Determining the Enantioselectivity of Chiral Catalysts by Mass Spectrometric Screening of Their Racemic Forms

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S *Supporting Information*

ABSTRACT: The enantioselectivity of a chiral catalyst can be determined from its racemic form by mass spectrometric screening of a nonequal mixture of two mass-labeled quasienantiomeric substrates. The presented method opens up new possibilities for evaluating catalyst structures that are not readily available in enantiomerically pure form.

High-throughput screening of chiral catalysts has become an important tool that can speed up catalyst discovery and optimization considerably.[1] Many efficient screening methods and automated techniques that allow fast measurement of ee values are presently available. Hence, screening of catalyst libraries, even if they contain large numbers of compounds, is usually no longer a bottleneck in the development of enantioselective catalytic processes. On the other hand, the synthesis of chiral ligands and catalysts is slow and labor-intensive. In particular, the requirement of high enantiomeric purity for a catalyst puts a limitation on the exploration of new catalyst structures. Potential catalysts often are not investigated because no straightforward method for the preparation of enantiomerically pure material is available. Screening methods that allow the enantioselectivity of a catalyst to be determined by testing its racemic form would strongly enhance the range of possible structures that can be explored. Moreover, structural optimization of a catalyst could be accelerated considerably in cases where the preparation of enantiomerically pure derivatives is difficult.

Two methods that allow the potential of chiral catalysts to be estimated by testing the racemic form have been reported. Kagan and co-workers[2] showed that it is possible to evaluate the enantiodiscrimination potential of a racemic catalyst in a sequence of two consecutive reactions at two prochiral units of a substrate, provided that the catalyst does not dissociate from the reactant between the first and second reaction. However, this condition is met only in special cases where there is a strong binding interaction between the catalyst and reactant.

Lloyd-Jones and co-workers[3] devised a new intriguing concept based on their at first sight counterintuitive deduction that in the kinetic resolution of a scalemic compound (0 < ee < 100%) with a racemic catalyst, the ee of the substrate changes upon conversion under pseudo-zeroth-order conditions (saturation conditions under which the reaction rate does not display a direct relationship with the substrate concentration). If the catalyst is 100% enantioselective (selectivity factor $s = k_{fast}/k_{slow} = \infty$), the R enantiomer of the catalyst reacts exclusively with one enantiomer

of the substrate and the S catalyst enantiomer with the other substrate enantiomer. Under pseudo-zeroth-order conditions, both the R and S enantiomers of the catalyst react at the same rate, implying that the two substrate enantiomers are consumed in equal amounts until all of the minor enantiomer has been converted to product. Consequently, the substrate ee increases with conversion. A completely unselective catalyst ($s = 1$), on the other hand, does not discriminate between the two substrate enantiomers, and therefore, the ee remains constant during the reaction. For a partially selective catalyst, some intermediate behavior is observed. The selectivity factor s can be estimated from the graph correlating the substrate ee with conversion.

The feasibility of this approach was demonstrated for the kinetic resolution of enantiomerically enriched cyclohex-2-enyl acetate (62−64% ee) through Pd-catalyzed allylic substitution. Although the experimentally observed graphs deviated considerably from calculated graphs based on an ideal pseudo-zeroth-order kinetic regime, the enantioselectivity order of different catalysts was correctly predicted. As pseudo-zeroth-order conditions are rather common in kinetic resolutions,[3,4] the method seems to be quite generally applicable. However, it cannot be applied to enantioselective reactions of prochiral substrates and allows only an approximate estimation of enantioselectivity.

We report here an approach based on the concept of Lloyd-Jones and our recently developed mass spectrometric screening method[5] that opens up new possibilities for racemic catalyst screening, as it allows fast and accurate determination of enantioselectivities for kinetic resolutions and reactions of prochiral substrates.

Using mass-labeled quasienantiomeric substrates, we have shown that the intrinsic enantioselectivity of a catalyst can be determined by monitoring of catalytic intermediates with electrospray ionization mass spectrometry (ESI-MS). The procedure is operationally simple because no workup, purification, or isolation steps are necessary. Moreover, in contrast to conventional screening methods based on product analysis, simultaneous screening of catalyst mixtures in homogeneous solution is possible. Originally, the method was applied to Pd-catalyzed kinetic resolution of allyl esters,[5a,b] but subsequently, the application range was extended to transformations of prochiral substrates by back-reaction screening. According to the principle of microscopic reversibility, the transition states of a reaction in the forward and reverse directions are the same, and therefore, the enantioselectivity determined for the back reaction is identical to that of the forward reaction. This method was successfully

