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Asymmetric Catalysis

Asymmetric Morita–Baylis–Hillman Reaction: Catalyst Development and Mechanistic Insights Based on Mass Spectrometric Back-Reaction Screening

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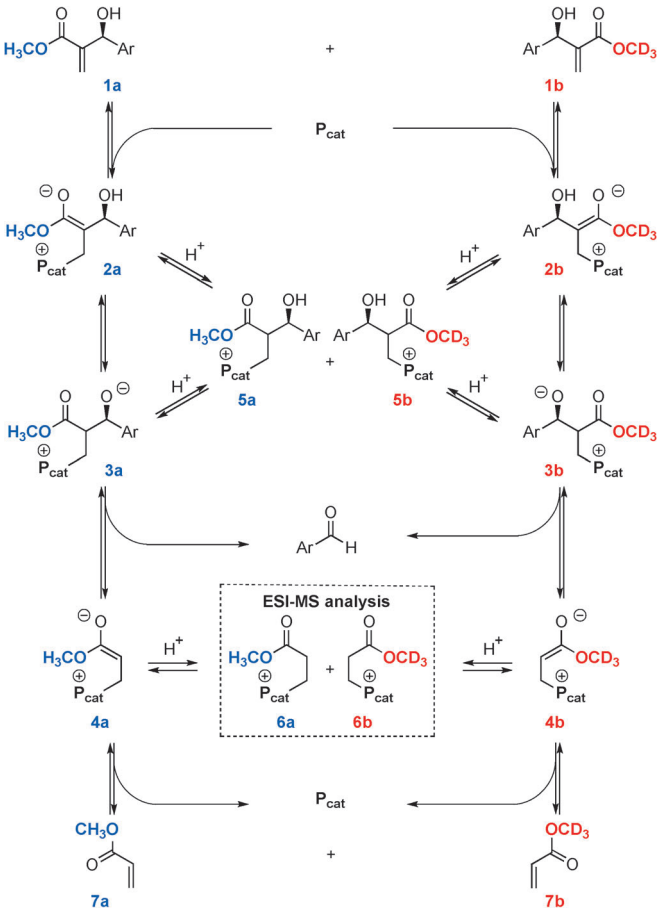
Abstract: An efficient protocol for the evaluation of catalysts for the asymmetric Morita–Baylis–Hillman (MBH) reaction was developed. By mass spectrometric back-reaction screening of quasi-enantiomeric MBH products, an efficient bifunctional phosphine catalyst was identified that outperforms literature-known catalysts in the MBH reaction of methyl acrylate with aldehydes. The close match between the selectivities measured for the forward and back reaction and kinetic measurements provided strong evidence that the aldol step and not the subsequent proton transfer is rate- and enantioselectivity-determining.

The Morita–Baylis–Hillman (MBH) reaction is a valuable synthetic method,[1] as the products are densely functionalized and can be easily modified in various ways.[2] In the last decade substantial progress has been made in the development of enantioselective variants.[3] However, although many chiral catalysts have been reported, their scope is generally limited. Especially for MBH reactions of simple acrylic esters with aldehydes, more efficient catalysts with broader application range are needed. Here we report a combinatorial approach to the development of chiral MBH catalysts based on a mass spectrometric screening method devised in our laboratory,[4] which has led to improved bifunctional chiral phosphine catalysts for MBH reactions of methyl acrylate with aldehydes. In addition, mass spectrometric data together with kinetic studies allowed us to identify the rate- and enantioselectivity-determining step.

Our screening method works as follows (see Scheme 1): Starting from a 1:1 mixture of mass-labeled quasi-enantiomeric MBH products **1a** and **1b**, a catalyst-mediated back reaction via intermediates **2a** and **2b** is induced, which then undergo cleavage to the aromatic aldehyde (in the present study 4-nitrobenzaldehyde) and the mass-labeled catalyst-substrate adducts **4a** and **4b**. If we assume a fast equilibrium between **1a** and **1b** and the corresponding catalyst adducts **2a** and **2b**, followed by a slow rate-determining C–C bond cleavage (Curtin–Hammet conditions), the ratio **4a**/**4b** will be identical to the enantiomeric ratio produced in the MBH reaction in the forward direction, according to the principle of microscopic reversibility. The ratio **4a**/**4b** can be reliably determined even at very low concentration by electrospray ionization mass spectrometry (ESI-MS). Under the conditions of ESI-MS analysis, **4a** and **4b** are protonated and their ratio is determined from the signal ratio of the corresponding cationic species **6a** and **6b**. This screening protocol is fast and operationally simple, as it does not require any work-up or purification steps. Moreover, mixtures of catalysts having different molecular masses can be screened simultaneously. By multicatalyst screening of combinatorial catalyst libraries, catalyst discovery and optimization can be considerably accelerated.



