Advanced Synthesis & Catalysis

Very Important Publication

DOI: 10.1002/adsc.201500224

Mass Spectrometric Screening of Racemic Amine Catalysts for Enantioselective Michael Additions

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Received: March 4, 2015; Revised: March 25, 2015; Published online: May 5, 2015

This paper is dedicated to Stephen Buchwald, a good friend and eminent scientist, on the occasion of his 60th birthday.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201500224.

Abstract: In extension of a concept of Lloyd-Jones, based on the combination of a racemic catalyst with a scalemic substrate, we have recently developed a method for determining the enantioselectivity of a chiral catalyst from its racemic form by mass spectrometric screening of a non-equal mixture of two mass-labeled quasi-enantiomeric substrates. After an initial proof of principle using palladium-catalyzed allylic substitution as test reaction, we report now the successful application of this approach to the screening of chiral amines as catalysts for the enantioselective Michael addition to α,β-unsaturated aldehydes. The results confirm that our method allows fast and reliable evaluation of chiral racemic catalysts. This opens up new possibilities for investigating catalyst structures that are not easily available in enantiomerically pure form.

Keywords: enantioselectivity; mass spectrometry; Michael addition; organocatalysis; racemic catalyst screening

Introduction

During the last two decades, organocatalysis has evolved into one of the major fields of asymmetric synthesis.[1] A major class of organocatalysts are primary or secondary amines derived from the chiral pool, typically from naturally occurring amino acids.[2] Catalysts of this type are readily available from inexpensive precursors but their structural diversity is limited. For the exploration of new applications and novel catalysts, it would be desirable to extend the range of possible catalyst candidates to amines that are not accessible from the chiral pool. However, the preparation of enantiopure chiral amines by asymmetric synthesis or resolution is often time-consuming and, therefore, may not be worth the effort, considering the high uncertainty in predicting the performance of a new catalyst. Hence, a method for determining the enantioselectivity of a catalyst by screening its racemic form would strongly enhance the range of possible structures that can be explored.

We have recently devised a mass spectrometric method of this kind and, as a proof of principle, demonstrated its viability by screening racemic palladium complexes as catalysts for enantioselective allylic substitution.[3] Our method is based on a concept originally developed by Lloyd-Jones and coworkers,[4] who showed that the enantiodiscrimination ability of a chiral catalyst can be deduced from kinetic resolution experiments with the racemic form.[5,6] In a proof-of-concept study they evaluated a series of racemic Pd catalysts in the kinetic resolution of a scalemic (enantioenriched but not enantiopure) allylic acetate (Figure 1). Kinetic analysis predicts that if the reaction shows zero-order rate dependence on substrate concentration (saturation conditions), the enantiomeric excess (*ee*) of the scalemic substrate increases with conversion. In the extreme case of a perfectly enantioselective catalyst (selectivity factor $s=\infty$) each catalyst enantiomer only reacts with one substrate enantiomer at the same rate until all of the minor enantiomer is converted to the product, so the

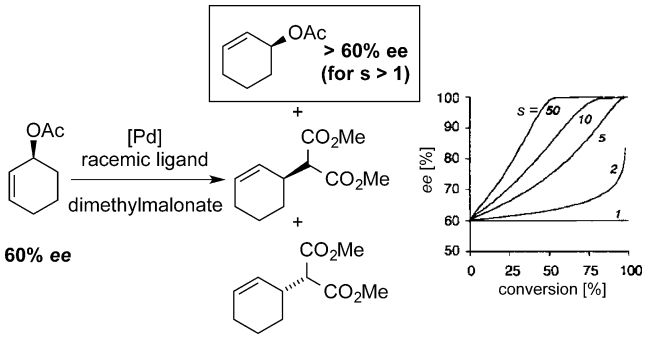
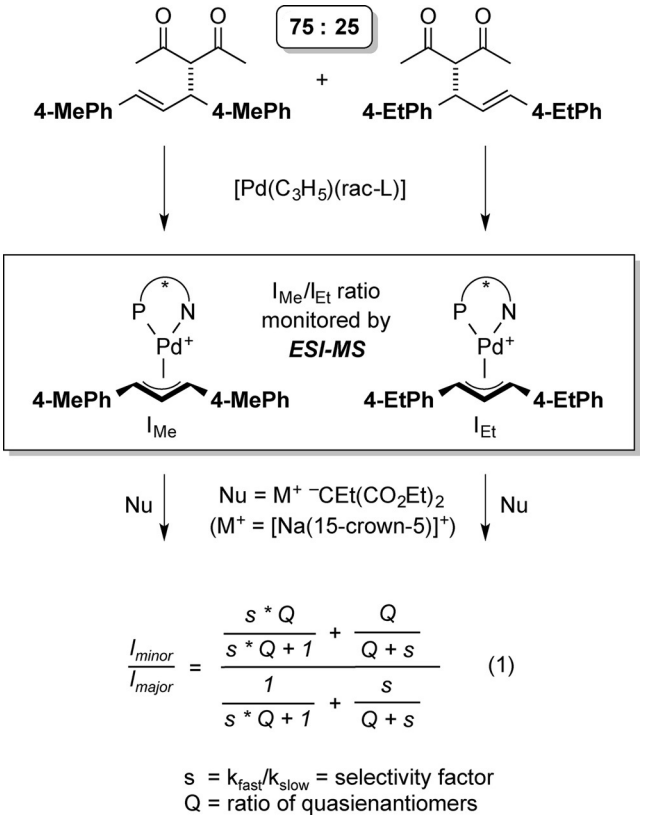


