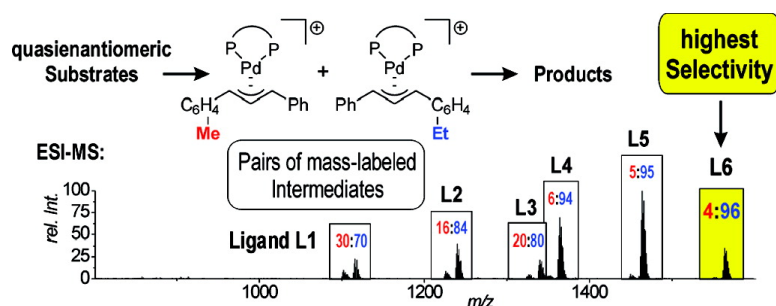


Combinatorial Ligand Development Based on Mass Spectrometric Screening and a Double Mass-Labeling Strategy

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Combinatorial Ligand Development Based on Mass Spectrometric Screening and a Double Mass-Labeling Strategy

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The development and fine-tuning of chiral catalysts which provide effective asymmetric induction in a specific transformation is often a labor-intensive and time-consuming process. Thus, screening methods that accelerate the identification and optimization of new catalysts are of considerable interest.¹

We have recently developed a screening method for chiral catalysts which induce kinetic resolution of racemic allyl esters **1**.² Starting from a 1:1 mixture of quasienantiomeric substrates **1a** and **1b**, the selectivity of chiral Pd catalysts can be determined by mass spectrometric quantification of the corresponding allyl-Pd intermediates **2a** and **2b** (Scheme 1).³

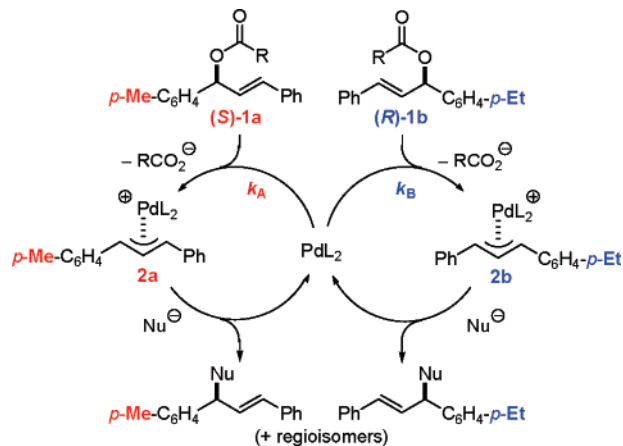
Electrospray ionization mass spectrometry (ESI-MS) is used as an analytical tool, as this technique allows selective detection of charged species in the presence of a large excess of neutral compounds.⁵ Our method benefits from operational simplicity and a fast, direct readout while avoiding completely any workup, isolation, or purification steps. All components are easily handled as solutions, and the detected ratio of mass-labeled intermediates **2a** and **2b** directly reflects the catalyst's intrinsic selectivity (k_B/k_A),⁶ unaffected by catalytically active impurities, partial dissociation of the chiral ligand-metal complex, or a noncatalytic background reaction leading to racemic product.

In previous experiments, we were able to show that this screening method can also be applied to catalyst mixtures. The enantioselectivities of five Pd catalysts were determined simultaneously in a single experiment.² Here we report on an extension of this concept and introduce a double mass-labeling strategy in the context of a catalyst optimization study.

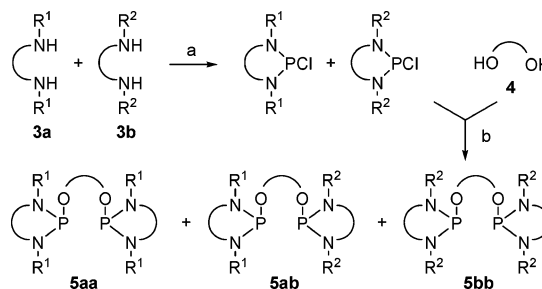
Starting from a set of readily available chiral diamines **3** and a chiral diol **4**, a library of ligands **5** can be prepared in two steps, as illustrated in Scheme 2 for two diamines **3a** and **3b**. The conventional way to identify the most effective ligand would be to prepare all possible products **5** from a given set of precursors **3** and to test them individually. Although symmetrical ligands such as **5aa** or **5bb** derived from two identical precursors **3** can be readily prepared, the synthesis of unsymmetrical derivatives such as **5ab** is less straightforward and most likely would require additional protection and deprotection steps in order to avoid formation of mixtures of symmetrical and unsymmetrical ligands. In addition, because the diamines and the diol are chiral, the influence of the relative configuration on the enantioselectivity has to be examined.

