Catalyst Screening (1)

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Mass Spectrometric Screening of Enantioselective Diels–Alder Reactions**

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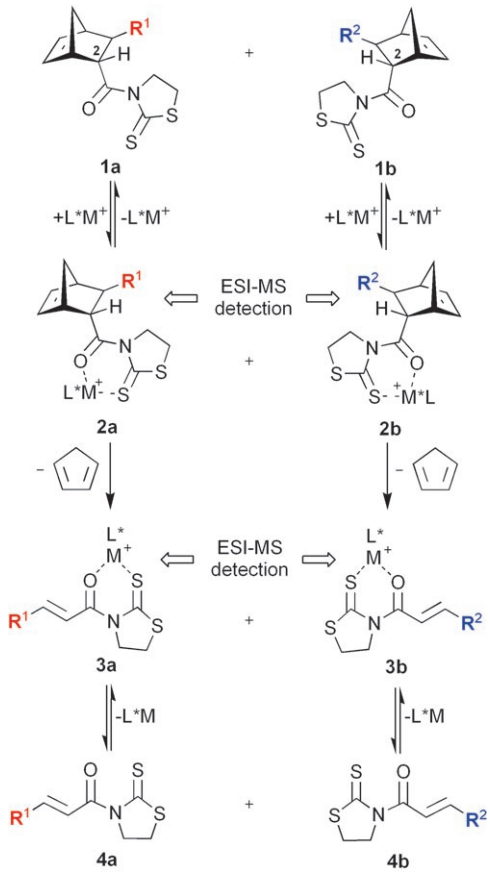
In the preceding communication[1] we introduced a new concept for screening chiral catalysts by mass spectrometric monitoring of catalytic reactions in the reverse direction. The use of mass-labeled quasienantiomeric[2] products as reactants in the screening process makes it possible to distinguish catalyst-bound intermediates with an opposite sense of chirality by mass spectrometry. According to the principle of microscopic reversibility, the transition states of the forward and the back reaction are identical and, therefore, the enantioselectivity determined from back-reaction screening is identical to that of the forward reaction. After having demonstrated the feasibility of this method for palladium-catalyzed allylic substitutions, we report now an extension to metal-catalyzed and organocatalytic Diels–Alder (DA) reactions.

The principle of our method is illustrated in Scheme 1. When a mixture of two mass-labeled quasienantiomeric Diels–Alder products **1a** and **1b** ($R^1 \neq R^2$) is treated with a chiral cationic Lewis acid L^*M^+, the two positively charged catalyst complexes **2a** and **2b** are formed, which can be distinguished by ESI-MS because of their different molecular masses. A Lewis acid which catalyzes the DA reaction of the dienophiles **4a** and **4b** also catalyzes the retro-DA reaction. Therefore, under appropriate conditions, the two catalyst–dienophile complexes **3a** and **3b** formed by loss of cyclopentadiene should be observable together with the complexes **2a** and **2b**. Given that the quasienantiomers **1a** and **1b** behave like real enantiomers, and if formation of the complexes **2a** and **2b** from **1a** and **1b** is fast and reversible, and if the subsequent retro-DA reaction is slow and irreversible, then the ratio **3a**/**3b** directly reflects the enantioselectivity of the catalyst. At elevated temperature under dilute conditions, especially during the initial phase of the retro-DA reaction when the concentrations of **4a**, **4b**, and cyclopentadiene are low compared to that of **1a** and **1b**, the DA reaction of **3a** and **3b** with cyclopentadiene is expected to be very slow, so the requirement of an essentially irreversible retro-DA reaction should be fulfilled. As ESI-MS allows the selective detection of charged species in the presence of a large excess of neutral compounds, it should be possible to monitor the signals of **3a** and **3b** even at low concentration.



Scheme 1. Retro-Diels–Alder reaction of two quasienantiomeric Diels–Alder products **1a** and **1b**. R^1 and R^2 represent mass labels.

