# The Multi-Substrate Screening of Asymmetric Catalysts

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**Abstract:** The principle of the one-pot multi-substrate screening is presented. This methodology has been successfully applied to various types of catalyzed enantioselective reactions: borane reduction of ketones, addition of organozinc on aldehydes, conjugate addition of diethylzinc on cycloalkenones or nitroalkenes, hydroformylation of olefins, hetero-Diels–Alder reaction on α-keto esters, enzymatic hydrolysis of glycerol-type monoesters as well as hydrogenation of 2-aryl-substituted terminal alkenes and enamides. The one-pot multi-catalyst screening methodology is also briefly discussed.



**Keywords:** asymmetric catalysis; high throughput screening; multi-catalyst screening; multi-substrate screening; one-pot screening

## 1 Introduction

There is a continuing need of new chiral catalysts for various enantioselective reactions. Several reasons encourage the search of new catalysts: to enhance the enantioselectivity or the catalytic activity in a given reaction, the need to avoid a patented catalyst, or to evaluate quickly a new family of chiral catalysts. A way to accelerate the discovery of improved chiral catalysts is to prepare libraries of chiral ligands or catalysts followed by a high throughput screening on a small scale. In the last seven years many review articles have been published on this topic.[1–5] The present review is focussed on a particular aspect of catalyst screening that was introduced in 1998 in these laboratories.[6] It is based on the one-pot evaluation of a given catalyst against a set of prochiral substrates. We named this approach the "one-pot multi-substrate screening" of a chiral catalyst. Independently, Gennari et al. proposed a similar method.[7]

## 2 Principle of the "One-Pot Multi-Substrate" Screening

The now well-established high throughput screening of asymmetric catalysts takes advantage of the possibilities of combinatorial chemistry[1–5] and of the fast evaluation of enantiomeric excesses on tiny amounts of material.[8–10] In these approaches the reactions are run in parallel, each experiment involving a catalyst and the reactants. The strategy "one catalyst per well" has been very useful to screen various catalysts and substrates and to optimize some experimental conditions. It may occur that a new chiral ligand of the catalyst was difficult to synthesize, and was isolated in small amounts. The first catalytic tests are then crucial to evaluate its potential before starting a new preparation. That is why it was proposed in 1998 to use a *library of prochiral substrates* in the screening of *one given new chiral catalyst*.[6,7] It was expected to get a set of information from one experiment. In this approach it is necessary to select some of representative prochiral substrates and to devise an analytical method able to give the enantiomeric excess of all the products deriving from the library of substrates. Chiral chromatographic separations were envisaged as the

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most convenient methods. The difficulty of the analysis is connected with the necessity to avoid overlaps between the pairs of enantiomers, it is also necessary that the peaks corresponding to the various starting substrates do not interfere with those of the products. Once the standard mixture of prochiral substrates has been set up it can be used with many different chiral catalysts or reagents.

The information extracted from the one-pot multi-substrate screening will be valid only if there are no interactions between the products and the catalysts or reagents (autoinduction).[11–15] In this review, progress made in the multi-substrate screening during the last five years is presented and discussed by considering the classes of transformations which have been investigated.

## 3 Reduction of Ketones

Asymmetric reduction of ketones remains important for applications and can be realized by various ways. Many chiral reagents have been tested, for example, boranes, modified borohydrides or aluminohydrides.

We have introduced the novel one-pot multi-substrate screening by taking the asymmetric reduction of a mixture of prochiral ketones using the oxazaborolidine (**1**) catalyst as a model case.[6] A variety of representative prochiral ketones was first arranged into five groups (I–V) (Figure 1). Reduction of mixture of four ketones (**2a**–**d**) (of group I, Figure 1) with the oxazaborolidine catalyst (**1**) provided the product mixture (four pairs of enantiomeric alcohols) (Scheme 1). Analysis of this mixture (obtained after usual work-up and solvent evaporation), as such, was performed in a single run on HPLC (chiral phase: Daicel Chiralcel OD-H). All eight peaks corresponding to the four pairs of enantiomers gave clear base-line separation without any overlaps with **2a**–**d** (group I). However, in the case of ketone mixtures belonging to groups II–V (Figure 1), the resulting concentrated reaction mixtures were subjected to preliminary flash chromatography and the product mixtures were collected into a rough three fractions A, B and C as depicted in Figure 1 [in every case, the fractions were made based on their $R_f$ values in order to avoid overlaps during the HPLC analysis (fraction A: $R_f = 0.62-0.52$; fraction B: $R_f = 0.45-0.40$ and fraction C: $R_f = 0.37-0.30$)]. Analysis of each fraction was done in a single run on HPLC (chiral phase: Daicel Chiralcel OD-H). All the peaks of every fraction A, B, and C of each group (Figure 1) provided clear base-line separation. Enantioselectivities obtained in this multi-substrate screening were consistent with those obtained in single substrate screening (mentioned in parenthesis in Scheme 1). Thus, screening of the oxazaborolidine, against several prochiral ketones, was achieved in a single reaction and in either a single run or more runs (as described above, so as to avoid overlaps) on a chiral HPLC column. Therefore, a novel high throughput screening protocol *via* the one-pot multi-substrate screening strategy was realized. Results obtained in case of group I prochiral ketones are presented in the Scheme 1.