Figure 1. Evaluation of a racemic catalyst based on the concept of Lloyd-Jones.[4] The diagram shows the theoretical curves for the increase of *ee* with conversion calculated for different selectivity factors (*s*) starting from scalemic acetate with 60% *ee*.



$$\frac{I_{minor}}{I_{major}} = \frac{\frac{s * Q}{s * Q + 1} + \frac{Q}{Q + s}}{\frac{1}{s * Q + 1} + \frac{s}{Q + s}} \quad (1)$$

Scheme 1. ESI-MS screening of racemic Pd-catalysts.

ee of the unreacted acetate eventually reaches 100%. An unselective catalyst ($s=1$), on the other hand, does not distinguish between the substrate enantiomers and, consequently, the *ee* of the allylic acetate remains constant throughout the reaction. Comparison of the experimentally observed correlation between the *ee* and conversion with theoretical charts, calculated for different selectivity factors, enabled estimation of the enantioselectivity of the corresponding enantiopure catalyst.

The relative selectivity order between different catalysts could be clearly established in this way. However, as the experimental data deviated from the calculated curves, expected for clean pseudo zero-order kinetics, a quantitative analysis was not possible. Restriction to kinetic resolutions and the labor-intensive data collection over the whole reaction course further limit the practicality of the method.

By combining the principle of the Lloyd-Jones method with a mass spectrometric back-reaction screening protocol developed in our lab,[7] we were able to overcome these limitations. As a first application of our method, we studied the Pd-catalyzed allylic substitution with acetylacetone as nucleophile (Scheme 1).[3]

When a 75:25 mixture of two quasi-enantiomeric mass-labeled allylation products[8] was treated with a racemic catalyst under the conditions previously developed for back-reaction screening,[7a] the corresponding allyl intermediates were detected by electrospray ionization mass spectrometry (ESI-MS). As explained above, a perfectly selective catalyst is expected to produce the two allyl intermediates in equal amounts under saturation conditions, whereas an unselective catalyst does not alter the initial ratio of 75:25. Thus, with increasing selectivity the ratio should decrease from 75:25 to 50:50. Assuming clean zero-order rate dependence on the substrate concentrations, the selectivity factor *s* can be directly calculated from the ratio of the two allyl intermediates (I_{minor}/I_{major}), which can be determined from the intensities of the ESI-MS signals of the major isotopomers, using equation (1).[3]

Under ideal conditions the calculated selectivity factor should be identical to the enantiomeric ratio obtained with the corresponding enantiopure catalyst in the forward reaction with acetylacetone as nucleophile. However, the calculated *s* values from racemic catalyst screening were found to be systematically lower than the values determined for the enantiopure catalysts, due to deviation from pseudo zero-order kinetics. Surprisingly, the *ee* values from racemate screening showed a very good linear correlation with enantioselectivities of the corresponding enantiopure catalysts (Figure 2). Based on this correlation it became possible to predict the enantioselectivity of a new catalyst with high accuracy from screening its racemic form.

In order to evaluate the scope of this approach and to examine whether the linear correlation shown in Figure 2 is a general phenomenon, we decided to investigate other reactions. Herein, we present the successful extension of our method to the screening of racemic amines as catalysts for organocatalyzed enantioselective Michael additions to α,β-unsaturated aldehydes.

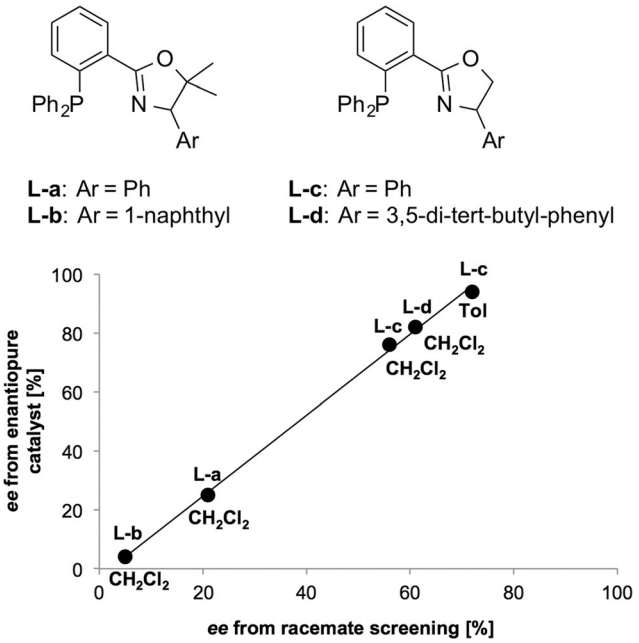


Figure 2. Correlation of the *ee* values from racemic catalyst screening with the enantioselectivities determined for the corresponding enantiopure catalysts.