Scheme 1. Screening Methodology
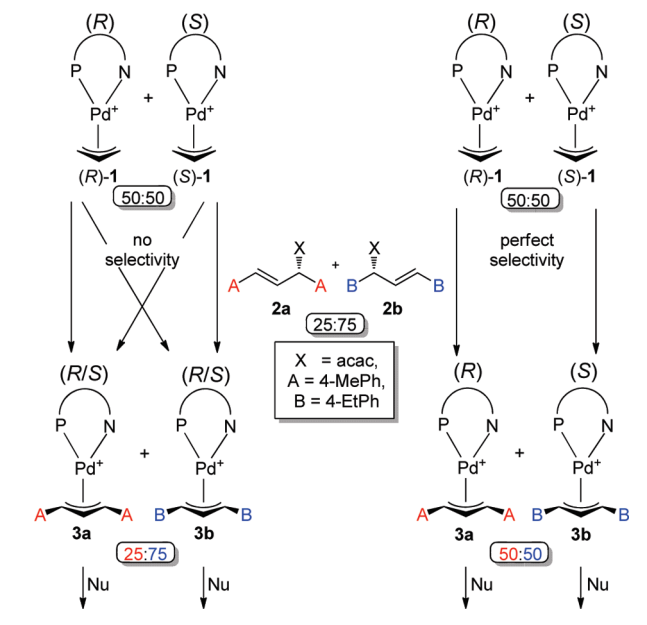
Scheme 2. Synthesis of Phox Derivatives 4a and 4b[a]
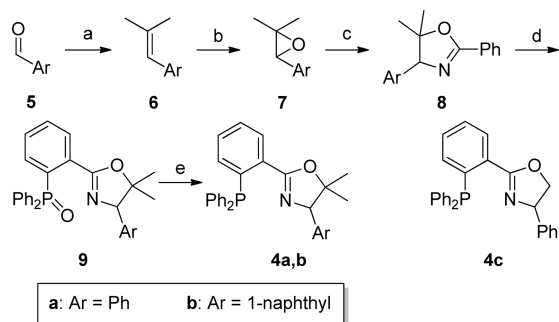
[a] Conditions: (a) (CH₃)₂CHPPh₃⁺I⁻, nBuLi, THF, 0 °C → RT, 4 h. (b) MCPBA, DCM, 0 °C, 2 h. (c) (1) PhCN, BF₃·OEt₂, 0 °C → RT, 3 h; (2) NaHCO₃, RT, 2 h. (d) (1) sBuLi, TMEDA, THF, −78 °C; (2) Ph₂PCl, −78 °C → RT, 18 h; (3) H₂O₂. (e) PhSiH₃, 120 °C, 40 h.

applied to Pd-catalyzed allylic substitutions,[5c] metal-catalyzed and organocatalytic Diels—Alder reactions,[5d] and Michael additions.[5e]

To demonstrate the potential of the MS-based methodology for screening of racemic catalysts, we chose the allylic substitution of 1,3-diarylallyl esters as a test reaction using acetylacetonate as the nucleophile and racemic Pd—phox complexes as catalysts (Scheme 1). We previously showed that this reaction can be screened in the reverse direction, with acetylacetonate functioning as a leaving group. The ee values from mass spectrometric screening closely matched the enantioselectivities determined for the preparative reaction of the corresponding allyl benzoates with acetylacetonate.[5c]

Starting from a 25:75 mixture of the quasienantiomeric substrates **2a** and **2b**, a perfectly enantioselective catalyst would be expected to produce the allyl intermediates **3a** and **3b** in a 50:50 ratio, whereas a completely unselective catalyst would yield a 25:75 ratio (Scheme 1). For a partially selective catalyst, the selectivity factor s, which is equivalent to the enantiomeric ratio