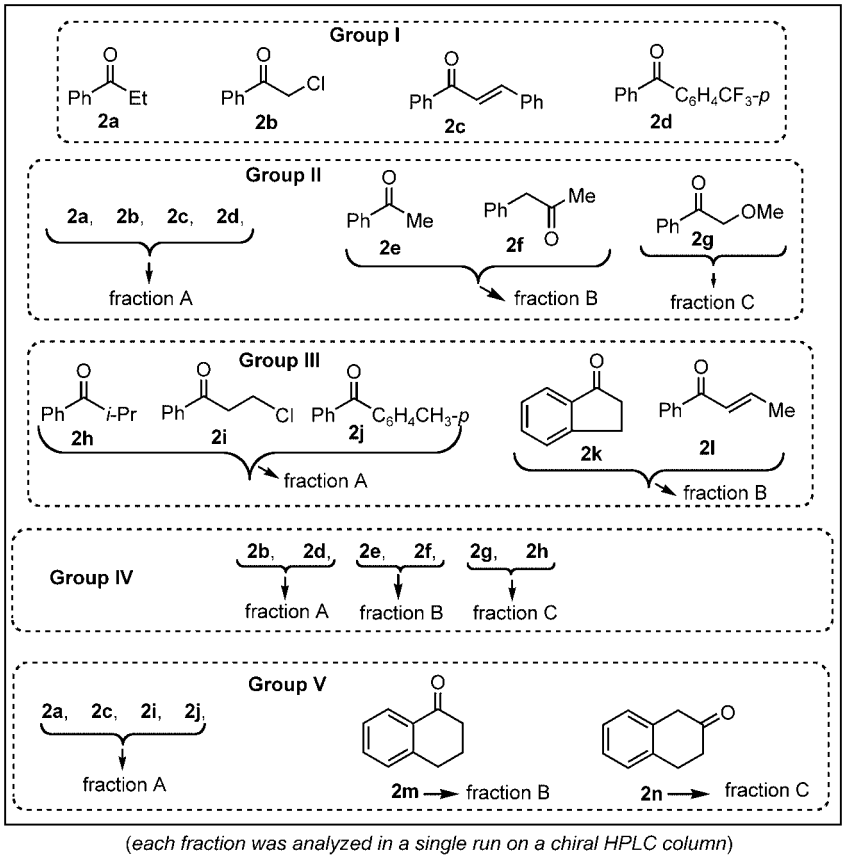
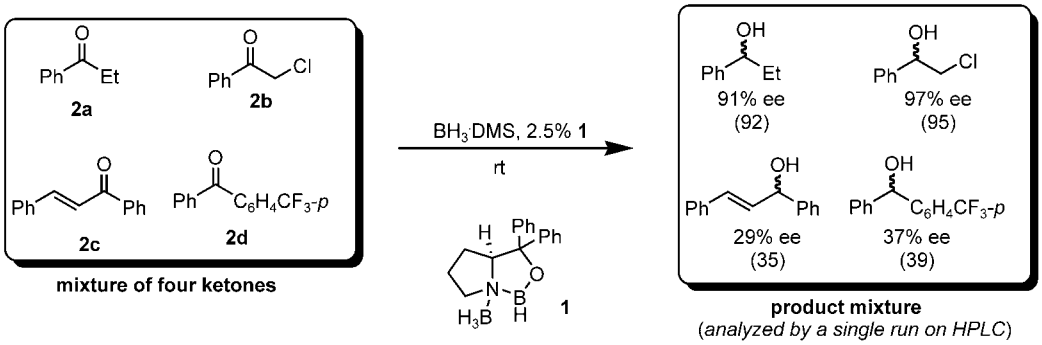



**Figure 1.** Classification of variety of prochiral ketones into groups I–V.[6]




**Scheme 1.** An example of asymmetric reduction of mixture of ketones using oxazaborolidine (**1**).[6]

## 4 Addition of Diethylzinc on Aldehydes

Gennari et al. have independently demonstrated the novel one-pot multi-substrate screening strategy for the fast optimization of disulfonamide ligands (**3**, Figure 2) in Ti(O-*i*-Pr)$_4$-mediated $Et_2Zn$ addition on a mixture of aldehydes (Scheme 2).[7] The tests were conducted in 30 different vessels, taking in each vessel, a mixture of four aldehydes (benzaldehyde, cyclohexanecarboxaldehyde, cinnamaldehyde and 4-chlorobenzaldehyde) thus providing 120 results at one-shot. These experiments clearly demonstrated the importance of multi-substrate screening in fast evaluation of a chiral catalyst. Analyses of the crude product mixtures were done in a single run on a GC column (eight peaks of four pairs

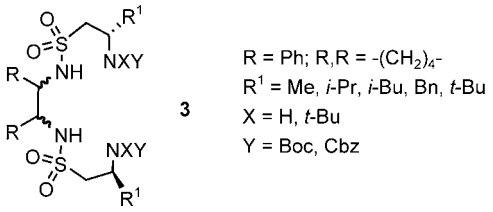
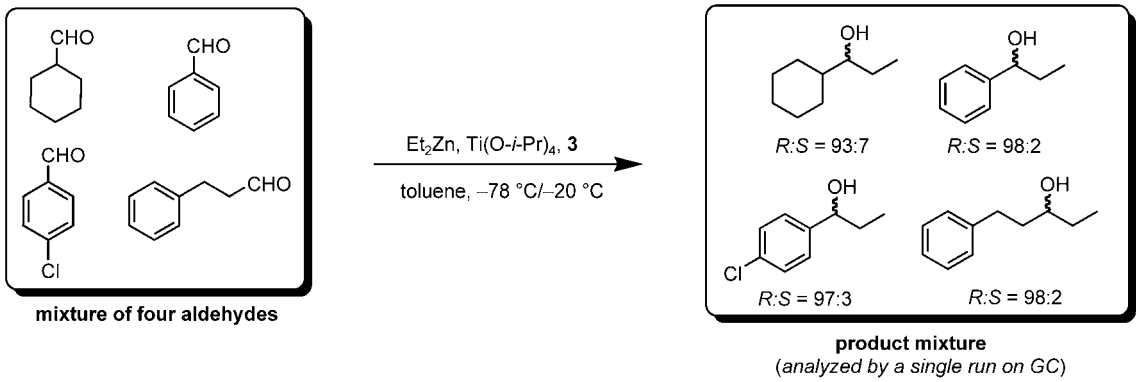



**Figure 2.** General structure of disulfonamide ligands **3**.[7]




**Scheme 2.** Asymmetric alkylation of mixture of aldehydes using disulfonamide ligands **3**.[7]

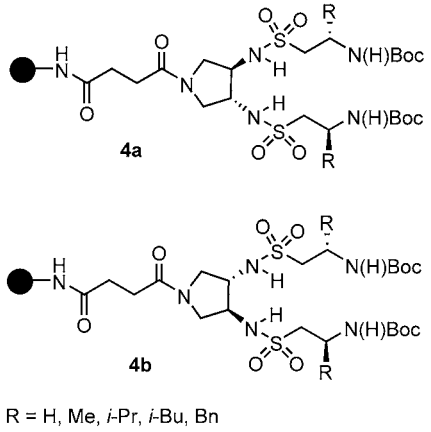



**Figure 3.** Structures of peptidosulfonamide-containing tweezers (**4**).[16]

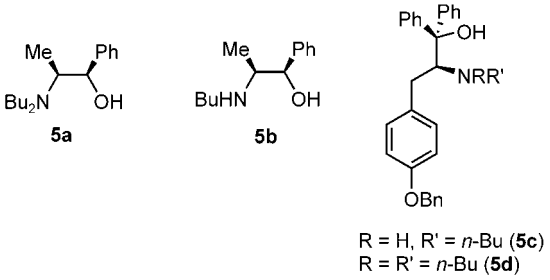



**Figure 4.** Structures of chiral amino alcohols **5a**–**d**.[17,18]

of enantiomers gave clear base-line separation). Results obtained in the case of the best catalyst [**3** with R = -$(CH_2)_4$-; $R^1$ = $PhCH_2$; X = H; Y = Boc) are described in Scheme 2.