Scheme 1. Principle of back-reaction screening.

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Initial studies showed that, upon treatment of MBH adducts derived from acrylic esters and 4-nitrobenzaldehyde with triphenylphosphine, signals of catalyst adducts resulting from C–C bond cleavage could be detected by ESI-MS. Next we had to find a suitable pair of quasi-enantiomeric MBH products. Alkyl esters differing in the number of C atoms, which we evaluated first, gave unsatisfactory results as they slightly differed in reactivity, resulting in unequal ratios of catalyst-substrate adducts with an achiral catalyst. Finally, methyl and trideuteromethyl esters **1a** and **1b** proved to be optimal as they possessed identical reactivity and gave rise to easily detectable signal pairs.

Successful application of back-reaction screening requires the C–C bond-forming step to be rate- and enantioselectivity-determining (see above). However, in several studies the proton transfer after the aldol step was found to be, at least in part, rate-determining.[6–8] We therefore conducted preliminary experiments with chiral catalyst **9a** (Figure 1). We were pleased

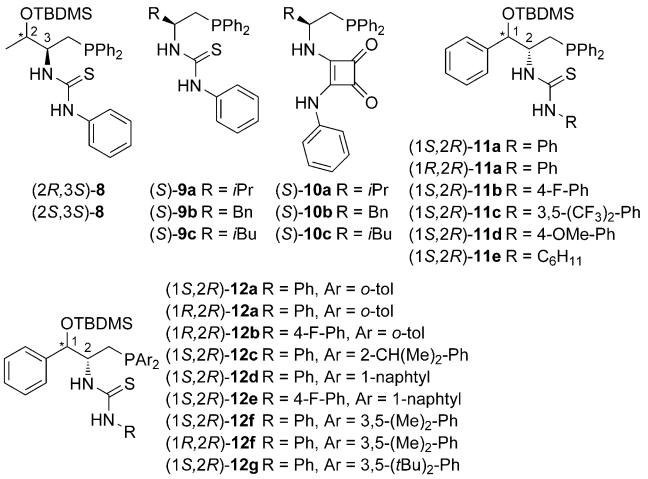


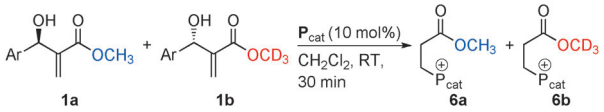
Figure 1. Phosphine-based organocatalysts.

to find that the ratios **6a**/**6b** produced in the back reaction closely matched the enantiomeric ratios determined for the preparative forward reaction, implying that our screening protocol should indeed be applicable. Encouraged by these results, we started a systematic evaluation of chiral MBH catalysts based on the screening protocol shown in Scheme 1.

The best enantioselectivities in the MBH reaction of simple acrylic esters with aldehydes so far were achieved by Yixin Lu and co-workers with threonine-derived bifunctional phosphine-thiourea catalysts such as (2*R*,3*S*)-**8**.[3c] Their modular nature seemed ideal for systematic structural optimization. We therefore synthesized an array of related phosphine-thiourea and -squaramide derivatives from commercially available amino alcohols (Figure 1; for additional catalysts and synthetic procedures see the Supporting Information).

For back-reaction screening, an equimolar mixture of quasi-enantiomers **1a** and **1b** was reacted with 10 mol% of catalyst in CH_2Cl_2 at room temperature. After 30 minutes the reaction mixture was diluted ten-fold with CH_2Cl_2 and a sample immediately injected into the spectrometer. The signals of the positively charged *retro*-MBH products **6a** and **6b** as well as the cationic species **5a** and **5b** generated by protonation of intermediates **2a**/**3a** and **2b**/**3b** were all clearly visible in high intensity. To validate the screening results, the ratios **6a**/**6b** measured by ESI-MS were compared to the enantiomeric ratios (e.r.) determined for the forward reaction by HPLC on a chiral stationary phase (Table 1). To our delight, the results from

Table 1. Screening of bifunctional organocatalysts.



