 127.8 (s), 132.8 (d), 139.5 (d), 141.3 (s), 206.5 (s).

Sodium 3-(4-Methoxybenzylidene) Camphorsulfonate (10c)

Yield: 12% after recrystallization from water; mp 176.9–180.9 °C.

^{1}H NMR (DMSO-d_6): δ = 0.16 (s, 3 H), 0.52 (s, 3 H), 0.99 (m, 1 H), 1.14 (m, 1 H), 1.68 (m, 1 H), 2.02 (m, 1 H), 2.47 (d, 1 H), 2.88 (d, 1 H), 3.28 (s, 3 H), 6.38 (d, 2 H), 6.60 (s, 1 H), 6.88 (d, 2 H).

^{13}C NMR (DMSO-d_6): δ = 19.5 (q), 20.5 (q), 25.4 (t), 47.1 (t), 48.7 (q), 55.5 (d), 57.8 (s), 114.7 (d), 126.8 (d), 131.7 (d), 139.7 (s), 160.2 (s), 206.0 (s).

Reduction of Acetophenones to Alcohols 13a–c; General Procedure

To a suspension of $NaBH_4$ (5.8 g; 0.16 mol) in EtOH (120 mL) was added at 0 ºC the acetophenone (0.32 mol) (in case of the *p*-Br acetophenone this was a solution in EtOH) dropwise, while maintaining the temperature below 10 ºC. After addition is complete, the reaction mixture was stirred overnight at r.t. After addition of water (100 mL), the mixture was stirred at r.t. for 15 min. The reaction mixture was extracted with Et_2O (3 × 100 mL). The combined ether layers were washed with brine, dried over Na_2SO_4, and concentrated to give a colorless liquid.

1-Phenylethanol (13a)

Yield: 98%.

^{1}H NMR ($CDCl_3$): δ = 1.54 (d, 3 H), 2.98 (br s, 1 H), 4.91 (q, 1 H), 7.32–7.45 (m, 5 H).

^{13}C NMR: δ = 25.1 (q), 70.2 (d), 125.5 (d), 127.4 (d), 128.5 (d), 145.9 (s).

1-*p*-Tolylethanol (13b)
Yield: 98%.

^{1}H NMR: δ = 1.14 (d, 3 H), 1.60 (br s, 1 H), 2.02 (s, 3 H), 4.54 (q, 1 H), 6.83 (d, 2 H), 6.93 (d, 2 H).

^{13}C NMR: δ = 20.8 (q), 24.8 (q), 70.0 (d), 125.2 (d), 129.0 (d), 137.0 (s), 142.8 (s).

1-(4-Bromophenyl)ethanol (13c)[26]
^{1}H NMR: δ = 1.40 (d, 3 H), 4.80 (q, 1 H), 7.20 (d, 2 H), 7.42 (d, 2 H).

^{13}C NMR: δ = 25.0 (q), 69.6 (d), 121.0 (s), 127.0 (d), 131.4 (d), 144.7 (s).

Formation of Thiourea Salts 14a–c; General Procedure
A mixture of the alcohol **12** (0.10 mol), thiourea (0.10 mol), 48% HBr (40 mL) and EtOH (50 mL) was refluxed overnight. After cooling to r.t., the reaction mixture was concentrated in vacuo, yielding a white solid or a syrup, depending on the substituent. This crude salt was used without further purification.

Hydrolysis of the Thiourea Salts 14 to the Thiols 15a–c; General Procedure
The thiourea salt **14** (0.10 mol) was dissolved or suspended in water (50 mL) and heated to 50 ºC. To this mixture was added dropwise 33% NaOH solution until no more cloudiness developed upon addition and the pH had risen to 10. The reaction mixture was stirred overnight at 50 ºC. After cooling to r.t., 30% HCl was added until pH 6. The reaction mixture was extracted with Et_2O (3 × 100 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated to a liquid. NOTE: the thiols have a distinct odor!

1-Phenylethanethiol (15a)
Yield: 75%.

^{1}H NMR: δ = 1.67 (d, 3 H), 4.23 (q, 1 H), 7.35 (m, 5 H).

^{13}C NMR: δ = 25.9 (q), 38.5 (d), 126.2 (d), 127.0 (d), 128.5 (d), 144.8 (s).

1-*p*-Tolylethanethiol (15b)
Yield: 87%.