Later, in 2000, Liskamp and co-workers successfully utilized this protocol for examining the peptidosulfonamide-containing tweezers in the solid phase (**4**, Figure 3) as catalyst for Ti(O-*i*-Pr)$_4$-mediated enantioselective $Et_2Zn$ addition on an aldehyde mixture.[16] They used a mixture of benzaldehyde, cyclohexanecarboxaldehyde, 4-chlorobenzaldehyde and phenylacetaldehyde and the resulting product mixture was analyzed on GC (chiracil-Dex CB column) in a single run. The results were in excellent agreement with those obtained in a separate experiment.

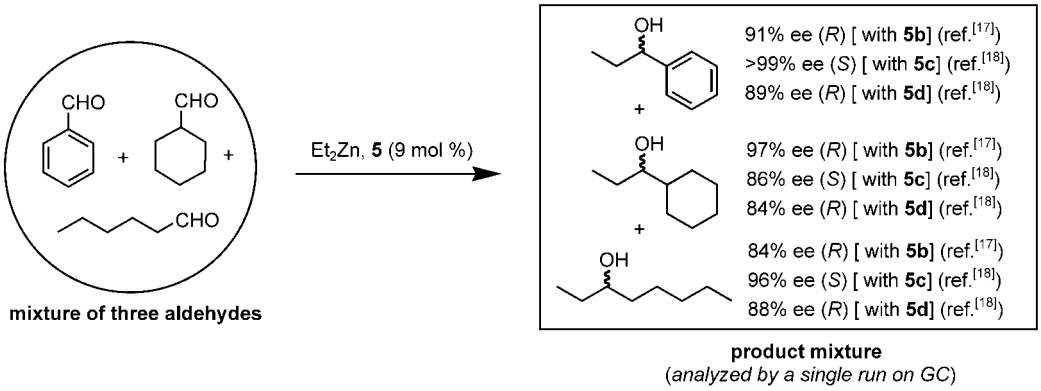
Wolf and Hawes[17] have taken advantage of this interesting high throughput screening methodology for evaluating the norephedrine-derived β-amino alcohols (**5a**, **5b**; Figure 4) as enantioselective catalysts for the addition of $Et_2Zn$ on a mixture of aldehydes. They considered benzaldehyde, cyclohexanecarboxaldehyde and hexanal as the representative aldehyde mixture (Scheme 3). The product mixture was analyzed using a GC column with cyclodextrin as internal standard which gave clear base-line separation for all six peaks of the three enantiomeric pairs. Subsequently, Wolf et al. also extended this fast evaluating multi-substrate protocol for screening (*S*)-tyrosine-derived amino alcohols (**5c**, **5d**; Figure 4) as catalysts for enantioselective alkylation of aldehyde mixtures using diethylzinc. They found that the secondary amino alcohol favoured the formation of the (*S*)-alcohol while the tertiary amino alcohol favoured the formation of the (*R*)-alcohol (Scheme 3).[18]

Recently, fluorous binols **6** were examined as reusable catalysts for enantioselective diethylzinc addition on aldehydes by Nakamura et al.[19,20] using this one-pot multi-substrate screening protocol in a fluorous-organic biphasic medium (Scheme 4). They chose a mixture of five aldehydes and the resultant crude product mixture was analyzed in a single run on GC with a β-Dex-capillary column without any purification.

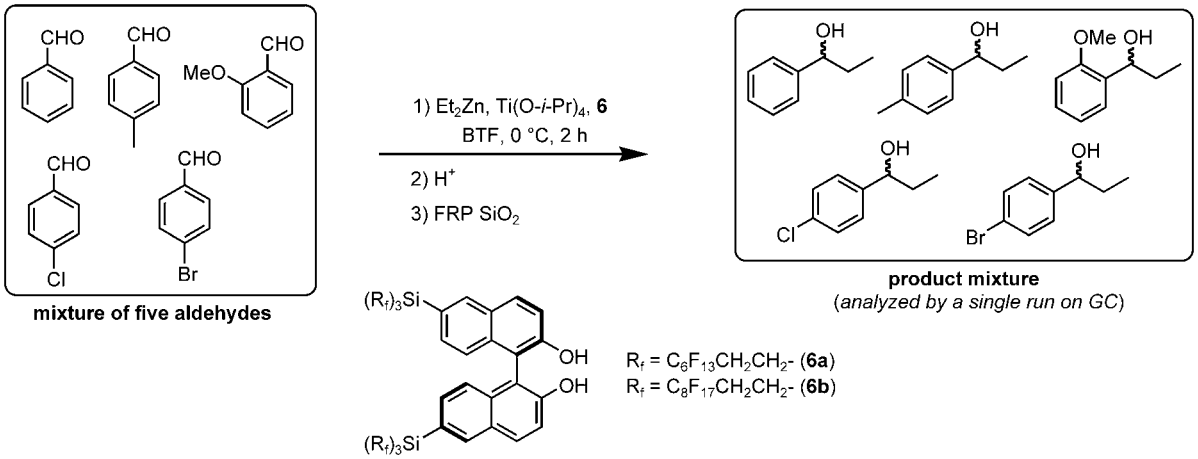
## 5 Conjugated Addition of Diethylzinc on Cycloalkenones

Fast screening of a family of chiral Schiff base ligands (**7**, Figure 5) in the copper-catalyzed conjugate addition of diethylzinc to cycloalkenones was used by Gennari and co-workers.[21,22] They employed a mixture of cyclohexenone/cycloheptenone as a representative substrate. Thus, the treatment of this mixture with diethylzinc in