Principle of the screening protocol for racemic Michael addition catalysts

We have recently developed an efficient protocol for the evaluation of chiral amines as catalysts for enantioselective Michael additions of malonates to α,β-unsaturated aldehydes,[9] based on our ESI-MS back-reaction screening approach (Figure 3).[7d] Initial studies showed that the reaction is reversible under catalytic conditions. Starting from a 1:1 mixture of mass-labeled quasi-enantiomeric Michael adducts **2** and **2′**, the signals of the corresponding iminium salts (**1-Im** and **1-Im'**) derived from the unsaturated aldehydes were clearly visible in the ESI mass spectrum, despite the fact that the back-reaction is endergonic implying that the retro-Michael products must be formed in very low concentration (Figure 3b). Under the condition that the enantioselectivity-determining step in the forward and reverse reaction is C–C bond formation and cleavage, respectively, the selectivity k_a/k_b in the retro-Michael reaction should be identical to the enantioselectivity of the forward reaction according to the principle of microscopic reversibility. This condition is met if the Michael adducts and the catalyst are in rapid equilibrium with the corresponding iminium and enamine intermediates (Curtin-Hammet conditions). In this case, the ratio **1-Im**/**1-Im'** monitored in the back-reaction and the enantiomeric ratio resulting from the preparative Michael addition should be the same. The results from back-reaction screening of

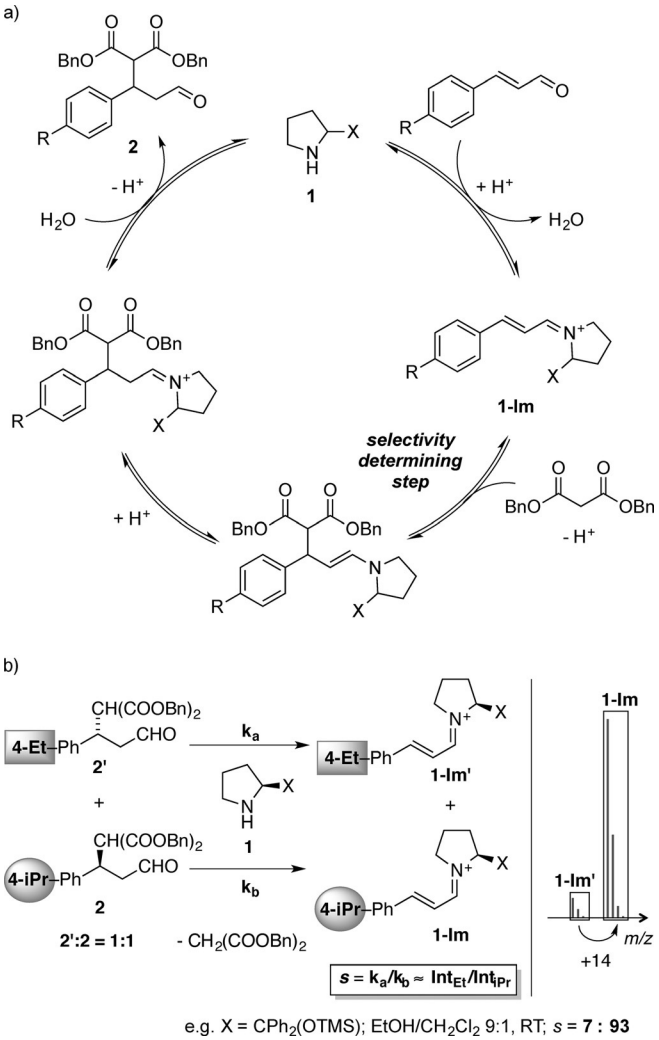


Figure 3. a) Simplified mechanism of the amine-catalyzed Michael addition. b) ESI-MS screening with enantiopure catalysts.

various chiral catalysts and catalyst mixtures confirmed this expectation.[7d] The results were in excellent agreement with the enantioselectivities determined for the corresponding preparative reactions, demonstrating that the enantioselectivity can be reliably determined in this way.

