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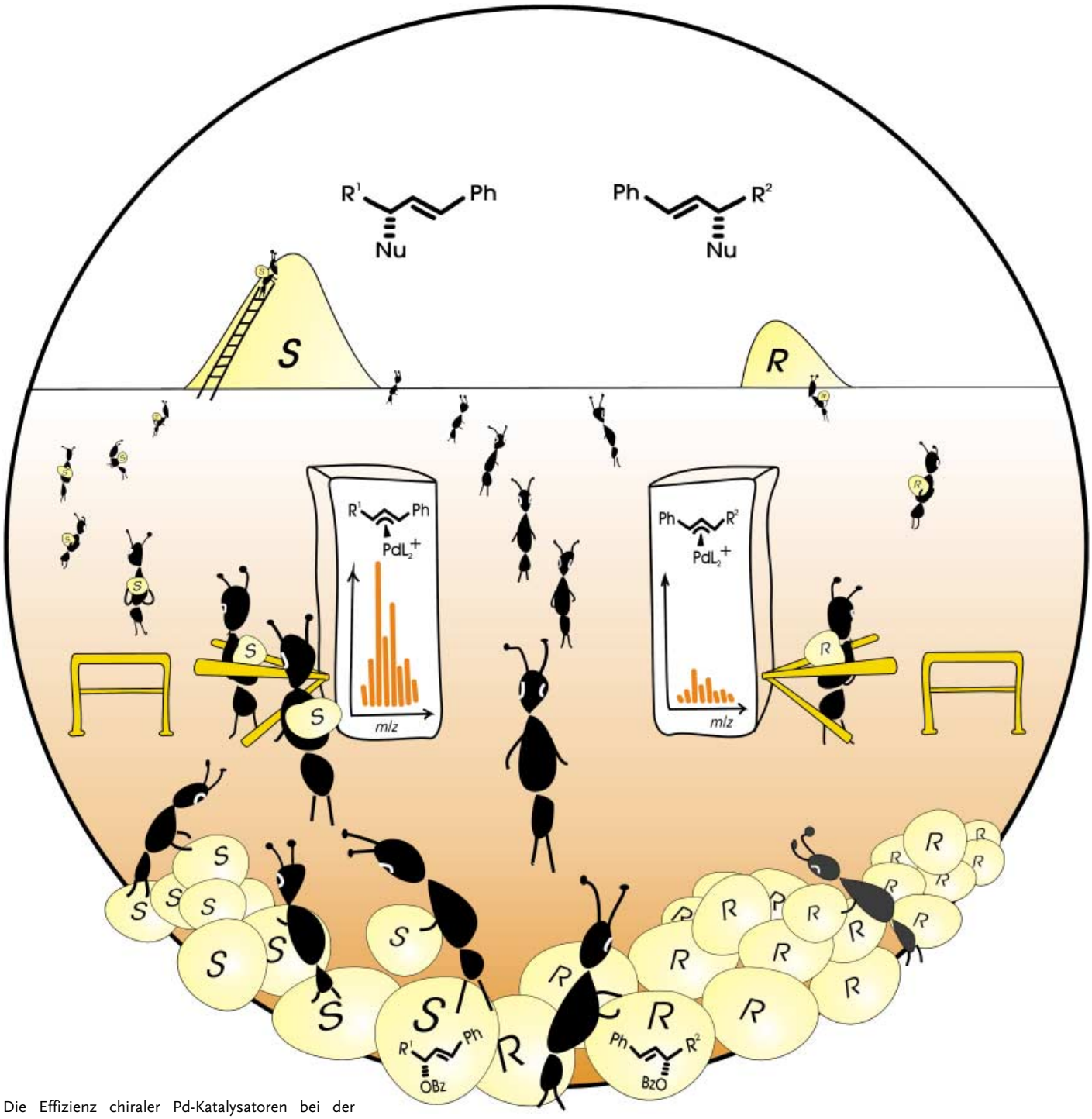

Die Effizienz chiraler Pd-Katalysatoren bei der kinetischen Racematspaltung von Allylestern kann leicht anhand von pseudoenantiomeren Substraten mit unterschiedlichen Massen ermittelt werden. A. Pfaltz und C. Markert zeigen auf den folgenden Seiten, dass die Elektrospray-Massenspektrometrie bestens geeignet ist für die Bestimmung der Allyl-Pd-Intermediate, die direkt die intrinsische Selektivität der Katalysatoren wiedergeben.