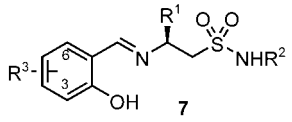
  




**Scheme 3.** Asymmetric alkylation of a mixture of aldehydes using chiral amino alcohols **5a**–**d**.[17,18]




**Scheme 4.** Asymmetric alkylation of mixture of aldehydes using fluorous binols **6**.[19,20]




$R^1$ = Me, *i*-Pr, *i*-Bu, Bn, *t*-Bu
$R^2$ = Bn, (*R*)-CH(Me)Cy, (*S*)-CH(Me)Cy, *i*-Pr, $CHPh_2$, *t*-Bu, (*R*)-CH(*i*-Pr)$CH_2$OH, (*S*)-CH(*i*-Pr)$CH_2$OH, (*R*)-CH(Me)Cy, (*S*)-CH(Me)Cy,
$R^3$ = H, 3,5-(Bu-*t*)$_2$, 3,5-$Cl_2$, 5,6-$(CH)_4$, 3-OMe/5-$NO_2$

**Figure 5.** General structure of the chiral Schiff base ligands **7**.[21,22]

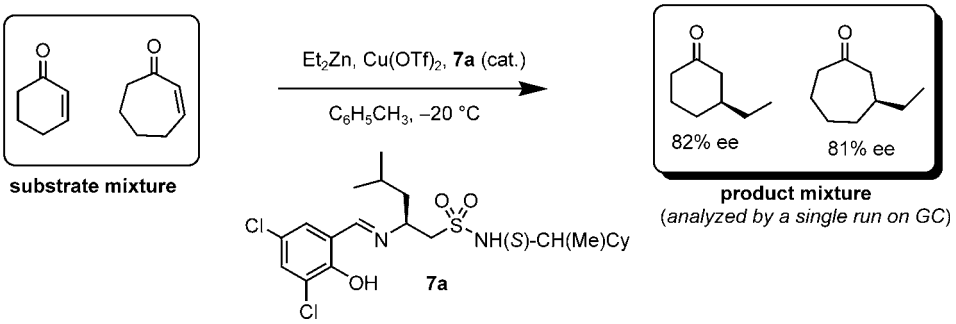
the presence of $Cu(OTf)_2$ provided the crude product mixture which was directly analyzed in a single run on a GC chiral capillary column. Using this fast optimization protocol, they screened a library of 125 ligands and found **7a** [**7** with $R^1$ = *i*-Bu; $R^2$ = (*S*)-CH(Me)Cy; $R^3$ = 3,5-$Cl_2$] to be the best ligand for this reaction which provided the addition products on cyclohexenone in 82% ee and on cycloheptenone in 81% ee (Scheme 5).

## 6 Conjugated Addition of Diethylzinc on Nitroalkenes

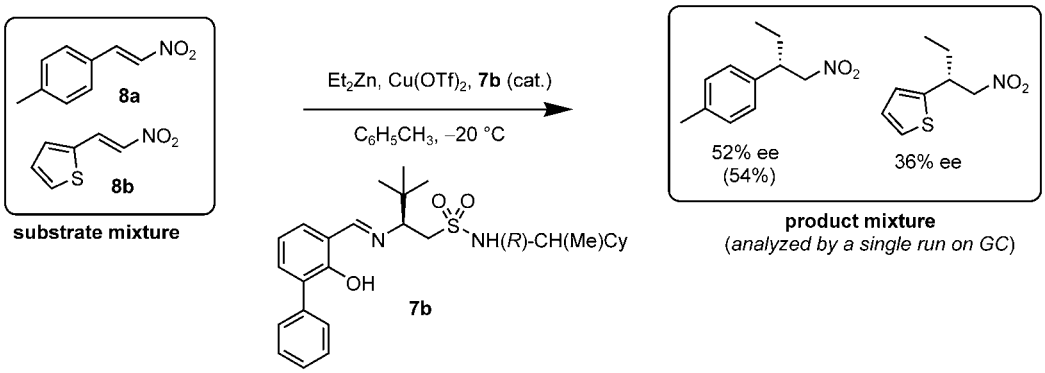
Gennari and co-workers[23] have also utilized this high throughput protocol of one-pot multi-substrate screening for optimizing the ligand with the general structure **7** (Figure 5), for the copper-catalyzed conjugate addition of diethylzinc to nitroalkenes. They have screened 125 ligands **7** (Figure 5), taking a mixture of **8a** and **8b** as the multi-substrate source. The resultant crude product mixtures were analyzed directly using a GC chiral capillary column in a single run. All four peaks corresponding to the two pairs of enantiomers gave baseline separation. The accuracy of the results obtained in this multi-substrate screen, with the best catalyst (**7b**), was also established by carrying out the reaction on a single substrate (value mentioned in parenthesis in Scheme 6). The results with the best catalyst **7b** [**7** with $R^1$ = *t*-Bu; $R^2$ = (*R*)-CH(Me)Cy; $R^3$ = 3-Ph] are presented in the Scheme 6.

Recently, Feringa and co-workers[24] have investigated the screening of a variety of copper-phosphoramidite catalysts **10**–**17** (Figure 6) for enantioselective conju-




**Scheme 5.** An example of asymmetric conjugate addition of $Et_2Zn$ on the mixture of cycloalkenones using chiral Schiff base **7a**.[21,22]




**Scheme 6.** An example of asymmetric conjugate addition of $Et_2Zn$ on the mixture of nitroalkenes using chiral Schiff base **7b**.[23]