Based on this protocol we investigated the analogous reaction of racemic catalysts starting from a scalemic 75:25 mixture of the same quasi-enantiomers **2** and **2'** (Figure 4). As explained above, a perfectly enantioselective catalyst is expected to produce a 50:50 ratio of the quasi-enantiomeric retro-Michael products **Im** and **Im'** under saturation conditions. For less selective catalysts the ratio will increase, reaching 75:25 for a completely unselective catalyst. Assuming an ideal zero-order rate dependence on the concentrations of **2** and **2′**, the enantioselectivity of the corresponding enantiopure catalysts can be calculated

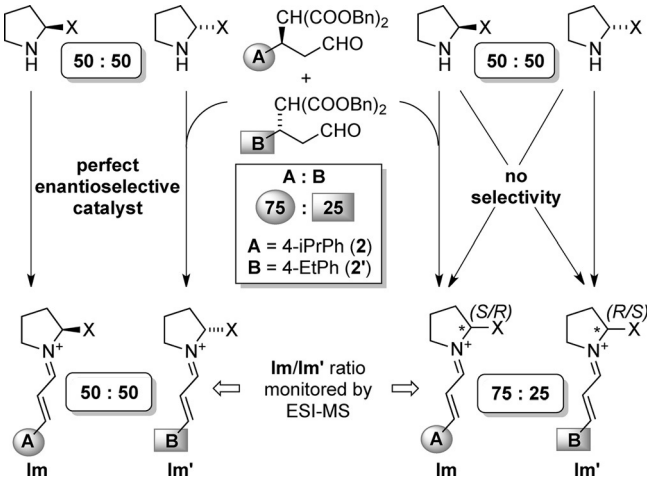


Figure 4. Principle of ESI-MS screening of racemic catalysts.

through equation 1 from the **Im/Im'** ratio determined by ESI-MS.

Results and Discussion

In the back-reaction screening of enantiopure catalysts for the Michael addition of benzyl malonate to cinnamaldehyde the TBS-protected prolinol **1a**[10] (TBS = tBuMe$_2$Si) was identified as a highly selective catalyst affording the product with an enantiomeric ratio of 97:3. Since amine **1a** also showed high activity and produced well detectable iminium intermediates in the back reaction, we chose this catalyst for our initial experiments. According to eq. 1 an enantiomeric ratio of 97:3 ($s = 32$) corresponds to a **Im/Im'** ratio of 54:46 in the racemate screening with a 75:25 mixture ($Q = 3$) of quasi-enantiomeric Michael products. However, under the standard protocol for ESI-MS back reaction screening with 10 mol% of catalyst we measured a ratio of 74:26, very close to the value expected for a completely unselective catalyst. We attributed this discrepancy to a deviation from pseudo zero-order kinetics at this relatively high catalyst loading, in line with observations made in racemic catalyst screening for allylic substitution (Scheme 1 and Figure 2), which showed that the discrepancy between the *ee* values from racemic and enantiopure catalyst screening increased with higher catalyst loading. Indeed, reduction of the catalyst loading to 1 mol% brought the ratio to 65:35 corresponding to 71% *ee* (Figure 5). Such a low catalyst loading is challenging because of the low intensity of the ESI-MS signals derived from catalytic intermediates. However, modified sample preparation, involving dilution with acetonitrile, resulted in clean spectra with a very good signal to noise ratio and strong signals of the iminium intermediates (**1a-Im/1a-Im'**) (Figure 5).

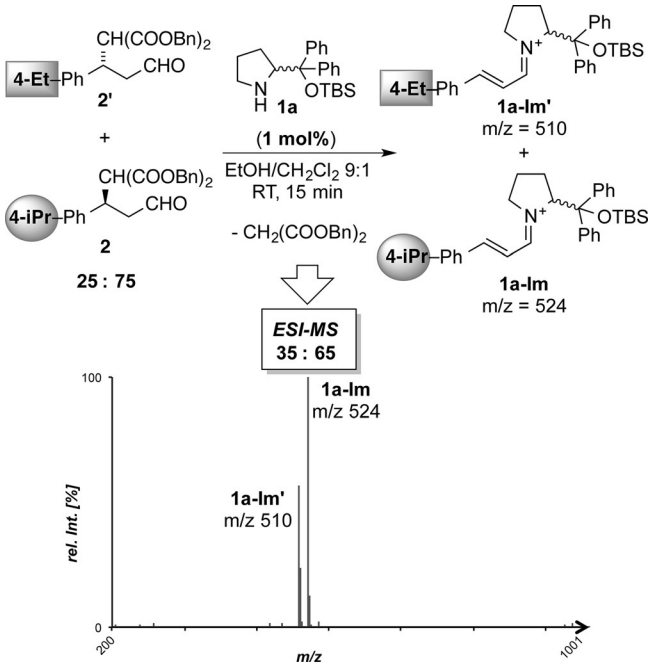


Figure 5. ESI-MS back reaction screening with 1 mol% of racemic catalyst **1a**. Below, typical ESI-MS spectra obtained under screening conditions.