Scheme 3. Screening Conditions
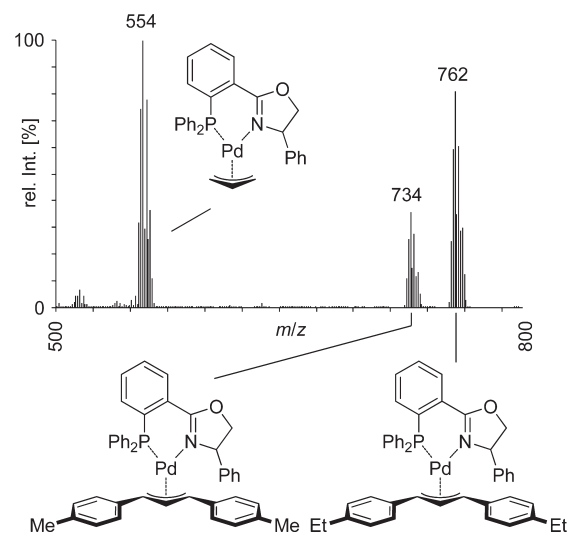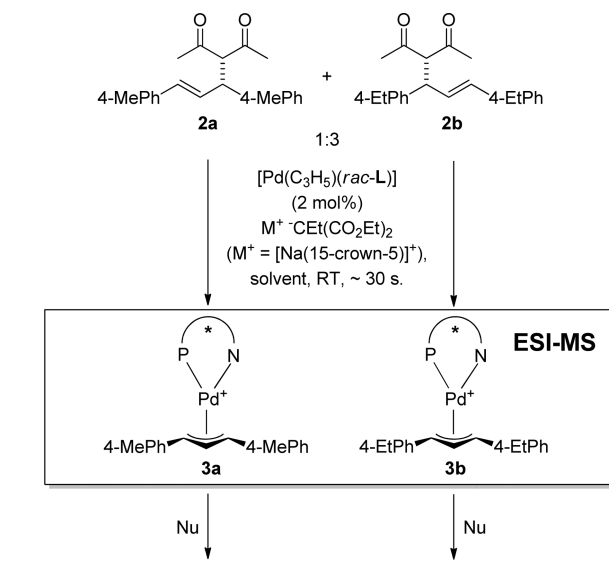
Figure 1. ESI-MS spectrum from screening with phox ligand **4c** in DCM. Substrate ratio: **2a**/**2b** = 1:3.15. Observed ratio of allyl intermediates: **3a**/**3b** = 30.5:69.5. Calculated selectivity: s = 3.5; ee = 56%.

produced by the forward reaction, can be calculated from eq 1, assuming pseudo-zeroth-order conditions [Q = [2a]/[2b] and I = signal intensity; see the Supporting Information (SI)].

$$\frac{I(\mathbf{3a})}{I(\mathbf{3b})} = \frac{\left(\dfrac{sQ}{sQ+1}\right) + \left(\dfrac{Q}{Q+s}\right)}{\left(\dfrac{1}{sQ+1}\right) + \left(\dfrac{s}{Q+s}\right)} \qquad (1)$$

For initial tests, the racemic 4-aryl-substituted phox ligands **4a**—**c** were used. Ligand **4c**, which is known to induce high enantioselectivity in allylic substitutions of 1,3-diarylallyl esters, was prepared by a literature procedure,[6] whereas the new ligands **4a** and **4b** were readily synthesized by the route shown in Scheme 2. The quasienantiomeric substrates **2a** and **2b** were
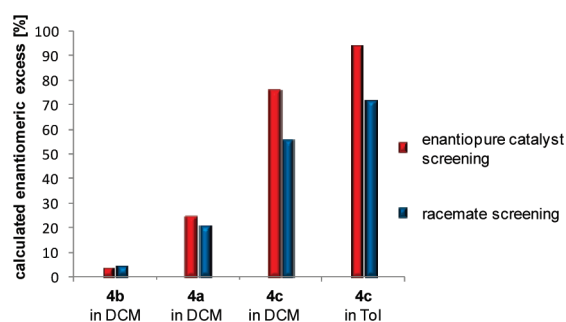
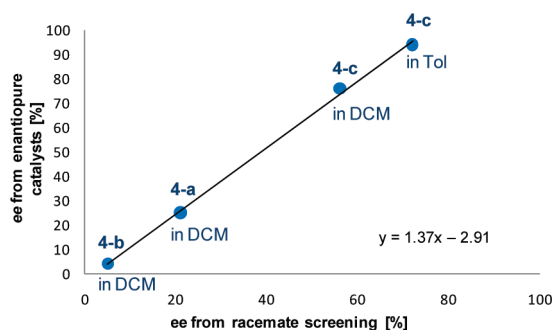**Figure 2.** Comparison of the screening methods.