Entry	Catalyst	ESI-MS screening **6a**/**6b**	Preparative reaction[a] e.r.
1	(*R*,*S*)-**8**	77:23	76:24
2	(*S*,*S*)-**8**	87:13	87:13
3	(*S*)-**9a**	68:32	66:34
4	(*S*)-**9b**	74:26	75:25
5	(*S*)-**9c**	71:29	72:28
6	(*S*)-**10a**	81:19	80:20
7	(*S*)-**10b**	85:15	85:15
8	(*S*)-**10c**	82:18	82:18
9	(*S*,*R*)-**11a**	9:91	10:90
10	(*R*,*R*)-**11a**	7:93	6:94
11	(*S*,*R*)-**11b**	12:88	13:87
12	(*S*,*R*)-**11c**	11:89	13:87
13	(*S*,*R*)-**11d**	13:87	13:87
14	(*S*,*R*)-**11e**	17:83	20:80
15	(*S*,*R*)-**12a**	6:94	6:94
16	(*R*,*R*)-**12a**	5:95	5:95
17	(*R*,*R*)-**12b**	7:93	6:94
18	(*S*,*R*)-**12c**	6:94	7:93
19	(*S*,*R*)-**12d**	4:96	5:95
20	(*S*,*R*)-**12e**	5:95	5:95
21	(*S*,*R*)-**12f**	21:79	21:79
22	(*R*,*R*)-**12f**	11:89	15:85 (11:89)[b]
23	(*S*,*R*)-**12g**	20:80	19:81

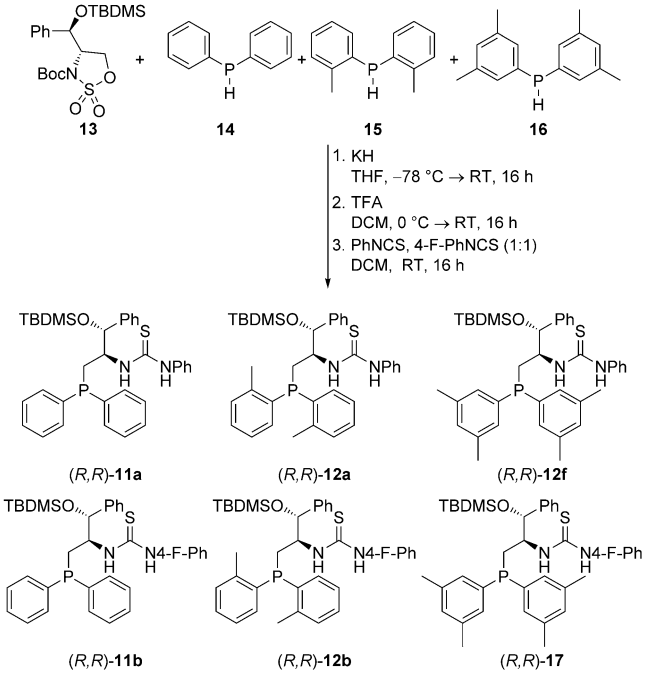
[a] Reaction conditions: **18a** (1.0 equiv), **7a** (1.5 equiv), catalyst (10 mol%), CH_2Cl_2, RT, 18 h. Determined by HPLC on a chiral stationary phase; [b] ratio in parentheses measured after 30 min.

back-reaction screening and from the corresponding preparative MBH reactions closely matched each other. Only in one case (entry 22) the e.r. was significantly lower than the selectivity of the back reaction. However, we found that this divergence was caused by slow catalyst-induced racemization of the MBH products under the reaction conditions.

Initial experiments with analogues of Lu's catalyst (2*R*,3*S*)-**8** lacking the silyloxy substituent gave similar or lower enantioselectivities (Table 1, entries 3–5). Replacement of the thiourea group by a squaramide unit led to improved e.r. values of up to 85:15 (entries 6–8). However, attempts to further optimize this class of squaramide derivatives were unsuccessful.[9] A more pronounced increase of the e.r. resulted when the methyl group of catalyst (2*R*,3*S*)-**8** was replaced by a phenyl group (cf. entries 1 and 9). Introduction of electron-donating or electron-withdrawing substituents into the *N*-phenyl group of (1*S*,2*R*)-**11a** had only a marginal effect, whereas a *N*-cyclo-

hexyl substituent lowered the e.r. from 90:10 to 80:20 (entries 9–14). Notably, the *like*-diastereomers induced better selectivity than the *unlike*-diastereomers (entries 1–2 and 9–10). Finally, a further significant increase in enantioselectivity was achieved by replacing the *P*-phenyl groups with more bulky *ortho*-tolyl, *ortho*-*i*Pr-phenyl, or 1-naphthyl groups (entries 15–19). Catalysts **12 f** and **12 g** with 3,5-dialkyl-substituted *P*-phenyl groups gave inferior results (entries 21 and 23).