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Enantioselectivity Determination

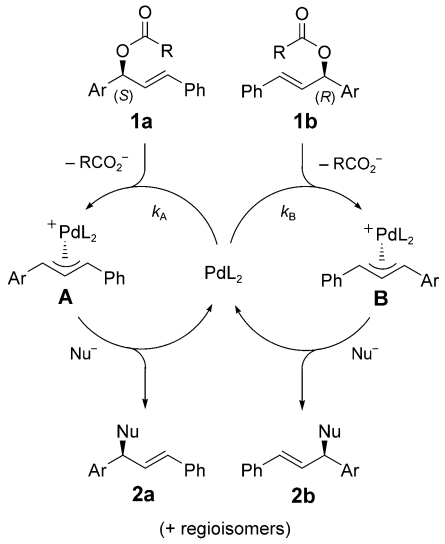
Screening of Chiral Catalysts and Catalyst Mixtures by Mass Spectrometric Monitoring of Catalytic Intermediates**

*Christian Markert and Andreas Pfaltz**

Combinatorial methods have become an important focus of research in asymmetric catalysis.[1,2] During the last few years efficient techniques have been developed for the high-throughput parallel screening of chiral catalysts.[3] However, parallel screening based on product analysis has potential pitfalls, since the enantioselectivity of a reaction is often lower than the inherent selectivity of the catalyst because of an unselective background reaction, catalytically active impurities, or partial dissociation of a chiral ligand from a metal catalyst. Problems of this kind would be avoided if the catalyst's ability for enantiodiscrimination could be determined directly from examining catalyst–reactant complexes rather than from product analysis. Here we report the realization of this concept for a palladium-catalyzed kinetic resolution of allylic esters by using electrospray mass spectrometry (ESI-MS) as an analytical tool.

Our work was inspired by an ingenious screening method for homogeneous polymerization catalysts developed by Chen:[4] by using ESI-MS, which is selective for ionic species, he could detect reaction intermediates derived from cationic metal catalysts. In this method the growing polymer chain remains bound to the catalyst during polymerization and so the most effective catalysts carry the longest chains. Thus, the chain length, which can be determined by ESI-MS, is a measure of the activity of a catalyst. Since the signals of the various catalyst intermediates all appear at different m/z values, the screening of catalyst mixtures of different molecular mass is possible. We thought that it should be possible to develop a method of this kind for measuring the inherent enantioselectivity of chiral catalysts directly. The kinetic resolution of allylic esters by palladium-catalyzed allylic substitution[5] seemed an ideal candidate for this endeavor (Scheme 1).

The first step of the catalytic cycle, formation of Pd–allyl complexes **A** and **B** is fast, while the second step, nucleophilic addition to the allyl system, to give products **2a** and **2b** as well as the corresponding regioisomers (nucleophilic attack at the position next to the Ph substituent), is slower and turnover-limiting. The cationic intermediates **A** and **B** correspond to the resting state of the catalytic cycle and, therefore, should



Scheme 1. Kinetic resolution of allylic esters **1a** and **1b**.

exist in sufficient concentration to be observable by ESI-MS. The ratio **A**:**B** reflects the catalyst's ability to discriminate between the two enantiomeric substrates **1a** and **1b**. Clearly, the two intermediates **A** and **B**, which are derived from the two enantiomers of the substrate, have the same molecular mass and, therefore, can not be distinguished by mass spectrometry. However, if we label **1a** and **1b** with two different alkyl groups at the *para* position of the aryl group (for example, Ar = 4-methylphenyl in **1a** and 4-ethylphenyl in **1b**), then the signals of **A** and **B** would appear at different positions in the mass spectrum and their ratio could be determined by integration. Since the *para*-alkyl substituents are too remote from the reactive part of the molecule to have a notable influence on the reaction, we expected the same selectivity as for the reaction of the parent enantiomers **1a** and **1b** with Ar = phenyl. Mass-labeled enantiomers (or pseudoenantiomers as they are often called) have been used before for determining the enantiomeric purity of chiral products.[6]

As a first test we treated an equimolar mixture of two pseudoenantiomers with an achiral Pd catalyst and used the anion of diethyl ethylmalonate as the nucleophile. The ESI mass spectrum indeed showed the expected signals corresponding to the allyl intermediates **A** and **B** with the characteristic isotope distribution for palladium (Figure 1). The two signal groups had the same intensity, as anticipated for an achiral catalyst. The reaction with a chiral, enantiomerically pure catalyst derived from ligand **3** showed a strong bias toward one of the two pseudoenantiomers (**A**:**B** = 9:91). The control experiment performed using the same catalyst but inversely labeled pseudoenantiomers (methyl and ethyl groups interchanged) gave a reversed ratio of 91:9.