^{1}H NMR: δ = 1.64 (d, 3 H), 2.32 (s, 4 H), 4.19 (q, 1 H), 7.11 (d, 2 H), 7.24 (d, 2 H).

^{13}C NMR: δ = 20.8 (q), 25.9 (q), 38.2 (d), 126.1 (d), 129.2 (d), 136.7 (s), 142.8 (s).

1-(4-Bromophenyl)ethanethiol (15c)
Yield: 64%.

^{1}H NMR: δ = 1.80 (d, 3 H), 4.12 (q, 1 H), 7.19 (d, 2 H), 7.38 (d, 2 H).

^{13}C NMR: δ = 25.7 (q), 37.9 (d), 120.6 (s), 128.0 (d), 131.6 (d), 144.8 (s).

Oxidation of Thiols 15a–c to 12a–c General procedure
The thiol **15** (36 mmol) was dissolved in HOAc (120 mL). H_2O_2 (110 mL, 30%, 2 equiv) was added dropwise, at such a rate that the temperature remained below 32 ºC. Beware of the induction time of the reaction; the temperature rise does not follow the addition immediately. After addition was complete and the thiol has reacted (according to TLC), Me_2S was added at 0 ºC until no more peroxides were present, as shown by a peroxide test. The reaction mixture was concentrated in vacuo (during evaporation the peroxide test was also applied), yielding an oil. This residue was suspended in H_2O (ca. 80 mL) and 33% NaOH was added until pH 7. The water-layer was washed with Et_2O (3 × 75 mL) and concentrated in vacuo to yield the sodium sulfonate, which was dried in vacuo at 60 ºC.

1-Phenylethanesulfonic Acid (12a)
Yield 77%.

^{1}H NMR (DMSO): δ = 1.51 (d, 3 H), 3.83 (q, 1 H), 7.27 (m, 5 H), 11.5 (br s, 1 H).

^{13}C NMR (DMSO): δ = 17.5 (q), 59.9 (d), 126.6 (d), 127.6 (d), 128.9 (d), 139.9 (s).

1-*p*-Tolylethanesulfonic Acid (12b)
Yield was not determined, since traces of DMSO remained.

^{1}H NMR (D_2O): δ = 1.74 (d, 3 H), 4.24 (q, 1 H), 7.34 (d, 2 H), 7.44 (d, 2 H).

1-(4-Bromophenyl)ethanesulfonic Acid 12c
Yield: 87%.

^{1}H NMR (D_2O): δ = 1.75, 4.00 (q, 1 H), 7.23 (d, 2 H), 7.39 (d, 2 H), (d, 3 H).

^{13}C NMR (D_2O): δ = 15.5 (q), 60.0 (d), 121.2 (s), 130.4 (d), 131.2 (d), 136.3 (s).

Resolution of 12a[13a]
Sulfonate (50 g; 0.24 mol) was dissolved in 10% HCl (150 mL). L-4-Hydroxyphenylglycine (40.1 g, 0.24 mol) was added together with 10% HCl (450 mL) and the mixture was heated until a clear solution was obtained. The mixture was allowed to crystallize at r.t. overnight. The resulting crystals were removed by filtration under suction, washed with ice water, furnishing 30.3 g (36%) of a white solid; $[\alpha]_D$ –83.9 (*c* 1, MeOH); HPLC (Ultron ES OVM, 20 mM KH_2PO_4–CH_3CN, 95:5): 87% ee. The salt was recrystallized from 10% HCl and a little MeOH to afford 22.8 g (27%) of a white solid. HPLC: 98% ee. The salt was suspended in H_2O (25 mL) and heated to 60 °C until a clear solution was obtained. NH_3 (6 N) was added until pH 7. The mixture was stirred at 0 °C for 2 h. The resulting solid was removed by filtration and the filtrate was passed over Amberlite IR-120. The column was eluted with H_2O. The eluent was concentrated in vacuo and stripped with toluene to obtain 14.5 g of the free sulfonic acid. HPLC: 98% ee.