To demonstrate the potential of our screening protocol for combinatorial catalyst development,[5] we synthesized a library of six different organocatalysts by a three-step procedure without purification or separation of the intermediates and final products (Scheme 2). The resulting crude catalyst library was then directly subjected to back-reaction screening.



Scheme 2. One-batch catalyst library synthesis.

For all catalysts the corresponding signals of intermediates **6 a** and **6 b** were detected (Figure 2). Although the selectivities obtained by multi-catalyst screening were somewhat lower compared to single-catalyst screening,[10] the selectivity order among the six catalysts was correctly displayed. So the most selective catalysts in a combinatorial library can be readily identified in this way.

From our screening experiments with 30 catalysts, three efficient catalysts (1*R*,2*R*)-**12 a**, (1*S*,2*R*)-**12 d**, and (1*S*,2*R*)-**12 e** have emerged, which all induce an e.r. of 95:5 in the reaction of methyl acrylate with 4-nitrobenzaldehyde. For further studies addressing the substrate scope, (1*R*,2*R*)-**12 a** was chosen because of its higher reactivity (Table 2).

Under optimized conditions,[9] a broad selection of aromatic and heteroaromatic aldehydes afforded high enantioselectivities and yields in the preparative reaction (Table 2, entries 1–12), except for 4-methylbenzaldehyde (entry 11), which

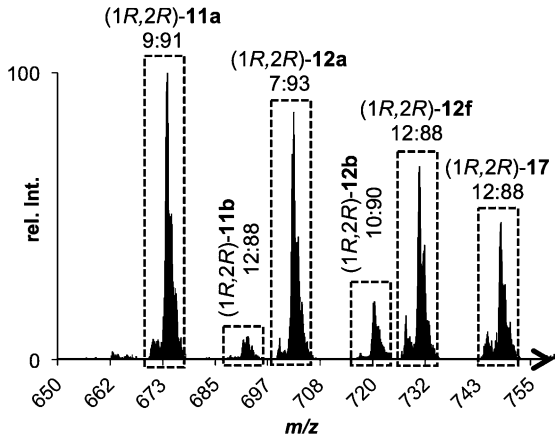
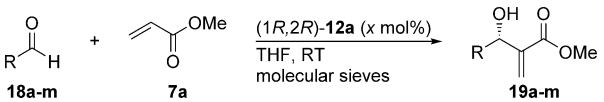


Figure 2. Multi-catalyst screening.

Table 2. Substrate scope of catalyst (1*R*,2*R*)-**12 a**.[a]



18a-m 7a 19a-m

Entry	R	Product	*x*	*t* [h]	Yield[b] [%]	*ee*[c] [%]
1	4-NO_2-Ph (**18 a**)	**19 a**	10	6	98	94
2	2-NO_2-Ph (**18 b**)	**19 b**	10	6	88	80
3	4-CN-Ph (**18 c**)	**19 c**	10	18	93	92
4	3,5-$(CF_3)_2$-Ph (**18 f**)	**19 d**	10	18	98	92
5	4-F-Ph (**18 e**)	**19 e**	20	48	69	90
6	4-Cl-Ph (**18 f**)	**19 f**	20	48	89	90
7	4-Br-Ph (**18 g**)	**19 g**	20	48	90	92
8	Ph (**18 h**)	**19 h**	20	72	82 (73)[d]	90 (90)[d]
9	2-pyridine (**18 i**)	**19 i**	20	72	95	90
10	2- furfural (**18 j**)	**19 j**	20	72	83	80
11	4-Me-Ph (**18 k**)	**19 k**	20	96	42	85
12	C_6H_{11} (**18 l**)	**19 l**	20	96	36	30

[a] **18** (0.1 mmol), **7 a** (0.15 mmol) in THF (0.1 mL); [b] after purification by preparative TLC; [c] determined by HPLC on a chiral stationary phase; [d] 1 mmol scale.

