Catalyst Screening (2)

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Mass Spectrometric Screening of Chiral Catalysts by Monitoring the Back Reaction of Quasienantiomeric Products: Palladium-Catalyzed Allylic Substitution**

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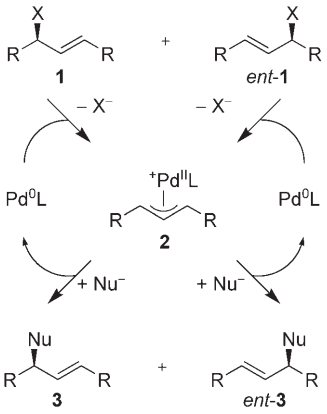
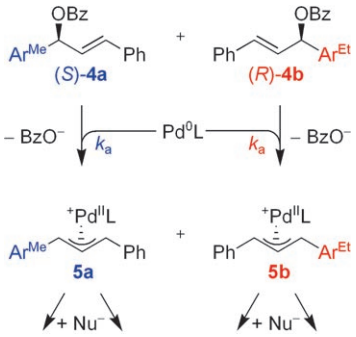
The enantioselectivity of a chiral catalyst is usually determined by measuring the enantiomeric excess of the reaction product. However, the *ee* value obtained from analysis of the product does not necessarily reflect the intrinsic enantioselectivity of the catalyst. A competing noncatalytic background reaction which produces a racemic product, catalytically active impurities, or dissociation of a chiral ligand from a metal catalyst can lead to low enantiomeric purity even though the catalyst itself is highly selective.

We recently reported a method for determining the intrinsic enantioselectivity of chiral catalysts by using quasienantiomeric substrates and electrospray ionization mass spectrometry (ESI-MS) as the analytical tool.[1–3] In contrast to previously developed screening methods for enantioselective reactions which also make use of quasienantiomeric substrates,[4,5] our method relies on the quantification of catalytic intermediates rather than analysis of the product.

As a first application, we studied the kinetic resolution of racemic allyl esters by using a palladium-catalyzed allylic substitution reaction (Scheme 1).[6] By starting with a 1:1 mixture of two mass-labeled, quasienantiomeric substrates (*S*)-**4a** and (*R*)-**4b**, the selectivity factor $s = k_a/k_b$ of a catalyst can be deduced from the ratio of the corresponding allyl intermediates **5a**/**5b** as determined by mass spectrometry (Scheme 2). As ESI-MS allows the selective detection of charged species in the presence of a large excess of neutral compounds, cationic intermediates such as **5a** and **5b** can be observed even at low catalyst loadings under conditions normally used for preparative catalytic reactions. The method is fast and reliable, does not require workup of the reaction mixture, and in contrast to methods based on product analysis allows the simultaneous screening of catalyst mixtures (if the catalysts have different molecular masses).



Scheme 1. General mechanism of the palladium-catalyzed allylic substitution of racemic substrates **1**. Nu = nucleophile.



Scheme 2. ESI-MS screening of catalysts for kinetic resolution using quasienantiomeric substrates **4a** and **4b** (Ar^{Me} = 4-MeC_6H_4, Ar^{Et} = 4-EtC_6H_4, $Nu^- = {}^-CEt(CO_2Et)_2$, Bz = benzoyl).

The screening of a large number of catalysts showed that the selectivity of a catalyst in the kinetic resolution step did not correlate with the enantioselectivity of the nucleophilic addition to the allyl intermediate **2**. It is this step that determines the enantioselectivity of the overall reaction leading from the racemic allyl ester **1** to the optically active substitution product **3** (Scheme 1). Many catalysts that gave high enantioselectivity in the overall reaction were inefficient in the kinetic resolution of allyl esters.