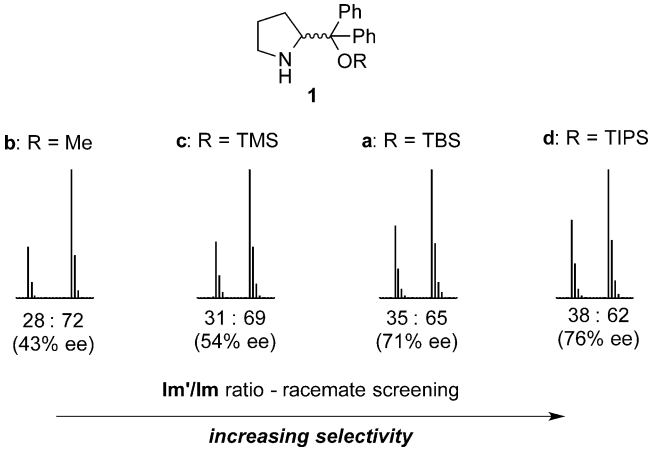


Figure 6. Im'/Im ratios monitored by ESI-MS. In brackets: enantioselectivity of catalysts **1a-d** calculated from eq. (1).

Although the *ee* value determined from racemic catalyst screening was still substantially lower than the actual enantioselectivity of the enantiopure catalyst (71 vs. 93% *ee*), we decided to go ahead with testing additional catalysts. In view of the results obtained for allylic substitution (Figure 2), we hoped that the racemic and enantiopure catalyst data would again show a linear correlation that could be used as a correction function. For a proof of principle, we chose four known silyl- and methyl-protected prolinol derivatives **1a–d** (Figure 6).[10]

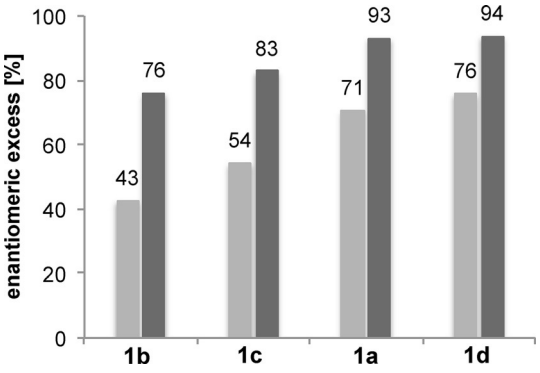


Figure 7. Calculated enantioselectivity from racemic catalyst screening (light grey bars) vs. the enantioselectivity determined for the corresponding enantiopure catalyst (dark grey bars).

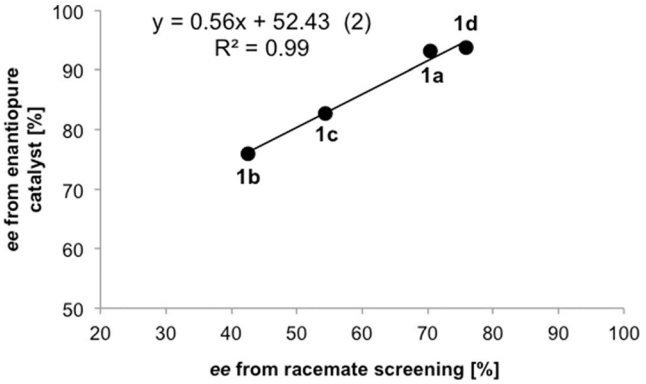


Figure 8. Linear correlation between the results from racemate and enantiopure catalyst screening.

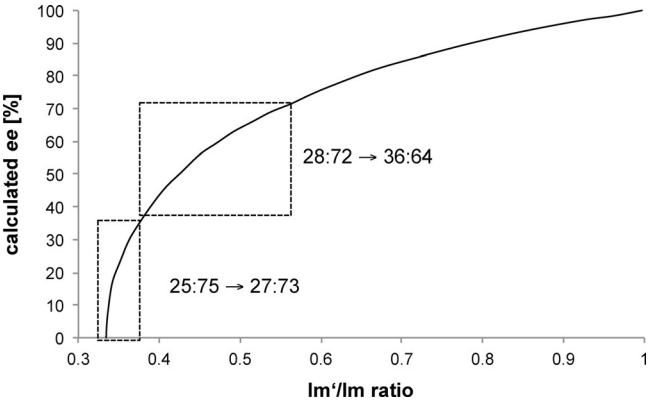


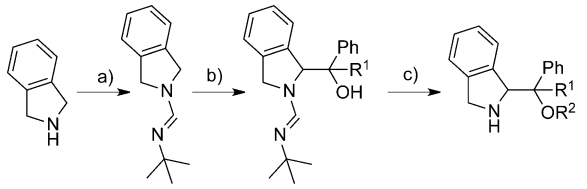
Figure 9. Dependence of the calculated theoretical enantioselectivity on the **Im'/Im** ratio in racemate screening (with Q = 1/3).