**Figure 3.** Correlation of screening results and actual ee.

obtained as enantiomerically pure compounds as previously described.[5c]

When a 24:76 mixture of the quasienantiomers **2a** and **2b** was treated with a catalyst generated in situ from [Pd-$(C_3H_5)(MeCN)_2$]OTf and the corresponding racemic phox ligand under the conditions previously developed for back-reaction screening, the characteristic signals of Pd—allyl intermediates **3a** and **3b** were observed (Scheme 3). A typical spectrum obtained from the reaction with the catalyst derived from **4c** in dichloromethane (DCM) is shown in Figure 1.

From the signal ratio of the major isotopomers of **3a** and **3b** at m/z 734 and 762, the selectivity factor s was calculated to be 3.5, corresponding to an ee of 56% for the forward reaction (eq 1; **3a**/**3b** = 30.5:69.5, Q = **2a**/**2b** = 1:3.15). The screening results for the three ligands **4a**−**c** are shown in Figure 2 (blue bars). The 5,5-dimethyl phox derivatives **4a** and **4b** gave only very low selectivities with calculated ee's of about 5 and 21%, respectively.[7] Obviously, the two geminal methyl groups, which alter the conformation of the oxazoline ring by interaction with the adjacent phenyl substituent, have a detrimental effect on the enantios-electivity. To determine whether other solvents would be tolerated, the more selective catalyst derived from ligand **4c** was also tested in toluene. In this solvent, an improved ee of 72% was obtained.

These results were compared with the ee values determined from back-reaction screening with the corresponding enantio-pure catalysts (Figure 2). For this purpose, racemic ligands **4a** and **4b** were resolved by semipreparative HPLC. Evidently, the enantioselectivities obtained with the enantiopure catalysts (red bars) deviated significantly from the values calculated for the racemic catalysts (blue bars). However, the enantioselectivity order was the same, demonstrating that the most selective catalysts and the best conditions (e.g., choice of solvent) can be readily identified by screening racemic catalysts.

Scheme 4. Synthesis of Phox Derivatives 4d−f[a]

d: Ar = 3,5-dimethyl-phenyl
e: Ar = 3,5-di-*tert*-butyl-phenyl
f: Ar = 9-anthracenyl
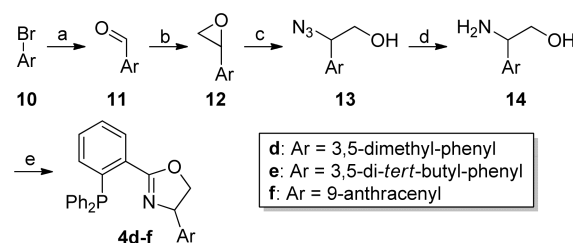
[a] Conditions: (a) (1) *n*BuLi, THF, −78 °C, 20 min; (2) DMF, −78 °C → RT, 1 h; H_2O. (b) $Me_3S^+I^-$, H_2O, KOH, MeCN, 60 °C, 4 h. (c) NaN_3, AcOH, 1:1 acetone/H_2O, 50 °C, 4 h. (d) H_2, 5 mol % Pd/C, EtOH, RT, 4 h. (e) (1) 2-(diphenylphosphino)benzonitrile, $ZnCl_2$, C_6H_5Cl, reflux, 7 days; (2) 2,2′-bipyridine, $CHCl_3$, RT, 2 h.

Table 1. Screening Results[a]

entry	ligand	ee from racemate screening [%]	corrected ee [%][b]
1	**4a**	21	26
2	**4b**	5	4
3	**4c**	56	74
4	**4c**[c]	72	96
5	**4d**	56	74
6	**4e**	61	81
7	**4f**	—[d]	—

[a] Screening was carried out in DCM; for conditions, see Scheme 3. [b] Obtained by applying the correction function shown in Figure 3. [c] Screening was carried out in toluene. [d] No intermediates were detected.

Surprisingly, when we plotted the actual ee values obtained from the enantiopure catalysts against the values from racemic catalyst screening, we found an excellent linear correlation between the two data sets (R^2 = 0.998; Figure 3).[8] Thus, it should be possible to determine the actual enantioselectivity of a chiral catalyst from its racemic form by applying the correction function obtained by linear regression.

To verify this assumption, we examined three additional racemic phox ligands (**4d**−**f**) having different 4-aryl substituents on the oxazoline ring (Scheme 4). Ligands **4d** and **4e** with 3,5-dimethyl- and 3,5-di-*tert*-butylphenyl substituents seemed to be of interest because of the beneficial effect of meta substituents on aryl groups observed in enantioselective hydrogenations, allylic substitutions, and Heck reactions.[9] The desired racemic ligands were easily synthesized from the corresponding aryl bromides via the sequence shown in Scheme 4. Clearly, the avoidance of enantioselective transformations or resolution steps, which would have been necessary for screening the enantiopure catalysts, saved a lot of time in this case.