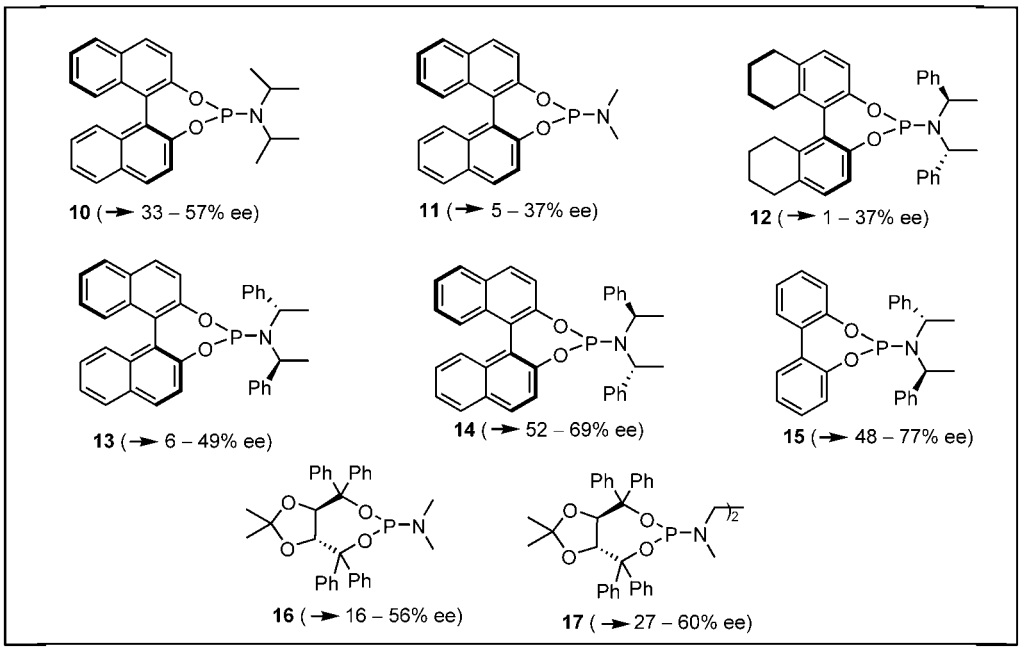
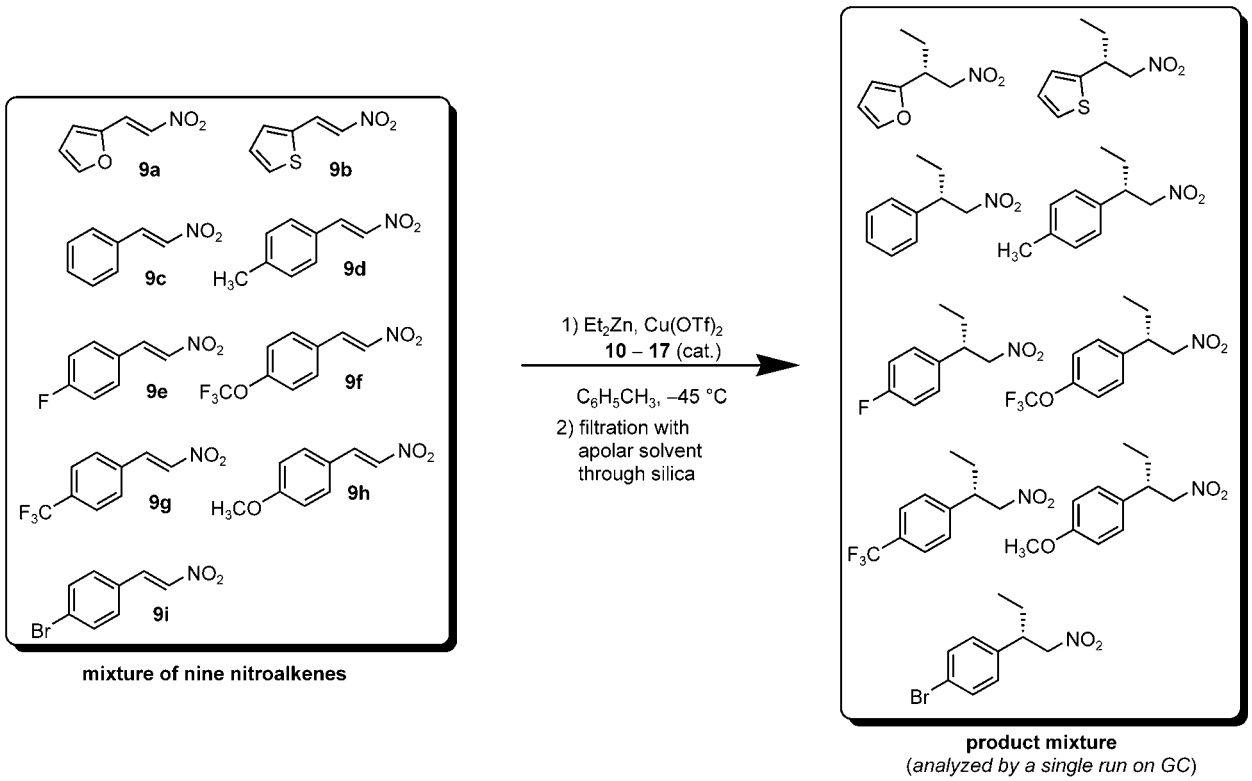



**Figure 6.** Structures of chiral phosphoramidite catalysts **10–17**.[24]




**Scheme 7.** Asymmetric conjugate addition of $Et_2Zn$ on the mixture of nitroalkenes using phosphoramidite catalysts **10–17**.[24]

gate addition of $Et_2Zn$ to nitroalkenes using the one-pot multi-substrate screening methodology (Scheme 7). A mixture of nine nitroalkenes was conveniently employed and the resultant product mixture of nine pairs of enantiomers, obtained after a quick filtration of the concentrated reaction mixture with an apolar solvent through a short column of silica, was analyzed in a single run on chiral GC (all 18 products, i.e., nine pairs of enantiomers gave clear base-line separation on an Astec A-TA chiral column). Phosphoramidites **14** and **15** provided the best results (Figure 6).