The racemic catalysts were synthesized from *N*-Boc-protected pyrrolidine by lithiation and subsequent reaction with benzophenone followed by *O*-protection (see supporting information). The enantiopure catalysts are commercially available or easily accessible starting from enantiopure diphenyl prolinol or proline using established procedures.[10,11] The enantioselectivities are known to increase with growing steric demand of the protecting group,[7d,12] so the four catalysts were expected to provide suitable data points in the moderate to high *ee* range.

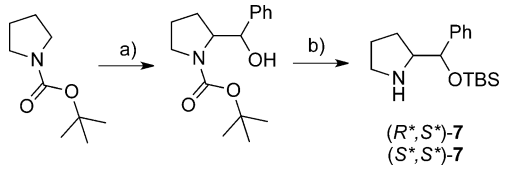
Racemate screening was conducted under the conditions described in Figure 5. The detected ratios of the iminium intermediates **Im** and **Im'** derived from the four catalysts are depicted in Figure 6 with the corresponding enantioselectivities calculated from equation 1.[13] According to the signal ratios the enantioselectivity should increase in the sequence **1b** < **1c** < **1a** < **1d**. For comparison back-reaction screening of the corresponding enantiopure catalysts was carried out, using a 1:1 mixture of the mass-labeled substrates **2** and **2'** under otherwise identical conditions (catalyst loading, reaction time, ESI-MS parameters). As shown in Figure 7 the same selectivity order was found for the enantiopure and the racemic catalysts confirming the validity of the racemate screening protocol for identifying the most selective catalysts among a set of racemic catalyst candidates.

As observed before in our allylic alkylation studies, the enantioselectivities derived from racemate screening data showed a good linear correlation with the enantioselectivities determined from the enantiopure catalysts (Figure 8). While equation 2 displays an excellent fit to the four data points ($R^2 = 0.99$), it is only valid for the moderate to high *ee* region (enantiopure catalysts inducing >50–60% *ee*). For less selective catalysts this linear relationship breaks down as can be seen from the y-intercept at 52% *ee* which in reality should be at 0% *ee*. This deviation from ideal behavior is not surprising, considering the course of the graph showing the calculated *ee* as a function of the **Im/Im'** ratio (Figure 9). Due to the strong curvature merging into an almost vertical slope between 20% and 0% *ee*, very small measuring errors in the ratios **2/2'** and **Im/Im'** result in very large errors of the *ee* calculated according to the linear correlation equation 2 (a change of the **Im/Im'** ratio from 75:25 to 74:26 corresponds to an increase in the calculated *ee* from 0% to 20%). However, the observed inadequate correlation in the low *ee* region does not impair the utility of the screening method, which primarily serves to identify the most selective members of a catalyst library. The exact values in the low *ee* region are not relevant, as long as they allow clear distinction of inferior catalysts that are not worth to be further investigated.

To examine the scope of our screening protocol we synthesized a series of new organocatalysts based on an isoindoline framework. As these compounds cannot be synthesized from readily available precursors from the chiral pool, they are difficult to obtain in enantiopure fashion. Compared to pyrrolidine-derived catalysts, the annulated phenyl ring of the isoin-



Scheme 2. Synthesis of racemic catalysts **6a–c**. Conditions: a) *N′-tert*-butyl-*N*,*N*-dimethylformamidine, toluene, reflux. b) For **5a**: *sec*-BuLi, THF, −78 °C; then benzophenone, −78 °C to r.t. For **5b**: *sec*-BuLi, THF, −78 °C; then benzaldehyde, −78 °C to r.t. c) (1) $LiAlH_4$, THF, reflux. (2) For **6a**: TMSOTf, NEt_3, CH_2Cl_2, 0 °C to r.t. For **6b**: TBSOTf, NEt_3, CH_2Cl_2, 0 °C to r.t. For **6c**: TBSOTf, NEt_3, CH_2Cl_2, −78 °C to r.t.



Scheme 3. Synthesis of racemic catalysts **7**. Conditions: a) *sec*-BuLi, TMEDA, Et_2O, −78 °C; then benzaldehyde, −78 °C to r.t., separation of diastereoisomers by FC. b) (1) AcOH/3 M HCl, r.t. (2) TBSOTf, NEt_3, CH_2Cl_2, 0 °C to r.t.