As quasienantiomeric DA products we chose the 4-ethylphenyl and 4-butylphenyl derivatives **1a** and **1b** (Figure 1), which were readily obtained in high enantiomeric purity by a [Cu(box)]-catalyzed DA reaction according to the procedure described by Evans et al. (box = bisoxazoline, (*S*,*S*)- or (*R*,*R*)-**5**).[3] As the *para*-substituted ethyl- and butylphenyl groups of **1a** and **1b** have essentially identical steric and electronic properties, we expected the two quasi-enantiomers to behave like real enantiomers in the retro-DA reaction.

Preliminary experiments showed that the retro-DA reaction was sufficiently fast at 100 °C to allow detection of the dienophile–catalyst complexes **3a** and **3b** by ESI-MS. When a 1:1 mixture of quasienantiomers (2*R*)-**1a** and (2*S*)-**1b** was treated with 20 mol % of the enantiomerically pure catalyst (*S*,*S*)-**5** in dichloromethane at 100 °C for 1 h, ESI-MS analysis

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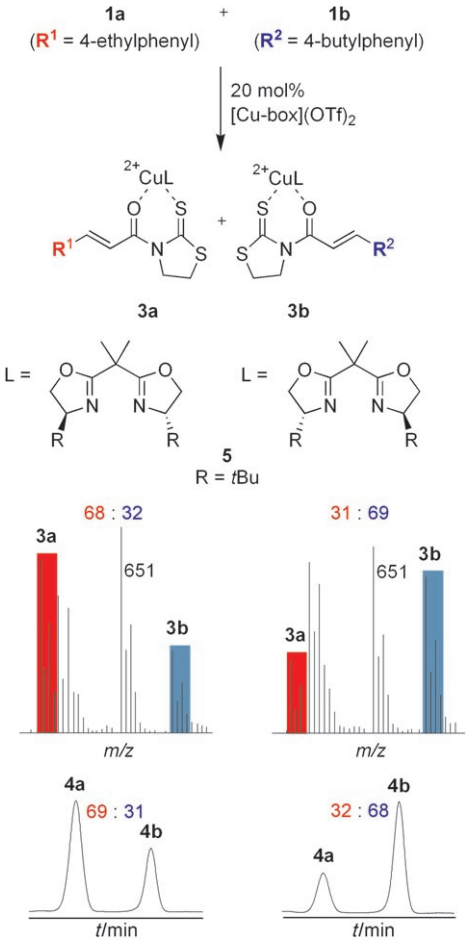
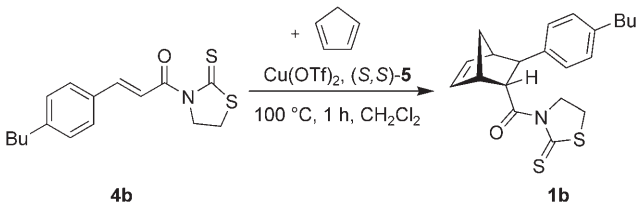


Figure 1. ESI-MS screening of the copper-catalyzed retro-DA reaction.



Scheme 2. The preparative DA reaction.

of the reaction mixture showed a 68:32 ratio of **3a**/**3b** at *m*/*z* 634 and *m*/*z* 662, thus indicating a preference of the catalyst for (2*R*)-**1a**. Essentially the reverse signal ratio of 31:69 was observed with the enantiomeric *R*,*R* catalyst, as expected. A 50:50 ratio was observed for **2a**/**2b** at *m*/*z* 700 and *m*/*z* 728. An additional signal cluster at *m*/*z* 651 was attributed to a complex with the composition $[Cu(\mathbf{5})_2]^+$. All the copper complexes were readily identified by their characteristic isotope pattern. Interestingly, only Cu^I complexes were observed, even though the catalyst was prepared from copper(II)triflate. Similar observations have previously been reported and attributed to redox reactions occuring during the electrospray process.[4]