In the initial phase of the reaction, when the two pseudoenantiomeric substrates are present in equal concentrations, the ratio **A**:**B** is equivalent to the stereoselectivity factor s, which is defined as the ratio of rate constants k_A:k_B of the faster- and slower-reacting substrate enantiomer, respectively. Screening by ESI-MS is extremely fast and requires

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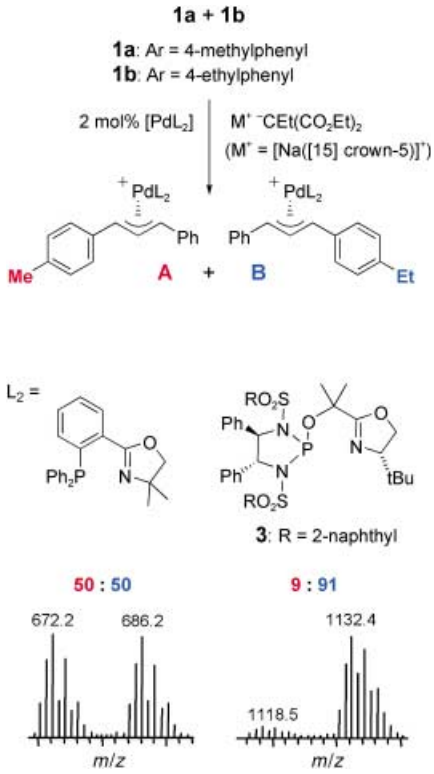
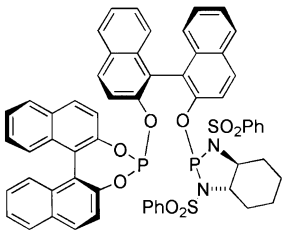


Figure 1. ESI-MS screening of Pd catalysts for the kinetic resolution of **1a** and **1b**.

minimal amounts of substrate compared to conventional screening, which necessitates taking samples at regular time intervals and analyzing them by HPLC on columns with chiral stationary phases. By using our ESI-MS screening technique we were able to test up to ten chiral catalysts per hour, which would have taken several days by conventional methods. We identified several ligands with *s* factors of >20 from a library of 60 ligands comprising mainly P,N ligands previously developed in our group[7] and commercially available diphosphanes.[8] An *s* factor of 100 was observed under optimized conditions using the most selective ligand **4**;[9] this value is



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significantly higher than the best selectivities previously reported for this reaction.[10] In several cases we compared the data from ESI-MS screening with results obtained from kinetic analyses of preparative reactions. Pleasingly, the *s* factors calculated from the curve obtained by plotting the enantiomeric excess of the remaining substrate against conversion closely matched the *s* factors determined by ESI-MS (deviation $<10\,\%$ for *s* factors in the range of 1–20).

The transition states of the first step in the catalytic cycle (**1a**→**A**, **1b**→**B**; Scheme 1) and the second step (**A**→**2a**, **B**→**2b**) have essentially the same geometry. Accordingly, ligands identified by our screening protocol for efficient kinetic resolution should also induce high selectivities in the second step and, therefore, produce high *ee* values in the nucleophilic addition to symmetrically substituted allyl systems (for example, **A**; Ar = Ph). This postulate has been verified in preparative reactions of the racemate **1a**/**1b** (Ar = Ph).

After establishing a reliable protocol for the screening of single catalysts, we wanted to test if our method could be used for screening mixtures of several Pd catalysts in one reaction. Preliminary experiments gave disappointing results, because rapid exchange of chiral ligands between the different Pd–allyl intermediates took place under the reaction conditions. This strongly affected the relative intensities of the signals corresponding to the two pseudoenantiomers, thus making the results unreliable. However, at lower temperatures (−78 °C instead of 23 °C) ligand exchange was suppressed while the catalytic reaction was still sufficiently fast. Figure 2 shows the results of a typical experiment carried out under these conditions.

Five different catalyst precursors were combined with the pseudoracemate **1a**/**1b** (50-fold excess based on the total Pd concentration) at −78 °C in toluene. The control spectrum before addition of the nucleophile showed the expected signals corresponding to the five Pd–allyl complexes (Figure 2a). The reaction was initiated by addition of malonate (2 equiv per equiv of Pd). Allyl transfer from Pd to malonate generated the active Pd^0 catalysts, which reacted with the two pseudoenantiomers to give the corresponding allyl intermediates (Figure 2b). The five catalyst precursors and the ten catalyst complexes derived from the two pseudoenantiomeric substrates all have different molecular masses and, therefore, could all be readily observed and identified in the ESI mass spectrum taken after a reaction time of two minutes. In addition to the selectivity factors, a qualitative reactivity order could be established from the spectrum. Complex **5** shows the lowest reactivity, as evident from the intense signal of the allyl precursor. Complexes **6** and **8** react significantly faster, as demonstrated by the complete consumption of the catalyst precursors. A selectivity order **8** > **7** > **6** ~ **5** ~ **9** is derived from the signal ratios, with complex **8** clearly being the most selective catalyst.