Resolution of 12b
Sulfonate **12b** (140.7 g, 0.63 mol) was suspended in 10% HCl (200 mL). L-4-Hydroxyphenylglycine (105.2 g, 0.63 mol) was added and heated until a clear solution was obtained. The mixture was allowed to crystallize at r.t. overnight. The resulting crystals were removed by filtration under suction, washed with ice water, furnishing 39.3 g (17%) of a white solid. HPLC showed unfortunately no base line separation. The salt was recrystallized from 10% HCl–MeOH to afford 15.1 g (6.5%) with 85% ee; $[\alpha]_D$ –74.2 (*c* = 0.5, MeOH). Due to low yield this salt was suspended in water (20 mL) and heated to 60 °C. NH_3 (6 N) was added until pH 7. The mixture was stirred at 0 °C for 2 h. The resulting solid was removed by filtration and the filtrate was passed over Amberlite IR-120. The column was eluted with H_2O. The eluent was concentrated in vacuo and stripped with toluene to obtain 14.5 g of free sulfonic acid, which still contained some H_2O.

Resolution of 12c
Sulfonate **12c** (2.0 g; 7 mmol) was suspended in 10% HCl (40 mL). L-*p*-Hydroxyphenylglycine (1.16 g, 7 mmol) was added and heated until a clear solution was obtained. The mixture was allowed to crystallize at r.t. overnight. The resulting crystals were removed by filtration under suction, washed with ice water, furnishing 0.45 g (15%) of a white solid, $[\alpha]_D$ –64.6 (*c* = 0.5, MeOH). Unfortunately no HPLC-method could be devised to determine the ee. Due to low yield this salt was suspended in water (5 mL) and heated to 60 °C. Ammonia (6 N) was added until pH 7. The mixture was stirred at 0 °C for 2 h. The resulting solid was removed by filtration and the fil-

trate was passed over Amberlite IR-120. The column was eluted with H_2O. The eluent was concentrated in vacuo and stripped with toluene to obtain 50 mg of free sulfonic acid, which still contained some H_2O.

Synthesis of Chalcones 17a–e; General Procedure
Acetophenone (4.2 g, 0.43 mol) was dissolved in 96% EtOH (100 mL) and H_2O (200 mL). NaOH (21.8 g) was added. The reaction mixture was cooled in ice and benzaldehyde (4.1 g, 0.43 mol) was added dropwise within 5 min. The reaction mixture was stirred at r.t. overnight. The solid formed was removed by filtration under suction. If precipitation did not occur, the reaction mixture was extracted with Et_2O (3 × 100 mL). The combined ether layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo to yield the desired products.

Chalcone 17a
Yield: 94%; yellow solid; mp 56.7–58.2 ºC (lit.[23] 55–57 ºC).

^{1}H NMR ($CDCl_3$): δ = 7.35–7.62 (m, 9 H), 7.76 (d, *J* = 15.7 Hz, 1 H), 7.97 (d, *J* = 7.3 Hz, 2 H).

^{13}C NMR ($CDCl_3$): δ = 119.6 (d), 125.6 (d), 125.9 (d), 126.0 (d), 126.1 (d), 126.5 (d), 128.1 (d), 130.3 (d), 132.4 (s), 135.7 (s), 142.3 (d), 188.2 (s).

HRMS: *m*/*z* calcd for $C_{15}H_{12}O$, 208.089; found, 208.089.

***p*-Methylchalcone 17b**
Yield: 99%; yellow solid, mp 93.2 ºC (decomp.) (lit.[24] 84–86 ºC).

^{1}H NMR ($CDCl_3$): δ = 2.35 (s, 3 H), 7.17 (d, *J* = 8.1 Hz, 2 H), 7.42–7.56 (m, 6 H), 7.75 (d, *J* = 15.8 Hz, 1 H), 7.97 (d, *J* = 7.0 Hz, 2 H).

^{13}C NMR ($CDCl_3$): δ = 21.3 (q), 121.0 (d), 128.3 (d), 128.5 (d), 129.6 (d), 132.0 (d), 132.5 (d), 138.2 (s), 141.0 (s), 144.8 (d), 190.6 (s).

HRMS: *m*/*z* calcd for $C_{16}H_{14}O$, 222.104; found, 222.106.

***p*-Methoxychalcone 17c**
Yield: 98%; yellow solid; mp 73.1–75.3 ºC (lit.[25] 73–74 ºC).

^{1}H NMR ($CDCl_3$): δ = 3.78 (s, 3 H), 6.87 (d, *J* = 8.8 Hz, 2 H), 7.34–7.56 (m, 6 H), 7.74 (d, *J* = 15.4 Hz, 1 H), 7.95 (d, *J* = 7.0 Hz, 2 H).

^{13}C NMR ($CDCl_3$): δ = 55.2 (q), 114.3 (d), 119.6 (d), 127.5 (s), 128.3 (d), 128.2 (d), 130.1 (d), 132.4 (d), 138.4 (s), 144.6 (d), 190.4 (s).