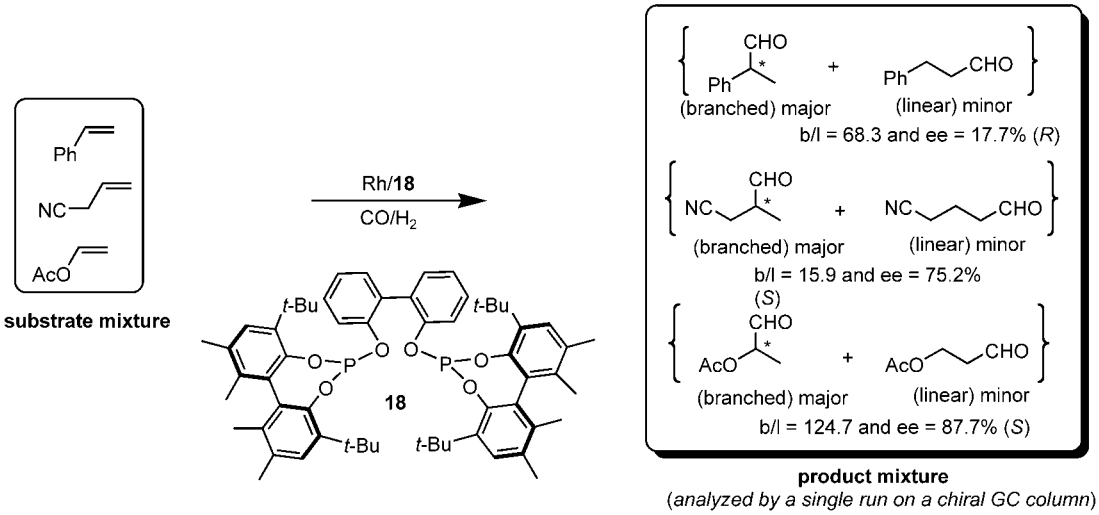
## 7 Hydroformylation of Olefins

Cobley et al.[25] have examined various chiral phosphite ligands in the Rh-catalyzed asymmetric hydroformylation reaction using the high throughput screening of multi-substrates approach. Interestingly, they adapted the multi-substrate approach in combination with a parallel reactor of eight cells and thus enhanced the overall efficacy of the high throughput screening. They employed a mixture of styrene, allyl cyanide and vinyl acetate as substrate in each cell, and in each cell a different ligand was taken. The resulting concentrated reaction mixtures, consisting of three pairs of enantiomers of the branched isomer (major product), three linear isomers (minor product) and three unreacted starting materials (i.e., overall a mixture of twelve compounds), was analyzed on a single run on chiral GC with an α-cyclodextrin column. All the twelve peaks corresponding to the above-mentioned compounds gave clear base-line separation. Using this parallel multi-substrate screening protocol, they found that catalyst **18** gave the best ee (88%) with the highest regioselectivity (branched:linear > 100:1) on vinyl acetate (Scheme 8).

## 8 Hetero-Diels–Alder Reaction on α-Keto Esters

A fast evaluation of chiral ligands (**19** – **22**, Figure 7) in the Lewis acid-catalyzed hetero-Diels–Alder reaction between Danishefsky's diene and a mixture of three sterically hindered α-keto esters (ethyl benzoylformate, ethyl 3-methyl-2-oxobutyrate and dihydro-4,4-dimethyl-2,3-furandione) was successfully achieved *via* the one-pot multi-substrate screening approach by Wolf and co-workers (Scheme 9).[26] $Cu(OTf)_2$, $Sc(OTf)_3$, $Yb(OTf)_3$ and $In(OTf)_3$ were employed as Lewis acids. Concentrated reaction mixtures (i.e., crude product mixtures) were analyzed in a single run on two chiral HPLC columns coupled in series (phenylglycine and Chiralpak AS). All nine peaks corresponding to three pairs of enantiomers of the products and three residual starting materials gave a clear base-line separation. The results obtained with catalyst **19** using $Cu(OTf)_2$ as Lewis acid are presented in Scheme 9. Enantioselec-




**Scheme 8.** An example of asymmetric hydroformylation of a mixture of olefins using chiral phosphite ligand **18**.[25]

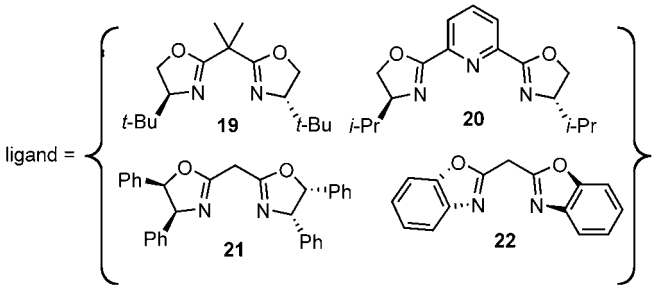
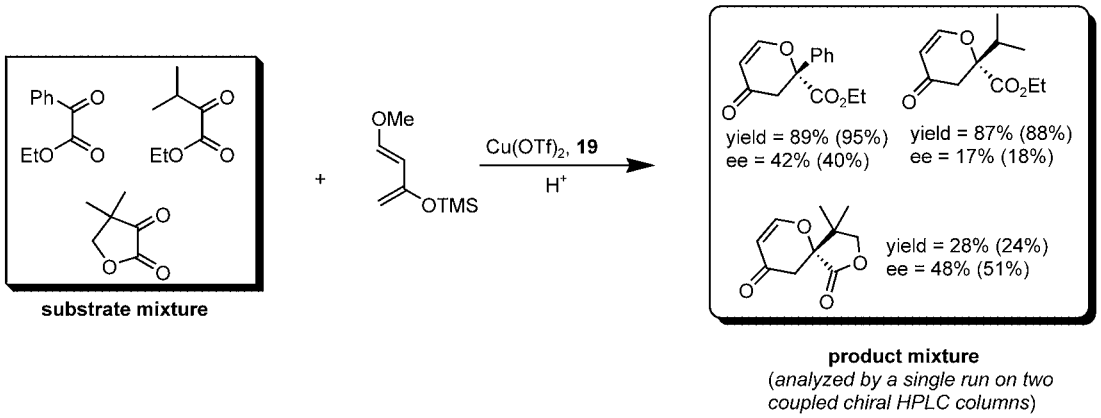



**Figure 7.** Structures of chiral bisoxazoline ligands **19–22**.[26]

tivities, obtained by this multi-substrate screening approach, were also found to be in excellent agreement with results obtained in the individual screenings (mentioned in parenthesis).

## 9 Enzymatic Hydrolysis of Long-Chain Aliphatic Glycerol-Type Monoesters

Recently, Goddard and Reymond[27] have employed the multi-substrate screening methodology for demonstrating enzyme activity fingerprinting of the enzymatic hydrolysis of monoesters (racemic or enantiomerically pure). A mixture of twenty long-chain aliphatic glycerol-type octanyl monoesters of different substitution patterns tagged with different UV chromophores was subjected to enzymatic hydrolysis using a variety of hydrolytic enzymes. The resultant product mixture of twenty 1,2-diols was successfully analyzed in a single run on reverse-phase HPLC. All the twenty peaks of the corresponding 1,2-diols showed a clear base-line separation. They established a colour-coded enzyme activity fingerprinting using the peak integration values obtained from the HPLC trace. Perhaps this approach could be adapted for an evaluation of the kinetic resolution efficiency of hydrolytic enzymes.