showed lower reactivity. Cyclohexane-carbaldehyde gave only low *ee* and yield. Overall, catalyst (1*R*,2*R*)-**12 a** clearly outperformed the best literature-known catalysts such as (2*R*,3*S*)-**8** in terms of enantioselectivity and yield.[3]

The results from back-reaction screening also provided insights into the catalytic cycle. Mechanistic studies of amine-catalyzed MBH reactions have shown that C–C bond formation and the subsequent proton transfer have similar activation barriers and, depending on the conditions, one or the other step may become primarily rate-limiting.[6,7] For phosphine-based catalysts only a computational study was reported, which predicted the proton-transfer step to be rate-determining.[8] However, Plata and Singleton have recently demonstrated that at present computational methods are unable to cope with the complex multi-step catalytic cycle of MBH reactions and, therefore, fail to produce reliable results.[7]

The close match between the selectivities obtained from back-reaction screening and the preparative forward reaction

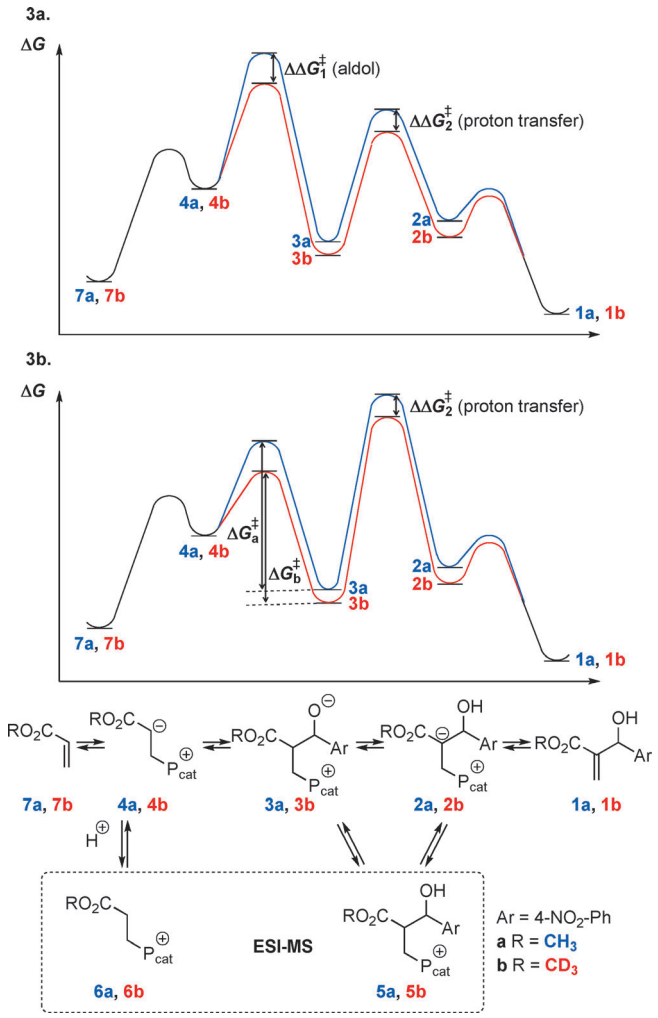


Figure 3. Qualitative energy profiles.

indicates that C–C bond formation is the rate- and enantioselectivity-determining step. A qualitative reaction coordinate consistent with the selectivity data is shown in Figure 3a. The consensus between the product e.r. of the forward reaction and the ratio **4a**/**4b** determined from the ESI-MS signals of **6a** and **6b** in the back reaction implies that both ratios depend on the same transition state. This is the case if the aldol step is the step with the highest energy barrier. If the proton transfer was rate-determining (Figure 3b), equilibration between intermediates **3a**/**3b** and **4a**/**4b** would occur, due to the now reversible aldol step. Thus, the ratio **4a**/**4b** would depend on both $\Delta\Delta G^{\ddagger}$ of the proton transfer and the equilibrium constants K(**3a**/**4a**) and K(**3b**/**4b**), which differ because of the unequal relative energies of **3a** and **3b**, whereas the enantioselectivity of the forward reaction would be determined solely by $\Delta\Delta G^{\ddagger}$ of the proton transfer. Accordingly, the ratio **4a**/**4b** would be expected to deviate from the e.r of the forward reaction, in contradiction to the observed match between the forward and back reaction.[11]

In addition, kinetic measurements were carried out to determine the reaction order in aldehyde by in situ ^{1}H NMR analysis of reaction process based on the signals of the methyl ester group of acrylate **7a** (3.73 ppm) and MBH adduct **19a** (3.71 ppm). Data were taken from four reactions, in which the aldehyde/acrylate ratio was varied from 0.5 to 3.0. The results clearly showed the reaction to be first order in aldehyde, providing further evidence that the aldol step is rate-limiting (see Figure 4 and the Supporting Information).