HRMS: *m*/*z* calcd for $C_{16}H_{14}O_2$, 238.099; found, 238.100.

***p*′-Methylchalcone 17d**
Yield: 89%; yellow solid; mp 69.5–75.9 ºC (lit.[25] 96–97 °C)

^{1}H NMR ($CDCl_3$): δ = 2.52 (s, 3 H), 7.34–8.04 (m, 11 H).

^{13}C NMR ($CDCl_3$): δ = 21.7 (q), 122.1 (d), 128.4 (d), 128.7 (d), 129.0 (d), 129.4 (d), 130.5 (d), 135.0 (s), 135.6 (s), 143.7 (s), 144.5 (d), 190.1 (s).

HRMS: *m*/*z* calcd for $C_{16}H_{14}O$, 222.104; found, 222.105.

***p*′-Methoxychalcone 17e**
Yield: 77%; yellow solid; mp 96.1 ºC (decomp.) (lit.[25] 106-107 °C).

^{1}H NMR ($CDCl_3$): δ = 3.97 (s, 3 H), 7.06 (d, 2 H), 7.48–8.15 (m, 9 H).

^{13}C NMR ($CDCl_3$): δ = 55.5 (q), 113.9 (d), 121.9 (d), 128.4 (d), 129.0 (d), 130.3 (d), 130.8 (d), 131.1 (d), 135.1 (s), 144.0 (s), 163.5 (s), 188.7 (s).

HRMS: *m*/*z* calcd for $C_{16}H_{14}O_2$, 238.099; found, 238.100.

Synthesis of Sulfonates 18; General procedure
The chalcone **17** (90 mmol) was dissolved in 96% EtOH (150 mL). $NaHSO_3$ (90 mmol) was dissolved in H_2O (100 mL) and added to the chalcone solution. The reaction mixture was heated to reflux. The reaction was usually complete within 3.5 h, but can conveniently be refluxed overnight. After cooling to r.t., the reaction mixture was concentrated in vacuo to give the end product **18**. If precipitation occurred after cooling, the product **18** was removed by filtration under suction.

Sodium 1,3-Diphenyl-3-oxo-propanesulfonate (18a)
Yield: 71%; white solid; mp 119.9–132.5 °C (lit.[15] 135 ºC).

^{1}H NMR (DMSO-d_6): δ = 3.61 (dd, *J* = 17.2, 9.9 Hz, 1 H), 3.83 (dd, *J* = 4.0, 17.2 Hz, 1 H), 4.20 (dd, *J* = 9.9, 4.0 Hz, 1 H), 7.12–7.24 (m, 3 H), 7.35 (d, *J* = 7.0 Hz, 2 H), 7.50–7.91 (m, 3 H), 7.92 (d, *J* = 7.3 Hz, 2 H).

^{13}C NMR (DMSO-d_6): δ = 40.2 (t), 60.2 (d), 125.2 (d), 126.3 (d), 126.8 (d), 127.6 (d), 128.2 (d), 132.0 (d), 135.7 (s), 137.9 (s), 196.9 (s).

Sodium 1-(*p*-Methylphenyl)-3-phenyl-3-oxo-propanesulfonate (18b)
Yield: 87%; white solid; mp 94.6–97.5 °C.

^{1}H NMR (DMSO-d_6): δ = 2.20 (s, 3 H), 3.53 (dd, *J* = 21.6, 9.8 Hz, 1 H), 3.76 (dd, *J* = 21.6, 4.2 Hz, 1 H), 4.12 (dd, *J* = 9.8, 4.2 Hz, 1 H), 6.96 (d, *J* = 8.1 Hz, 2 H), 7.18 (d, *J* = 8.1 Hz, 2 H), 7.43–7.59 (m, 3 H), 7.87 (d, *J* = 6.8 Hz, 2 H).

^{13}C NMR (DMSO-d_6): δ = 20.8 (q), 41.4 (t), 61.1 (d), 128.2 (d), 128.3 (d), 129.0 (d), 129.4 (d), 133.4 (d), 135.5 (s), 136.1 (s), 137.0 (s), 198.3 (s).

Sodium 1-(*p*-Methoxyphenyl)-3-phenyl-3-oxo-propanesulfonate (18c)
Yield: 99%; white solid.