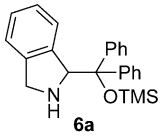
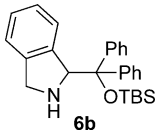
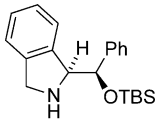
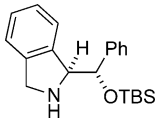
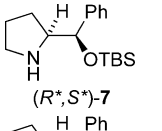
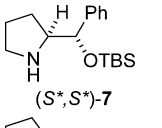
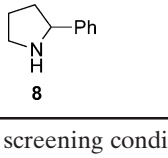
doline derivatives alters the geometry of the nitrogen containing heterocycle as well as the conformation of the substituent at the stereogenic center through steric interactions. In order to see how these effects of the extra phenyl ring influence the enantioselectivity, we prepared isoindoline derivatives **6a** and **6b**, which are analogues of the previously evaluated catalysts **1c** and **1a** bearing TMS and TBS ether substituents. In addition, we synthesized both diastereomers of isoindoline **6c** (Scheme 2) and pyrrolidine **7** containing an additional stereogenic center (Scheme 3).[14]

The isoindoline derivatives were synthesized starting from *N*-protected isoindoline by lithiation and subsequent trapping with benzophenone or benzaldehyde, respectively. Initial experiments with *tert*-butylcarbamate as directing group failed as they led to decomposition. Eventually the desired products were obtained using a formamidine protecting group as reported by Beeley and Rockell (Scheme 2).[15] The reaction with benzaldehyde led to a mixture of the diastereomeric isoindoline derivatives (*S**,*R**)- and (*S**,*S**)-**6c**, which was separated by flash column chromatography. The relative configuration of the two isomers was established by X-ray analysis of the HCl salt of the (*S**,*S**)-isomer (see supporting information).

In order to correlate the results from racemic and enantiopure catalyst screening, we also synthesized the two enantiopure amines (1*R*,2*S*)- and (1*S*,2*S*)-(**7**) from *N*-Boc-(*S*)-prolinol by oxidation to the aldehyde and subsequent Grignard reaction with phenylmagnesium bromide. Samples of enantiopure catalysts **6a–c** were obtained from the racemates by semi-preparative HPLC on a chiral stationary phase.

The racemic and enantiopure forms of the six new organocatalysts were then subjected to ESI-MS back-reaction screening using the standard protocol described above (Table 1). As a further structural variant, the commercially available racemic 2-phenylpyrrolidine **8** and an enantiopure sample obtained by HPLC resolution on a chiral phase were also included in this study. For both the enantiopure and racemic catalysts, the *ee* values listed in the table were aver-

Table 1. ESI-MS screening results of the new catalysts.[a]

entry	catalyst	racemate sceening *ee* [%]	corrected value *ee* [%][b]	enantiopure catalyst *ee* [%]
1	 **6a**	47	78	79
2	 **6b**	58	85	87
3	 (*S**,*R**)-**6c**	44	77	78[c]
4	 (*S**,*S**)-**6c**	23	65	66
5	 (*R**,*S**)-**7**	33	71	70
6	 (*S**,*S**)-**7**	0	–[d]	49
7	 **8**	0	–[d]	2

[a] For screening conditions see Figure 5.
[b] Values corrected using the linear regression depicted in Figure 8 ($y = 0.56x + 52.43$).
[c] 2 mol% of catalyst used.
[d] No correction possible due to low catalyst selectivities.

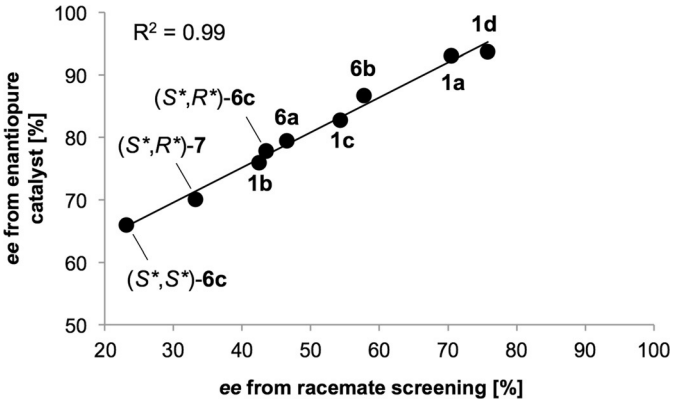


Figure 10. Linear correlation for all catalysts with an enantioselectivity > 60 %.

aged from four independent measurements (see supporting information).

For all catalysts investigated, the back reaction took place and the intermediates **Im** and **Im'** were clearly detected by ESI-MS. Using equation 1, the **Im/Im'** ratios obtained from the racemic catalysts were converted to the theoretical *ee* values expected under ideal zero-order kinetics. These values were then corrected using the linear correlation function shown in Figure 8. Gratifyingly, the results confirmed the validity of this protocol. For the moderately to highly selective catalysts (*ee* > 60 %; entries 1–5) the corrected *ee* values from racemic catalyst screening closely matched the data obtained from the corresponding enantiopure catalysts. These results confirmed the validity of the linear correlation function established in our initial experiments with four catalysts (Figure 7). Linear regression analysis including all catalysts in the *ee* range of > 60 % again showed an excellent fit with an R^2 value of 0.99. Apparently, the enantioselectivity of a new moderately to highly enantioselective catalyst can be reliably determined with remarkable accuracy using this protocol. The data in Table 1 also allowed clear distinction of the less selective catalysts (*S**,*S**)-**7** and **8** (entries 6 and 7) from the group of potentially useful catalysts (entries 1–5).