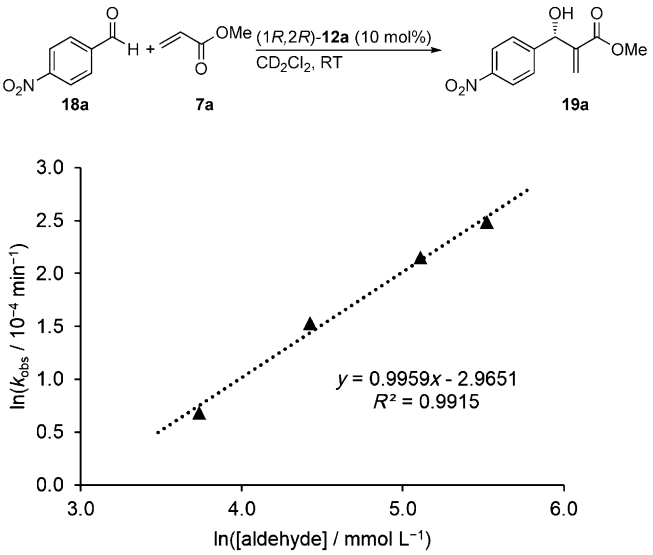


Figure 4. Kinetic analysis of the MBH reaction of methyl acrylate with 4-nitrobenzaldehyde. Double logarithmic plot of the dependence of the reaction rate on the initial aldehyde concentration. The data points correspond to aldehyde concentrations of 41.7, 83.3, 166.7, and 250.0 mmol L^{-1} and a constant acrylate concentration of 83.3 mmol L^{-1}. Linear fit for **18a**: $y = 0.9959x - 12.175$ ($R^2 = 0.99$), consistent with first order in **18a**.

In conclusion, we have demonstrated the potential of mass spectrometric back-reaction screening for the evaluation of catalysts for asymmetric MBH reactions. Screening of 30 bifunctional phosphines has led to an efficient catalyst for the reaction of methyl acrylate with aldehydes, showing improved enantioselectivity and scope compared to previously reported catalysts. In addition, the results from back-reaction screening and additional kinetic studies have provided evidence that the enantioselectivity is determined in the C–C bond-forming step, which is turnover-limiting.

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Keywords: asymmetric catalysis · high-throughput screening · mass spectrometry · Morita–Baylis–Hillman · organocatalysis

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[10] The deviation of the ratios **6a**/**6b** from the actual e.r. values is likely caused by the high catalyst loading (30 mol%) that had to be used in order to obtain satisfactory signal to noise ratios. Under these conditions the assumption of a rapid pre-equilibrium between **1a** and **2a**, and **1b** and **2b**, is no longer valid.
[11] For an analogous analysis of the conjugate addition of aldehydes to nitroolefins, see: F. Bächle, J. Duschmalé, C. Ebner, A. Pfaltz, H. Wennemers, *Angew. Chem. Int. Ed.* **2013**, *52*, 12619 – 12623; *Angew. Chem.* **2013**, *125*, 12851 – 12855.

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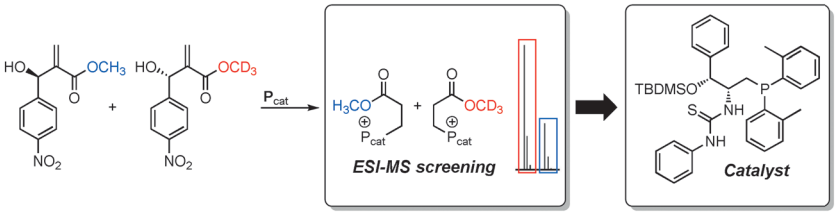

Mass spectrometric catalyst screening for the asymmetric Morita–Baylis–Hillman (MBH) reaction of methyl acrylate has led to the bifunctional phosphine (1*R*,2*R*)-**12a** that outperformed previously reported catalysts in terms of enantioselectivity and scope. In addition, mass spectrometric data and kinetic studies provided evidence for C–C bond formation as the enantioselectivity- and rate-determining step.