Herein we report an extension of our screening method which allows the determination of the enantioselectivity in the nucleophilic addition step and can, therefore, be used to evaluate the intrinsic enantioselectivity of chiral catalysts for the overall allylic substitution process. Instead of screening the forward reaction, we monitored the back reaction of quasienantiomeric products that leads to the corresponding mass-labeled allyl–palladium complexes. According to the principle of microscopic reversibility, the transition states of

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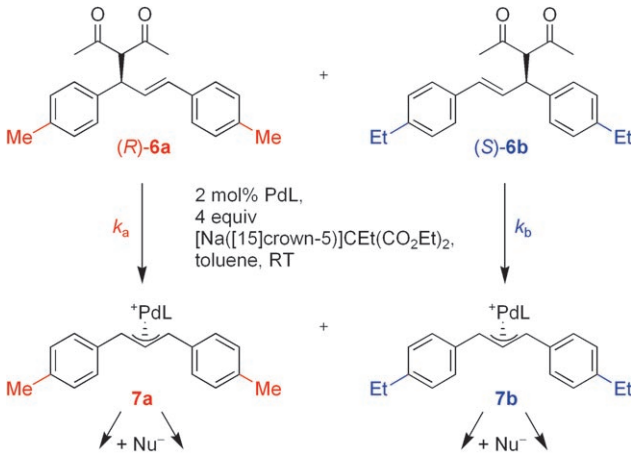
the forward and back reaction are identical, thus the enantioselectivity determined in this way is the same as the enantioselectivity of the forward reaction.

To find a suitable nucleophile which showed sufficient reactivity as a leaving group, we initially screened a range of allylation products **3** (R = Ph) derived from Meldrum's acid, phthalimide, acetyl acetone, and dimethyl malonate. In all cases the corresponding allyl complexes generated by elimination of the nucleophile were detected in the ESI mass spectra when the reactions were carried out under conditions typically used for preparative allylic substitutions (2 mol% catalyst, toluene, RT). From the relative intensities of the signals corresponding to the precatalyst $[Pd(C_3H_5)L]^+$ and the substituted allyl complex **2** (R = Ph), a qualitative order of leaving-group reactivity could be established for the four allylation products. As expected, the reactivities correlated with the pK_a values of the conjugated acids in the order Meldrum's acid > phthalimide > acetyl acetone > dimethyl malonate. On the basis of these results we decided to develop a screening protocol for the reaction of the quasienantiomeric allylation products (*R*)-**6a** and (*S*)-**6b** derived from acetyl acetonate (Scheme 3), which is a sufficiently reactive leaving group and has similar properties to those of other widely used

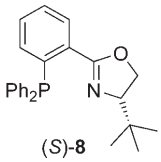
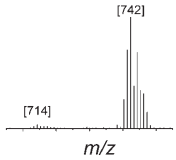
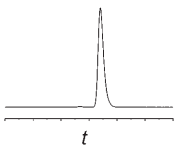
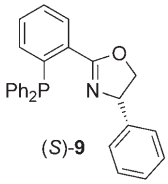
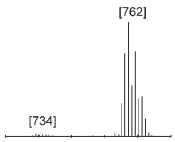
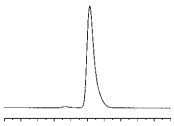
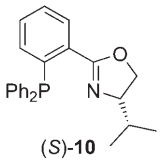
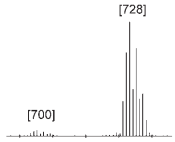
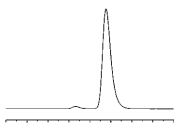
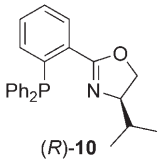
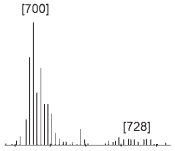
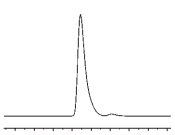
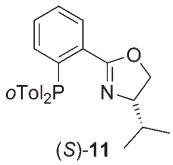
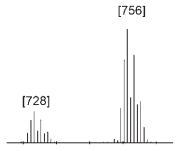
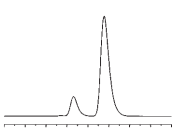
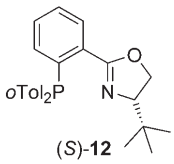
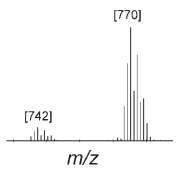
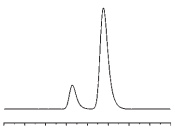


Scheme 3. Back-reaction screening of the nucleophilic addition step of allylic substitution with acetyl acetonate.