^{1}H NMR (DMSO-d_6): δ = 3.54 (dd, *J* = 17.2, 9.9 Hz, 1 H), 3.70 (s, 3 H), 3.79 (dd, *J* =16.8, 4.0 Hz, 1 H), 4.13 (dd, *J* = 9.3, 3.7 Hz, 1 H), 6.76 (d, *J* = 8.8 Hz, 2 H), 7.24 (d, *J* = 8.8 Hz, 2 H), 7.48–7.89 (m, 3 H), 7.91 (d, *J* = 7.0 Hz, 2 H).

^{13}C NMR (DMSO-d_6): δ = 41.6 (t), 55.1 (q), 60.7 (d), 113.1 (d), 128.2 (d), 129.0 (d), 130.4 (d), 131.4 (s), 133.3 (d), 137.1 (s), 158.2 (s), 195.6 (s).

Sodium 1-Phenyl-3-(*p*-methylphenyl)-3-oxo-propanesulfonate (18d)
Yield: 87%; white solid; mp 88.9–95.7 °C.

^{1}H NMR (DMSO-d_6): δ = 2.42 (s, 3 H), 3.64 (dd, *J* = 9.5, 17.2 Hz, 1 H), 3.84 (dd, *J* = 4.0, 16.8 Hz, 1 H), 4.24 (dd, *J* = 4.0, 9.9 Hz, 1 H), 7.19–7.42 (m, 7 H), 7.87 (d, 2 H).

^{13}C NMR (DMSO-d_6): δ = 21.8 (q), 41.4 (t), 62.1 (d), 126.9 (d), 128.0 (d), 128.6 (d), 129.9 (d), 134.9 (s), 139.6 (s), 144.1 (s), 191.0 (s).

Sodium 1-Phenyl-3-(*p*-methoxyphenyl)-3-oxo-propanesulfonate (18e)
Yield: 80%; white solid; mp 122.5–124.5 °C.

^{1}H NMR (DMSO-d_6): δ = 3.46–3.40 (dd, *J* = 9.9, 17.0 Hz, 1 H), 3.68–3.78 (2 dd, *J* = 4.0, 16.9 Hz, 2 H), 3.89 (s, 3 H), 4.26 (dd, *J* = 3.7, 9.5 Hz, 1 H), 7.05–7.42 (m, 7 H), 7.95 (d, 2 H).

^{13}C NMR (DMSO-d_6): δ 41.4 (t), 56.1 (q), 62.0 (d), 126.9 (d), 128.0 (d), 129.9 (d), 130.3 (d), 130.8 (d), 139.6 (s), 161.9 (s), 163.7 (s), 196 (s).

3-Dimethylamino-1-phenyl-propan-1-ol (22a)
In a 1 L round-bottomed flask attached to a reflux condenser were placed acetophenone (100 g, 0.83 mol), dimethylamine hydrochloride (88.3g, 1.08 mol), and paraformaldehyde (32.6 g, 1.16 mol). After the addition of concentrated HCl (1.5 mL) in 95% EtOH (135 mL), the mixture was refluxed for 2 h. While still warm, it was diluted with acetone (300 mL), allowed to cool to r.t., and then chilled overnight in the refrigerator. The large crystals were filtered and washed with acetone and dried overnight at 45 °C to give 147.9 g (83%) of **21a**. To a well stirred solution of **21** (190.6 g, 0.89 mol) in H_2O (1.5 L) at 0 °C was added $NaBH_4$ (42.9 g, 1.13 mol) in small portions over several hours. The solution was stirred overnight and allowed to warm to r.t. The solution was treated sequentially with acetone, concentrated HCl and 5 N NaOH. The aq solution was extracted several times with CH_2Cl_2. The combined organic layers were dried and concentrated.

Yield: 144.9 g (91%).

^{1}H NMR ($CDCl_3$): δ = 1.71–1.91 (m, 2 H), 2.29 (s, 6 H), 2.38–2.54 (m, 1 H), 2.56–2.74 (m, 1 H), 4.92 (dd, *J* = 4.8, 7.0 Hz, 1 H), 7.18–7.41 (m, 5 H).

^{13}C NMR ($CDCl_3$): δ = 34.9 (t), 45.3 (q), 58.1 (t), 75.2 (d), 125.6 (d), 126.9 (d), 128.2 (d), 145.2 (s).

API-ES-MS: *m*/*z* = 180.1 ($M + H^+$).