The enantioselectivities determined by ESI-MS were confirmed by HPLC analysis of the reaction mixtures, which showed virtually the same dienophile ratios **4a**/**4b** as the corresponding mass spectrometric signal ratios **3a**/**3b** (Figure 1). The reaction was also carried out in the forward direction on a preparative scale with the 4-butylphenyl-substituted dienophile **4b** (Scheme 2). Except for the higher concentration of the dienophile (0.1 M instead of 0.02 M), the conditions used were the same as in the screening experiments. The enantiomeric ratio of the *endo* product **1b**, measured by HPLC on a column with a chiral stationary phase, was 64:36, which is in good agreement with the screening results.

We next screened a series of differently substituted box ligands under these conditions (Table 1). The results obtained by ESI-MS were again in good agreement with the HPLC analyses and showed the same selectivity order **5a** > **5b** > **5c** > **5d** > **5e** for the different box ligands, with the highest enantiomeric ratio for the 2-naphthyl-substitued derivative **5a**. The small deviations observed between the ESI-MS and HPLC data are likely due to a relatively high background noise in the MS spectra caused by traces of unknown Cu species and/or errors in the HPLC analyses. The same selectivity order and very similar enantiomeric ratios for the *endo* product were obtained in the analogous preparative DA reactions performed at the same temperature (100 °C). Higher *ee* values and a different selectivity order was observed when the reactions were carried out at −35 °C (**5a** (97 % *ee*) > **5c** (95 % *ee*) > **5b** (89 % *ee*) > **5d** (23 % *ee*) > **5e** (17 % *ee*)). These results are in contrast to the findings of Evans et al.,[3] who found that the *tert*-butylbox derivative **5c** was by far the most efficient ligand of this series in the analogous DA reaction with an unsubstituted acrylimide at −35 °C. To demonstrate the scope of our screening method, we tested a number of additional chiral ligands, including phox[5] and bisimine[6] ligands, which all gave only moderate to low enantioselectivities. Again, the results were in good agreement with HPLC analyses of the reaction mixtures and the corresponding preparative DA reactions.

We then turned to organocatalytic DA reactions, which should be ideal for ESI-MS screening because metal-free catalysts have a much narrower isotope distribution than Cu

Table 1: ESI-MS screening of Cu^{II}-box catalysts.[a]

Ligand	ESI-MS **3a**/**3b**	HPLC[b] **4a**/**4b**	Preparative reaction[c] *endo* e.r.
5a (R = 2-naphthyl)	86:14	90:10	88:12
5b (R = Ph)	80:20	85:15	86:14
5c (R = *t*Bu)	68:32	69:31	64:36
5d (R = *i*Pr)	61:39	58:42	56:44
5e (R = benzyl)	55:45	51:49	52:48

[a] Conditions for ESI-MS screening: 100 °C, 1 h, 0.02 M in CH_2Cl_2. The ratio of **3a**/**3b** was determined by integration of the signals corresponding to the major isotope. [b] The reaction mixture was filtered through a plug of silica gel and then subjected to HPLC analysis on a Chiralcel OD-H column. [c] 0.1 M solution of **4b** (R^2 = 4-butylphenyl), cyclopentadiene (10 equiv), 20 mol % Cu^{II} catalyst, CH_2Cl_2, 1 h, 100 °C. Product **1b** was analyzed by HPLC on a Chiralcel OD-H column.