C nucleophiles, such as malonate esters. The required enantiomerically pure quasienantiomers were synthesized by palladium-catalyzed allylic alkylation starting from the corresponding benzoates (see the Supporting Information).[7]

The precatalysts were prepared in situ from $[Pd(C_3H_5)(MeCN)_2]OTf$ (Tf = triflate) and an equimolar amount of the corresponding chiral ligand in toluene. An equimolar mixture of (*R*)-**6a** and (*S*)-**6b** (2.5 equiv each, based on Pd) was added and the reaction started by activation of the precatalyst with the crown ether sodium salt of diethyl ethylmalonate (4 equiv based on Pd). After 30 s at room temperature, a sample was taken, diluted with dichloromethane, and directly injected into the mass spectrometer. As shown in Table 1, the signals of the allyl complexes **7a** and **7b**, formed by elimination of acetyl acetonate, were clearly visible and showed the characteristic isotope pattern of Pd. The ratios of the signal heights of these two signal clusters correlated very well with the enantiomeric ratios, determined by HPLC analysis, of the products obtained in the corresponding preparative reactions of racemic 1,3-diphenyl-2-propenyl benzoate with acetyl acetonate.[8] Depending on the reactivity of the catalyst, variable amounts of unreacted $[Pd(C_3H_5)L]^+$ were visible in addition to the signals of **7a** and **7b**. Phox derivatives (*S*)-**8**, (*S*)-**9**, (*R*)-**10**, and (*S*)-**10** were clearly the most effective ligands, whereas the analogous bis(*ortho*-tolyl)-substituted phosphanes (*S*)-**11** and (*S*)-**12** induced only moderate enantioselectivity. The two enantiomeric ligands (*S*)-**10** and (*R*)-**10**

Table 1: ESI-MS screening of allylic alkylation using quasienantiomers (*R*)-**6a** and (*S*)-**6b** (Scheme 3).

Ligand	Screening **7a**/**7b**	Preparative reaction[a] *R*/*S*
 (*S*)-**8**	3 : 97 	1 : 99 
 (*S*)-**9**	2 : 98 	1 : 99 
 (*S*)-**10**	4 : 96 	2 : 98 
 (*R*)-**10**	96 : 4 	98 : 2 
 (*S*)-**11**	20 : 80 	14 : 86 
 (*S*)-**12**	17 : 83 	17 : 83 

[a] HPLC analysis (Daicel Chiracel AD-H, heptane/isopropanol 97:3, flow rate 0.9 mL min^{-1}, 20 °C, 254 nm): $t_R(R)$ = 16.3 min, $t_R(S)$ = 17.9 min.

gave exactly the reverse signal ratio, thus confirming that quasienantiomers (*R*)-**6a** and (*S*)-**6b** behave like real enantiomers.

In an additional control experiment with inversely labeled quasienantiomers, an exactly reverse signal ratio was again observed. Overall, the results obtained with ligands **8**–**12** demonstrate that ESI-MS screening of the back reaction is a fast and reliable method for evaluating libraries of chiral catalysts.

The elimination of acetyl acetonate is an endergonic and, consequently, reversible reaction. However, at the initial stage of the reaction the concentration of acetyl acetonate is much lower than that of diethyl ethylmalonate, so the addition of acetyl acetonate to the allyl–palladium complexes **7a** and **7b** is negligible. Therefore, it is important to take samples at the very beginning of the reaction. After longer reaction times, we observed that the signal ratios decreased slowly because of racemization of the quasienantiomers (*R*)-**6a** and (*S*)-**6b** through reversible elimination/readdition of acetyl acetone.

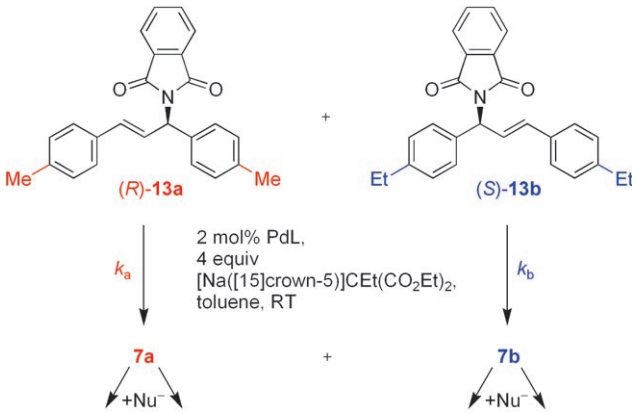
The equilibrium between the allylation products **6a** and **6b** and the corresponding allyl complexes **7a** and **7b** must lie almost entirely on the side of **6a** and **6b**, as these are known to be stable products. Nevertheless, the high sensitivity of ESI-MS makes reliable detection and accurate quantification of the allyl intermediates possible, despite their low concentration.