**Scheme 9.** An example of the asymmetric hetero-Diels–Alder reaction using a mixture of α-keto esters.[26]

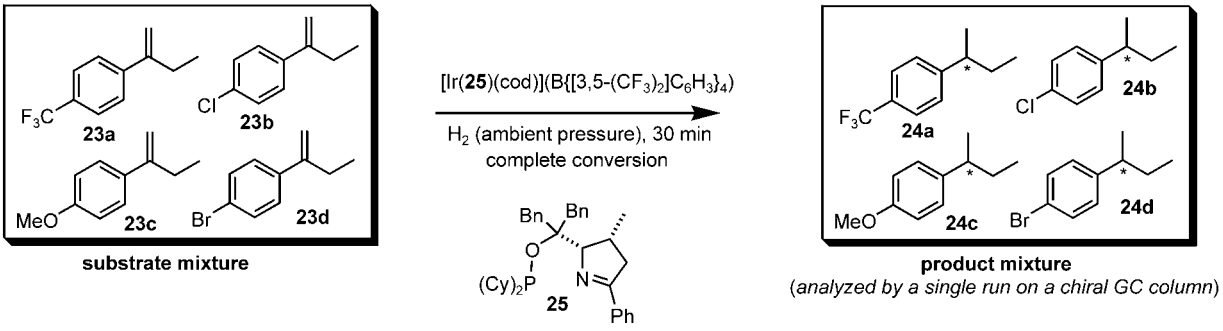
## 10 Hydrogenation of Terminal Alkenes and Enamides

Very recently two articles have appeared on this topic. Pfaltz and co-workers[28] have found that iridium complexes derived from phosphinite-oxazoline ligands provided better enantioselectivities in the hydrogenation of 2-aryl-substituted terminal alkenes. Subsequently, they also examined the enantioselective hydrogenation of a mixture of four 2-aryl-substituted terminal alkenes (**23a**–**23d**) with the catalyst **25** at ambient pressure (Scheme 10). The resultant product mixture [consisting of four enantiomeric pairs of the corresponding hydrogenated products (**24a**–**24d**)] was analyzed in a single run on a GC γ-CD chiral column. All the eight peaks corresponding to the four enantiomeric pairs showed a clear base-line separation. Enantioselectivities obtained *via* this multi-substrate approach were identical to those obtained in single substrate reactions.

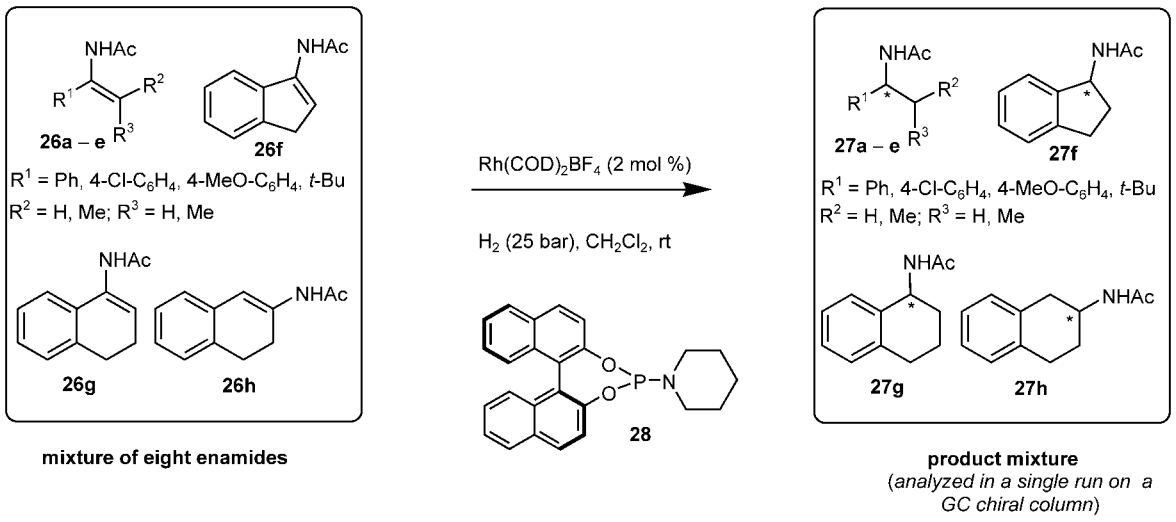
During the investigations of asymmetric hydrogenation using Rh complexes derived from chiral monodentate phosphoramidite ligands, Feringa and co-workers[29] have described the hydrogenation of a mixture of enamides (Scheme 11). Analysis of the mixture of eight amides (**27a**–**h**) was achieved in a single run on GC (CP-chirasil-Dex-CB column) providing clear base-line separation for all the sixteen peaks of the corresponding eight enantiomeric pairs of amides (**27a**–**h**) in the mixture. They successfully demonstrated the hydrogenation of a mixture of five enamides (out of eight enamides **26a**–**h**) with the chiral Rh complex derived from phosphoramidite **28**. The ees obtained in this multi-substrate screening were found to be consistent with those obtained in separate experiments with single substrates.

## 11 The "One-Pot Multi-Catalyst" Screening

By analogy with the multi-substrate screening (one catalyst/several substrates) one may consider the alternative situation of multi-catalyst screening (one substrate/several catalysts). The screening of a mixture of catalysts in solution seems impracticable, since it is impossible to identify the origin of (*R*)- and (*S*)-products




**Scheme 10.** An example of enantioselective hydrogenation of mixture of four 2-aryl-substituted terminal alkenes.[28]




**Scheme 11.** Enantioselective hydrogenation of mixture of enamides.[29]

generated by separate catalysts in competitive pathways. However, if one catalyst amongst a mixture of catalysts is especially active and enantioselective, it will dominate the reaction giving products of high ee. Here, useful information is obtained. If one catalyst is highly active but not enantioselective, then racemic products will be observed and will obscure the effect of more enantioselective catalysts. If two catalysts of similar reactivities provide the products of opposite absolute configurations, then the overall result is the formation of a racemic product. These problems can be surmounted in some appropriate reactions. Some of the successful results achieved in this direction are briefly discussed in the following.