The results show that it is indeed possible to obtain reliable selectivity data from catalyst mixtures in homogeneous solution. In principle, there is no restriction on the number of catalysts that can be screened simultaneously, as long as the signals do not overlap. However, the reactivity of the individual catalysts should be on the same order, otherwise the signals corresponding to the least-reactive catalysts become too small. In addition to speed, the fact that the results reflect the inherent enantioselectivity of the catalyst is a big advantage of this method. The same methodology should also be applicable to allylic substitutions starting from *meso* substrates bearing two enantiotopic leaving groups.[5] There are also other reactions that proceed through ionic catalyst–reactant complexes and, therefore, could be amenable to this screening method.

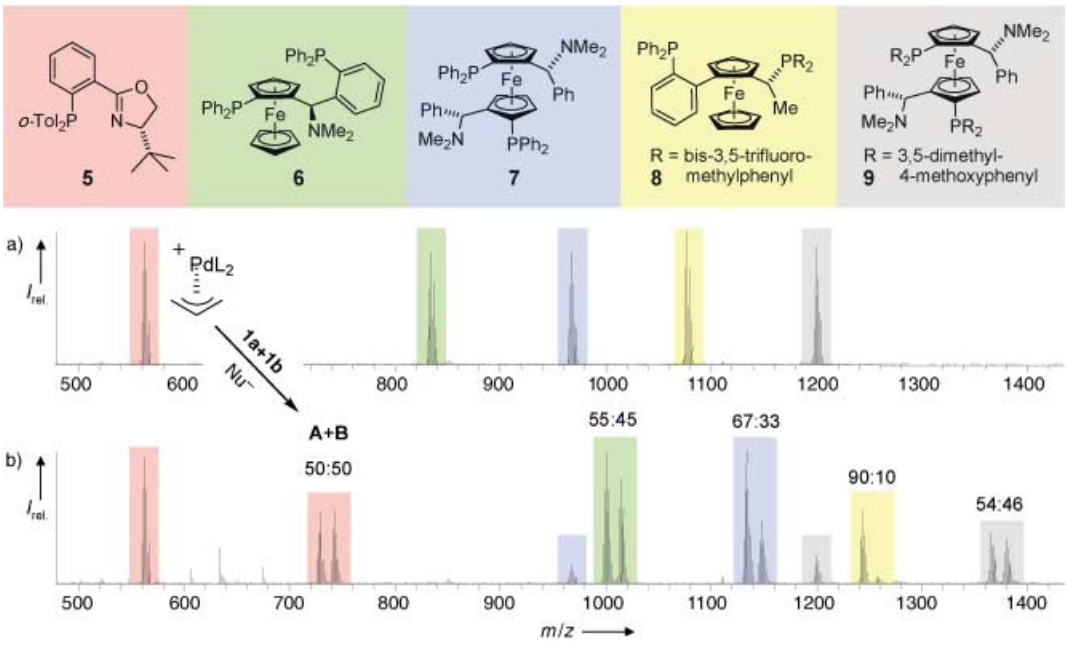

Figure 2. Simultaneous screening of a mixture of five Pd catalysts.

Experimental Section

Substrates **1a** and **1b** were prepared according to reference [11]. In a typical reaction, a precatalyst solution (100 μL, 2.5 mM in toluene, prepared from equimolar amounts of ligand and $[Pd(C_3H_5)(MeCN)_2]OTf$) (Tf = triflate) was mixed with a solution of **1a** and **1b** (100 μL, 125 mM in toluene, 2 × 25 equiv per equiv of Pd). The reaction was started by addition of two equivalents of a nucleophile solution (50 μL, 10 mM in toluene; prepared from NaH, diethyl ethylmalonate, and [15]crown-5 in THF with subsequent evaporation to dryness). The screening of single catalysts was performed at room temperature, whereas mixtures of complexes were tested at −78 °C. After stirring the reaction mixture for 2 min, a sample was taken, diluted to 10^{-5} M (dichloromethane) and analyzed by ESI-MS (MAT Finnigan LCQ). Reactions in Figure 1 were repeated several times with consistent results (relative ESI-MS integrations could be reproduced with deviations of less than ±3%).

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