From the screening results the following conclusions can be drawn regarding the influence of the substituent at the stereogenic center and the annulated phenyl ring. Consistent with our previous study,[7d] the enantioselectivity increases with the steric size of the oxygen protecting group (TIPS **1d** > TBS **1a** > TMS **1c** > Me **1b**; TBS **6b** > TMS **6a**; Figure 10). The two diastereomeric pyrrolidine derivatives (*S**,*S**)-**7** and (*R**,*S**)-**7**) with only one phenyl substituent are considerably less selective than the diphenyl-substituted analogue (**1d**). Apparently, the steric hindrance exerted by the two phenyl groups and the silyloxy substituent is essential for efficient enantiodiscrimination. The additional stereogenic center in catalysts (*R**,*S**)-**7**/(*S**,*S**)-**7** and (*S**,*R**)-**6c**/(*S**,*S**)-**6c** causes a clear match/mismatch effect. The additional annulated phenyl ring in catalysts **6a** and **6b** has a negative effect on the *ee* (83 vs. 79 % for **1c**/**6a**; 93 vs. 87 % for **1a**/**6b**). For the monophenyl-substituted analogues, on the other hand, the effect is positive (Table 1, entries 3 vs. 5 and 4 vs. 6), which can be explained by steric repulsion between the substituent at the stereogenic center and the adjacent aromatic H atom of the annulated phenyl ring. This interaction forces the phenyl and silyloxy groups to orient themselves toward the active site of the catalyst, resulting in greater steric hindrance in this region compared to the conformationally more flexible pyrrolidine analogues. In summary, among the various structural variants evaluated in this study, the proline-derived pyrrolidine derivatives **1a** and **1c**, of the structural type originally introduced by Hayashi and Jørgensen,[10] remain the catalysts of choice for the investigated enantioselective Michael addition.

Conclusions

In an initial proof of principle study using palladium-catalyzed allylic substitution as test reaction,[3] we had demonstrated that our mass spectrometric screening method combined with the scalemic substrate approach of Lloyd-Jones[4] enabled determination of the enantioselectivity of a chiral catalyst from its racemic form. We now wanted to explore other applications in order to evaluate the scope of our racemic catalyst screening protocol. The results presented here for the enantioselective organocatalyzed Michael addition confirm that our method allows fast and reliable evaluation of chiral racemic catalysts. As observed in the allylic substitution, the *ee* values from racemic catalyst screening were smaller than those determined for the enantiopure catalysts, but could be corrected by means of a linear correlation function. The corrected *ee* values were in excellent agreement with the actual enantioselectivities of the respective enantiopure catalysts. Because racemic compounds that are not derived from the chiral pool are in general more readily accessible than the enantiopure forms, our screening protocol considerably extends the possibilities for rapid evaluation of new catalyst structures.

Experimental Section

General Remarks

ESI-MS spectra were measured on a Varian 1200 L Quadrupol MS/MS spectrometer using mild desolvation conditions (39 psi nebulizing gas, 4.9 kV spray voltage, 19 psi drying

gas at 200 °C, 50 V capillary voltage). The samples were diluted immediately with CH_3CN prior to their analysis and measured using direct injection. The spectra were acquired in the centroid mode. Every spectrum consisted of at least 30 scans and the selectivity was calculated from the ratios of the peak heights of the major isotopomers of **Im** and **Im'**.

General procedure for the ESI-MS screening of racemic organocatalysts

A GC-vial was charged with a scalemic 3:1 mixture of (*R*)-**2** (4.30 mg 9.38 μmol, 0.75 equiv) and (*S*)-**2'** (1.39 mg, 3.13 μmol, 0.25 equiv). The mixture was dissolved in EtOH/CH_2Cl_2 (85 μL/10 μL) and a solution of the corresponding racemic organocatalyst in EtOH (5 μL, 0.025 M, 1 mol%) was added. The mixture was stirred for 15 min at room temperature. The reaction mixture was diluted with CH_3CN (1 mL) and subjected to ESI-MS analysis.

General procedure for the ESI-MS screening of enantiopure organocatalysts

A GC-vial was charged with an equimolar mixture of (*R*)-**2** (2.87 mg 6.25 μmol, 0.50 equiv) and (*S*)-**2'** (2.78 mg, 6.25 μmol, 0.50 equiv). The mixture was dissolved in EtOH/CH_2Cl_2 (85 μL/10 μL) and a solution of the corresponding enantiopure organocatalyst in EtOH (5 μL, 0.025 M, 1 mol%) was added. The mixture was stirred for 15 min at room temperature. The reaction mixture was diluted with CH_3CN (1 mL) and subjected to ESI-MS analysis.

Acknowledgements

Financial support of this work by the Swiss National Science Foundation is gratefully acknowledged. We thank Dr. Markus Neuburger (Laboratory for Chemical Crystallography, University of Basel) for the crystal structure analysis.

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