The new ligands were screened in DCM under the conditions used for ligands **4a**−**c** (Table 1). The 3,5-dimethylphenyl derivative **4d** induced exactly the same selectivity as the parent phenyl-phox ligand **4c** (56% ee, corresponding to a corrected value of 75% ee calculated from the linear regression equation shown in Figure 3). The di-*tert*-butylphenyl derivative **4e** gave a slightly higher ee of 61%, corresponding to a corrected value of 81% ee. This result was in excellent agreement with the ee of 82% determined for the enantiomerically pure ligand. The bulky meta *tert*-butyl substituents apparently have a small but distinct posi-tive effect on the enantioselectivity, whereas the influence of the smaller methyl substituents in **4d** is negligible. With the catalyst

derived from ligand **4f**, no intermediates were observed. Preparative experiments were consistent with this result, as they showed that under the conditions used for screening, less than 5% product had formed after 24 h. Apparently, the sterically demanding anthracenyl-substituted ligand does not form an active catalyst.

The results in Table 1 and the very good linear correlation between the calculated ee values from racemic catalyst screening and the actual ee values from the corresponding enantiopure catalysts demonstrate that it is possible to determine the enantioselectivity of a chiral catalyst from the racemic form in a reliable manner. Especially for catalysts providing ee's in the 50−100% range, the results are remarkably accurate.[7] However, two questions remain: why are the ee values obtained from the racemic catalysts about 25% lower than the actual enantioselectivities determined from the enantiopure catalysts, and why do the data from the racemic and the enantiopure catalysts show this linear correlation? We assume that the ee difference results from a deviation from ideal pseudo-zeroth-order kinetics.[3,4] If the turnover rates of the two enantiomeric catalysts show some dependence on the substrate concentration, the proportion of intermediate **3b** derived from the more abundant quasienantiomer **2b** should be higher than that under pseudo-zeroth-order conditions, resulting in a lower predicted selectivity when eq 1 is applied. In this case, the observed linear correlation would imply that the deviation from pseudo-zeroth-order conditions affects the ee values of the different catalysts by the same degree.

Our assumption is supported by the observed dependence of the ee difference on the substrate/catalyst (S/C) ratio (see Table 2 in the SI).[10] The calculated ee values for the racemic ligand **2e** increased from 58 to 76% when the S/C ratio was raised from 25:1 to 200:1. As expected, at lower catalyst loading, the deviation from the enantioselectivity of the enantiopure catalyst was smaller. However, because of the low signal intensities at S/C ratios of ≥ 100:1, the results proved to be less accurate than with the standard 50:1 ratio generally used. These results indicate that even under conditions that deviate from an ideal pseudo-zeroth-order regime, reliable ee values can be obtained.

In summary, we have shown that on the basis of the concept of Lloyd-Jones,[3] the enantioselectivity of a chiral catalyst can be readily determined from its racemic form by mass spectrometric screening of a nonequal mixture of two quasienantiomeric substrates. The experimental protocol is simple and fast, as no workup or product isolation is necessary. As we have demonstrated for the screening of enantiopure catalysts,[5] it should also be possible to evaluate mixtures of racemic catalysts simultaneously. Our method should be a valuable addition to existing screening methods, especially for evaluating new catalyst structures that are not readily available in enanantiomerically pure form.

ASSOCIATED CONTENT

S **Supporting Information.** Experimental procedures, characterization data for all reactions and products, and detailed screening procedure and results. This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) The error margins in the data of the less selective catalysts (ligands **4a** and **4b**) are relatively high because the difference between the measured signal ratio, $I(3a)/I(3b)$, and the ratio of quasienantiomeric substrates, Q, is extremely small in the 0−30% ee range [e.g., for 20% ee and $Q = 25:75$, $I(3a)/I(3b)$ is 26:74]. Consequently, small measurement errors lead to large errors in the calculated ee values. In five reactions, the ee values for **4a** varied from 17 to 26% (see Table 1 in the SI). Values in the 50−100% ee range are much more accurate because they are based on a substantially larger difference between the signal ratio and Q. For ligand **4e**, the values from four screening experiments were between 61 and 62% ee (see Table 1 in the SI).

(8) Theoretically, the line should go through the zero point. The observed deviation probably results from the relatively large error margins of the ee values below 30% ee (see ref 7).

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