We thought that our mass spectrometric screening method would enable a much more effective approach to identify the optimal ligand, without the need of preparing each ligand separately. By statistical condensation of a mixture of diamines under the conditions shown in Scheme 2, it should be possible to prepare a library of ligands of type **5** in a single batch and to screen the corresponding catalyst mixture, prepared *in situ* by complexation with Pd, simultaneously in a single experiment. To demonstrate this concept, we chose sulfonamides of *trans*-1,2-cyclohexanedi-

Scheme 1. Pd-Catalyzed Allylic Substitution⁴ Starting from Quasienantiomeric Substrates **1a** and **1b**



Scheme 2. Preparation of Modular Ligands **5a**



^a Conditions: (a) PCl_3 , NEt_3 , THF, $-78^\circ\text{C} \rightarrow \text{rt}$; filter, evaporate; (b) chiral diol **4**, NEt_3 , THF, $-78^\circ\text{C} \rightarrow \text{rt}$; filter, evaporate.

amine (**3**) and *trans*-(3,4)-1-benzyl-3,4-pyrrolidinediol (**4**) as readily available chiral building blocks.⁷

The first experiment was designed to identify the optimal (*matched*) relative configuration. Accordingly, the (*R,R*)-diamine **3a** ($\text{R}^1 = \text{PhSO}_2$) and the quasienantiomeric (*S,S*)-diamine **3b** ($\text{R}^2 = 4\text{-Me-PhSO}_2$) were mixed and condensed with phosphorus trichloride and (*S,S*)-diol **4** (Scheme 2 and Figure 1). Filtration through a plug of silica gel and removal of all volatiles under vacuum yielded the expected mixture of three ligands **6aa**, **6ab**, and **6bb**. As our screening method is quite tolerant to impurities, we subsequently found that simple filtration without the use of silica gel provided ligand mixtures of sufficient purity for complexation with $[(\text{MeCN})_2\text{Pd}(\text{allyl})]\text{OTf}$ and subsequent screening.^{2,6} The spectra of the precatalysts and the screening results are shown in Figure 1.

The combination of mass-labeled substrates **1a** and **1b** and mass-labeled quasidiastereomeric ligands allowed us to determine the selectivity of each catalyst in the mixture. With a 6:94 ratio of allyl intermediates, the Pd complex of ligand **6bb** was clearly the most selective catalyst. As the three ligands bear sterically and electroni-

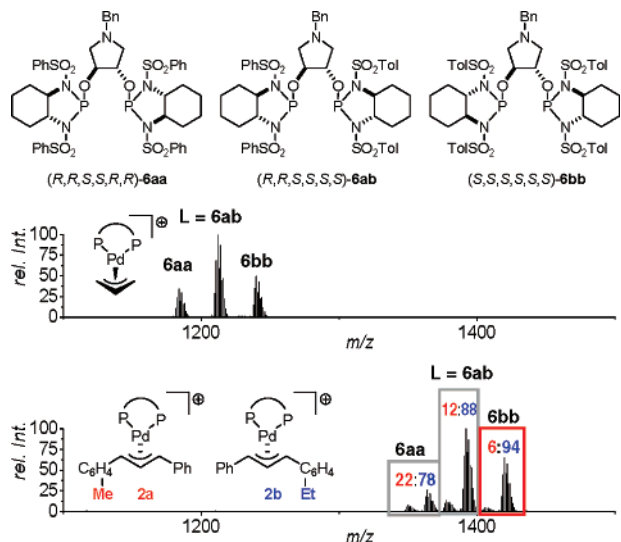


Figure 1. Structures of quasideastereomeric ligands **6aa**–**6bb** and ESI-MS spectra of the corresponding Pd-allyl precatalysts and reaction intermediates.

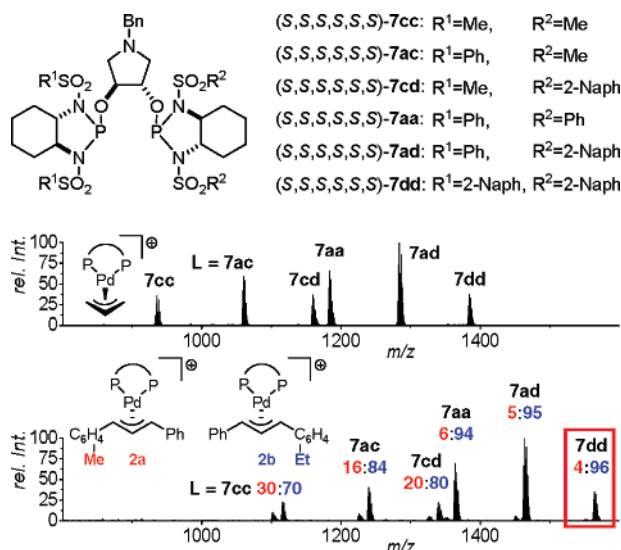


Figure 2. Structures of ligands **7cc**–**7dd** and ESI-MS spectra of the corresponding Pd-allyl precatalysts and reaction intermediates.

cally very similar phenyl- and *p*-tolyl-groups at their diamine units, we assumed that they behave like real diastereomers. Thus, we concluded that the *all-S* configuration of ligand **6bb** corresponds to the matched combination of stereocenters. As seen from the MS signals, all three ligands show the same sense of asymmetric induction. Apparently, the stereoselectivity is mainly controlled by the (*S,S*)-diol bridge. A control experiment with interchanged phenyl and tolyl groups confirmed this result (Supporting Information).