or other transition-metal catalysts and, therefore, cause less problems with respect to overlapping signals. As a first test, we chose the DA reaction of cinnamaldehyde with cyclopentadiene in the presence of imidazolidinone **6**·HCl as the catalyst. This reaction, originally developed by MacMillan and co-workers,[7] proceeds via iminium ion intermediates, which should be observable by ESI-MS. The required quasienantiomeric DA products (2*S*)-**7a** and (2*R*)-**7b** were readily prepared in enantiomerically pure form by reduction of the corresponding DA products **1**. Back-reaction screening was performed in dichloromethane at room temperature by using 20 mol% of the catalyst. After a reaction time of 24 h, ESI-MS analysis of the reaction mixture showed the signals of the iminium ions **8a** and **8b** at *m*/*z* 375 and *m*/*z* 389, respectively, in a 88:12 ratio (Figure 2). The control experiment with inversely labeled quasienantiomers (Pr and Bu interchanged) gave the expected reverse ratio of 12:88. In line with these results, an enantiomer ratio of 87:13 was measured for the *endo* product of the corresponding preparative DA reaction with cinnamaldehyde at room temperature. The ESI-MS spectra were much cleaner than those observed for the copper-catalyzed reactions, with no signal overlap and with higher signal-to-noise ratios.

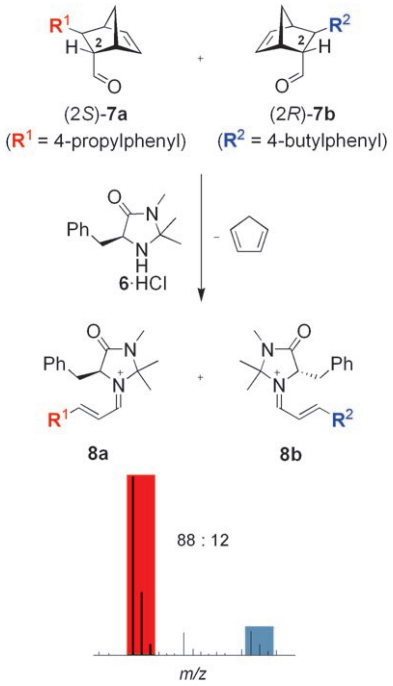


Figure 2. ESI-MS screening of organocatalysts.

With a reliable screening protocol at hand, we tested whether mixtures of different organocatalysts could be screened simultaneously. The results obtained with a solution of the three catalysts **9**, **10**·HCl, and **6**·HCl are shown in Figure 3. Spectra recorded after a reaction time of 1 h at 50 °C showed signal ratios for the corresponding dienophile–catalyst adducts that closely matched the data obtained by screening individual catalysts. These results clearly show that multicatalyst screening in solution is indeed feasible, which opens up new possibilities for the high-throughput screening of organocatalyst libraries of this type.

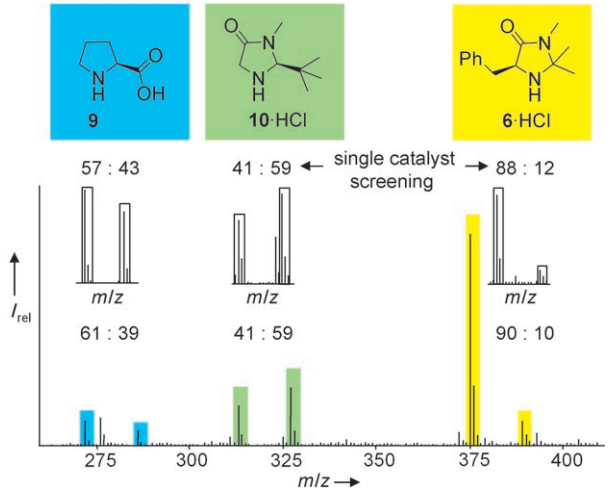


Figure 3. Simultaneous screening of three organocatalysts.

On the basis of the results obtained for the palladium-catalyzed allylic substitution reactions[1] and DA reactions, we expect back-reaction screening by ESI-MS to be applicable to various other classes of reactions. In organocatalysis, for example, there are many reactions which proceed through cationic intermediates and, therefore, should be amenable to ESI-MS screening. The option to evaluate mixtures of catalysts simultaneously offers the possibility to screen catalyst or ligand libraries prepared by combinatorial methods without the need to isolate each catalyst or ligand. Hence, this strategy could speed up ligand development considerably.

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