3-Methylamino-1-phenylpropan-1-ol (24a)
In a 2 L round-bottomed flask attached to a reflux condenser were placed acetophenone (88.8 g, 0.74 mol), benzylmethylamine hydrochloride (110 g, 0.7 mol), and paraformaldehyde (44.4 g, 2.5 mol) in EtOH (500 mL). After the addition of concd HCl (1 mL), the mixture was refluxed for 2 h and allowed to cool to r.t. overnight. The large crystals were filtered and dried overnight at 45 °C to give 126.84 g (63%) of **23a**. The free amine **23a** can be obtained by extraction of a solution of the salt in H_2O/dil. Na_2CO_3 with EtOAc. A mixture of **23a** (56.6 g; 0.22 mol), EtOAc (300 mL) and 10% Pd/C (5.5 g) was stirred at 5 bar H_2-pressure for 6 days. The reaction was monitored by ^{1}H NMR. The reaction mixture was filtered over celite and concentrated in vacuo.

Yield: 35.42 g (96%).

^{1}H NMR ($CDCl_3$): δ = 1.66–1.74 (m, 2 H), 2.31 (s, 3 H), 2.68–2.77 (m, 2 H), 3.85 (br, 2 H), 4.76–4.83 (m, 1 H), 7.12–7.25 (m, 5 H).

^{13}C NMR ($CDCl_3$): δ = 36.0 (q), 37.3 (t), 49.9 (t), 74.5 (d), 125.7 (d), 126.9 (d), 128.2 (d), 145.4 (s).

API-ES-MS: *m*/*z* = 166.3 ($M + H^+$).

3-Amino-3-phenylpropionic Acid Methylester (25a)
Benzaldehyde (212 g; 2.0 mol) and NH_4OAc (308 g; 4.0 mol) were dissolved in EtOH (2 L). The solution was stirred at 45 °C. A solution of malonic acid (208 g, 2.0 mol) in EtOH (1 L) was added. The mixture was stirred overnight at 60 °C and then at reflux for 6 h. The reaction mixture was cooled to 5 °C. The resulting precipitate was collected by filtration and washed with ice-cold EtOH. The white solid was dried in vacuo, to give 188.4 g (57%) of 3-amino-3-phenylpropionic acid. The acid was dissolved in MeOH (3 L) and cooled to 5 °C. To this mixture was added dropwise $SOCl_2$ (108 mL) and the mixture was stirred overnight at r.t. The solution was refluxed for 2 h and subsequently concentrated to dryness. To the white residue was added 2 M Na_2CO_3 (1 L) and the mixture was extracted with EtOAc (3 × 2 L). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo.

Yield: 168 g (83%); yellow oil.

^{1}H NMR ($CDCl_3$): δ = 2.07 (s, 2 H), 2.75 (d, 2 H), 3.76 (s, 3 H), 4.50 (t, 1 H), 7.41 (m, 5 H).

^{13}C NMR ($CDCl_3$): δ = 43.7 (t), 51.0 (d), 52.4 (q), 126.0 (d), 126.9 (d), 128.2 (d), 145.0 (s), 171.9 (s).

3-Amino-3-phenylpropan-1-ol (26a)
To a cooled solution (5 °C) of $NaBH_4$ (85.5 g, 2.26 mol) in THF (930 mL) was added **25a** (50 g, 0.28 mol). H_2SO_4 (62 mL) was added dropwise. The reaction mixture was stirred overnight at r.t. The mixture was recooled to 5 °C and MeOH (93 mL) and NaOH (2 L, 5 M) were added dropwise, respectively. The mixture was heated at reflux for 2 h. The solution was cooled to r.t. and the organic layer was removed. The aqueous layer was extracted with CH_2Cl_2 (3 × 500 mL). The combined organic layers were dried over Na_2SO_4 and concentrated to dryness. The residue was purified by heating at reflux temperature in concentrated NaOH (300 mL). H_2O (300 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 600 mL). The organic layer was dried over Na_2SO_4 and concentrated to dryness.

Yield: 27.4 g (65%); pale brown solid.

^{1}H NMR ($CDCl_3$): δ = 1.96 (m, 2 H), 3.90 (m, 2 H), 4.20 (m, 1 H), 7.38 (m, 5 H).

^{13}C NMR ($CDCl_3$): δ = 39.6 (t), 55.7 (d), 61.4 (t), 125.6 (d) 126.8 (d), 128.4 (d), 146.2 (s).

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