After having established a reliable protocol for the screening of single catalysts, we applied our method to the screening of mixtures of Pd complexes. As shown previously, rapid ligand exchange between the different allyl–palladium species takes place when the reaction is carried out at room temperature. However, at lower temperatures (−20 °C) ligand exchange is considerably slowed down while the back reaction still proceeds. In contrast to the kinetic resolution process investigated before,[1] no reaction was observed at −78 °C. Screening a mixture containing three catalysts derived from (*S*)-**8**, (*S*)-**9**, and commercially available (*R*)-1-[(*S*)-2-diphenylphosphanyl)ferrocenyl]ethyl-di-3,5-xylylphosphane[9] at −20 °C yielded ratios of 10:90, 8:92, and 22:78, respectively, for the corresponding allyl complexes **7a** and **7b**, whereas selectivities of 3:97, 2:98, and 20:80, respectively, were obtained from the screening of single catalysts. Although the ratios are lower in the multicatalyst screening, the order of selectivity remains the same and the most efficient catalyst can be readily identified.

We also successfully applied back-reaction screening to an allylic amination reaction in which phthalimide was used as the nucleophile (Scheme 4 and Table 2). When the quasienantiomeric *N*-allylphthalimides (*R*)-**13a** and (*S*)-**13b** were treated under the conditions used for the screening reactions with acetyl acetonate as the nucleophile, the signals of the corresponding allyl–palladium intermediates **7a** and **7b** were again observed in the ESI mass spectra.

For comparison, the corresponding preparative reactions of racemic 1,3-diphenyl-2-propenyl benzoate with the potassium phtalimide salt and 2 mol% of catalyst prepared in situ from [{PdCl(C_3H_5)}$_2$] were carried out in dichloromethane at room temperature. No conversion was observed under the conditions used for ESI-MS screening in toluene. The enantioselectivities induced by ligands **8**–**12** are very similar to those measured for the analogous reactions with acetyl acetonate. The enantiomeric ratios determined by ESI-MS correlate well with the results from analysis of the products from the preparative reactions. The somewhat lower selectivities determined by ESI-MS may be due to the different conditions applied in the preparative reactions and/or the reversibility of phthalimide elimination (see above). However, despite these small deviations, ESI-MS screening reveals the correct selectivity order and, therefore, allows reliable identification of the most selective catalysts.[10]

The concept of back-reaction monitoring considerably enhances the application range of ESI-MS-based screening. In addition to kinetic resolution, enantioselective reactions of prochiral substrates, which are the most common transformations in asymmetric catalysis, can now be studied. Although the method is not truly general, because it is only applicable to reactions proceeding via charged intermediates that are related to the enantioselective step, there are many important metal-catalyzed and also organocatalytic transformations that fulfill these requirements. We have recently developed a screening protocol for enantioselective Diels–Alder reactions by monitoring the retro-Diels–Alder reaction of quasienantiomeric products, which is reported in the following communication.[11]



Scheme 4. Back-reaction screening of the nucleophilic addition step of allylic amination with phthalimide.

Table 2: ESI-MS screening of allylic amination using quasienantiomers (*R*)-**13a** and (*S*)-**13b** (Scheme 4).

Ligand	Screening **7a**/**7b**	Preparative Reaction[a] *R*/*S*
(*S*)-**8**	97:3	>99:1
(*S*)-**9**	94:6	99:1
(*S*)-**10**	96:4	99:1
(*S*)-**11**	78:22	81:19
(*S*)-**12**	78:22	81:19

[a] HPLC analysis (Daicel Chiracel OD-H, heptane/isopropanol 99:1, flow rate 0.5 mL min^{-1}, 20 °C, 254 nm): $t_R(S)$ = 37.6 min, $t_R(R)$ = 51.8 min.

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[8] One of the referees pointed out that the experimental conditions of the back reaction were different from those of the preparative forward reaction because of the absence of benzoate ions. For this reason, back-reaction screening was repeated in the presence of one equivalent of [nBu$_4$N]OBz relative to the nucleophile. It was found that the presence of benzoate ions has no influence on the ratio **7a**/**7b**.

[9] Solvias ligand kit: Solvias AG, P.O. Box, 4002 Basel, Switzerland; www.solvias.com.

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