Tian and Coates[30] have employed a mixture of titanium catalysts in the screening of stereoselective polymerization. They argued that, in living polymerization reactions, as the catalyst always stays on the growing chain of the polymer (i.e., no exchange of catalyst among substrates) and each stereochemical event is continuously recorded on the growing polymer (which is in contrast with the asymmetric transformation of small molecules where stereochemical events of a given catalyst are disconnected), screening of a mixture of catalysts in one-pot is possible. They successfully demonstrated this principle by using a mixture of titanium complexes as catalysts in the polymerization of propylene.

Asymmetric combinatorial screening of catalysts prepared *in situ* may afford interesting results if the catalyst is difficult to prepare independently. Reetz and coworkers have recently reported the use of mixture of two different monodentate ligands in combinatorial screening of various enantiopure BINOL-derived monophosphonites as ligands for enantioselective Rh-catalyzed hydrogenation.[31–34] In the reaction, with a mixture of two different monodentate ligands ($L^x$ and $L^y$) and the metal (M), a mixture of three catalysts ($ML_2$), two from homocombinations [$M(L^x)_2$, $M(L^y)_2$] and one from the heterocombination ($ML^xL^y$), is formed [actually, preparation of the pure heterocombination catalyst ($ML^xL^y$) separately is impossible]. By comparing the results obtained in the case of an individual pure homocombination catalyst [$M(L^x)_2$ and $M(L^y)_2$] with the results obtained in the case of the *in situ* prepared catalyst mixture [$M(L^x)_2$, $M(L^y)_2$ and $ML^xL^y$], they found that in some cases the catalyst with the heterocombination of ligands offered better selectivities than the usual homocombination catalysts.[31–34] Also, certain heterocombination catalysts provided even opposite selectivities when compared to the corresponding homocombination catalysts.[33] This led to the discovery of novel heterocombination catalysts from already existing ligands. These experiments clearly demonstrated the usefulness of employing a mixture of ligands in high throughput screening for finding a hit-pair of ligands for optimized catalysts. Feringa and coworkers[35] have also, independently, observed similar results when a mixture of two different monophosphoramidites was employed in one-pot in the Rh-catalyzed asymmetric hydrogenation of β-dehydroamino acids. These authors also extended the technique of employing a mixture of two different monodentate ligands to the asymmetric Rh-catalyzed Michael addition of arylboronic acid to activated alkenes.[36] In the case of this reaction too, they have found that the heterocombination catalysts provided the products in very high yield with best selectivities when compared to their corresponding homocatalysts.

Recently, Markert and Pfaltz[37] have developed an interesting multi-catalyst screening approach based on the ESI-MS technique in the palladium-catalyzed kinetic resolution of pseudo-racemic allyl acetates which bear a remote label. A mixture of five chiral ligands in the presence of a palladium complex was employed as the multi-catalyst source. They calculated the selectivity factor ($s = k_{rel}$) by measuring the relative amounts of pseudo-racemic allylpalladium intermediate ionic species using ESI-MS. All ten peaks, belonging to two pairs of pseudo-racemic allylpalladium ionic intermediate species, generated *via* the reaction between pseudo-racemic allyl acetates and the equimolar mixture of five chiral ligands, were clearly identified in the ESI-MS with varying integration ratios. These ratios provided the information to calculate $k_{rel}$ for each $PdL_2$ complex. The authors found that these values reflect the final enantioselectivities after nucleophilic attack of the π-allyl intermediates.

## 12 Discussion

The multi-substrate technology results in the screening of various asymmetric catalysts in several types of reactions. The values of enantioselectivities correlated well with the values provided by independent screenings. This means that in the cases which have been studied there were no perturbations introduced by the coexistence of several substrates and products. It reflects the absence of autoinduction in the catalytic systems which have been already investigated. Of course, it is not a general conclusion and caution is needed in the case of new classes of catalysts. Care is also needed for reactions where the ee is conversion- and catalyst loading-dependent. In such cases the enantioselectivities will be only an approximate but useful indication of the behaviour of the catalytic reaction. The usefulness of this approach is bound to the information obtained for one representative prochiral substrate of a class of substrates. The proper selection of the various reactions is dependent on the analytical methods involved to get separation of all the pairs of enantiomeric products. Useful information is now available on the analysis of mixtures of alcohols (Fig. 1 and Schemes 1–4) of cycloalkenones (Scheme 5), of β-substituted nitroalkenes (Scheme 7)

of aldehydes (Scheme 8), hetero-Diels–Alder adducts (Scheme 9), 2-aryl-substituted butanes (Scheme 10) and secondary amides (Scheme 11). Some of these findings pave the road for other catalytic reactions: for example, arylalkyl alcohols have been obtained by CBS reduction of aryl alkyl ketones,[6] the same products may be obtained by asymmetric addition of an organometallic species onto aromatic or aliphatic aldehydes or by benzylic hydrosilylation of substituted aromatic aldehydes. In each new reaction some precautions or adjustments are needed in order to avoid overlaps with the residual prochiral substrates. In principle, a chiral reagent could be used instead of a chiral catalyst in the one-pot multi-substrate screening. There are up to now no reports of this approach.

## 13 Conclusion

The one-pot multi-substrate screening has been developed successfully for various types of asymmetric catalyzed reactions. It can speed-up the evaluation of a catalyst by the appropriate selection of characteristic prochiral substrates (for example, aromatic versus aliphatic aldehydes). One of the difficulties of this approach is the ee measurements in a mixture of products and starting materials. Some sets of prochiral substrates have been identified for that purpose. In all the cases under investigation, there is a quite good correlation with the enantioselectivities obtained in independent reactions (one catalyst *versus* one substrate). This could not be a fully general conclusion, especially for reactions where autoinduction is possible (see above). However, the results already published show that the one-pot multi-substrate screening is a simple and useful methodology in asymmetric catalysis. Many classes of reactions have not been investigated and deserve further evaluation.[38] The methodology of one-pot multi-catalyst screening (several catalysts *versus* one substrate) is also possible in some special situations.

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