In a subsequent experiment, the structure of ligand **6bb** was further varied by introduction of different sulfonamide groups. As before, a mixture of all six possible ligands was prepared from three different sulfonamides and tested simultaneously (Figure 2).

ESI-MS screening revealed that sterically more demanding sulfonamide substituents induce higher selectivities, a trend also

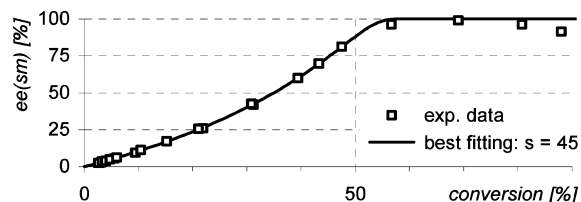


Figure 3. Evolution of the substrate ee with conversion in a preparative kinetic resolution using ligand **7dd** (HPLC).

observed for the less easily accessible unsymmetrical ligands **7ac**, **7cd**, and **7ad**. Having identified **7dd** as the best ligand in this series, we finally synthesized and characterized it as a single compound. ESI-MS testing of the corresponding Pd catalyst confirmed the high selectivity induced by this ligand, in agreement with a preparative kinetic resolution⁸ and HPLC analysis (Figure 3).

In summary, we have demonstrated that mass spectrometric screening of quasiautomeric substrates can considerably simplify structural optimization of chiral catalysts. Starting from a mixture of suitable building blocks, libraries of modular ligands can be readily prepared in a single batch and evaluated by simultaneous screening. Because the time-consuming synthesis and purification of individual ligands are avoided in this way, catalyst optimization can be accelerated significantly. We are currently evaluating this method for other classes of enantioselective reactions.

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Supporting Information Available: Experimental procedures and characterization data for all reactions and products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

References

- (1) (a) Archibald, B.; Brümmer, O.; Devenney, M.; Gorer, S.; Jandeleit, B.; Uno, T.; Weinberg, W. H.; Weskamp, T. In *Handbook of Combinatorial Chemistry*; Nicolaou, K. C., Hanco, R., Hartwig, W., Eds.; Wiley-VCH: Weinheim, 2002; pp 885–990. (b) Hoveyda, A. H. In *Handbook of Combinatorial Chemistry*; Nicolaou, K. C., Hanco, R., Hartwig, W., Eds.; Wiley-VCH: Weinheim, 2002; pp 991–1016.
- (2) Markert, C.; Pfaltz, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 2498–2500.
- (3) Mass-labeled enantiomers have been used before for determining the enantiomeric purity of chiral products: (a) Horeau, A.; Nouaille, A. *Tetrahedron Lett.* **1990**, *31*, 2707–2710. (b) Reetz, M. T.; Becker, M. H.; Klein, H. W.; Stöckigt, D. *Angew. Chem., Int. Ed.* **1999**, *38*, 1758–1761. (c) Yao, S.; Siuzdak, G.; Finn, M. G. *J. Org. Chem.* **2003**, *68*, 2540–2546. (d) For a review on quasiautomers, see: Zhang, Q.; Curran, D. P. *Chem.–Eur. J.* **2005**, *11*, 4866–4880 and references therein.
- (4) Reviews: (a) Trost, B. M.; Lee, C. In *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: New York, 2000; pp 593–649. (b) Pfaltz, A.; Lautens, M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Heidelberg, 1999; pp 833–886. (c) Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395.
- (5) Chen, P. *Angew. Chem., Int. Ed.* **2003**, *42*, 2832–2847.
- (6) Na[15-c-5]CET(CO₂Et)₂ is used as a convenient bench-stable malonate nucleophile that exhibits good solubility in a variety of solvents. Because **2a** and **2b** react at the same rate, **2a/2b** is equal to k_A/k_B at low conversion when **1a/1b** = 1. Thus samples were taken in the initial phase after ca. 1–2 turnovers.
- (7) Hilgraf, R.; Pfaltz, A. *Adv. Synth. Catal.* **2005**, *347*, 61–77.
- (8) Using racemic 1,3-diphenylallylbenzoate as substrate, a k_{rel} of 45 was observed in the range 0–47% conversion. At higher conversion, the observed ee values no longer correlated with the catalyst intrinsic selectivity indicating slow catalyst decomposition or the onset of an unselective background reaction.

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