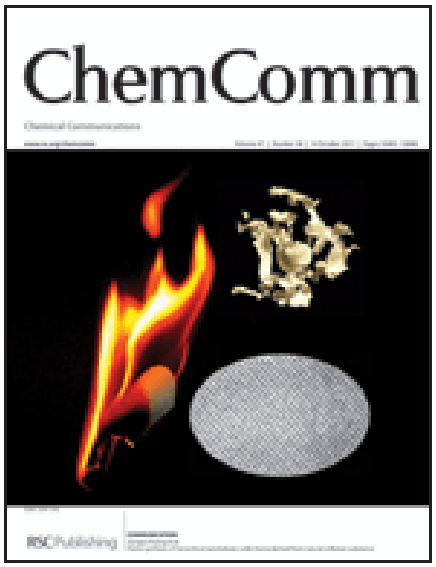

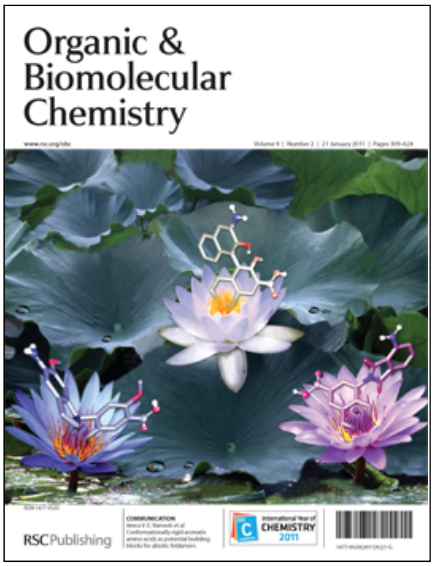

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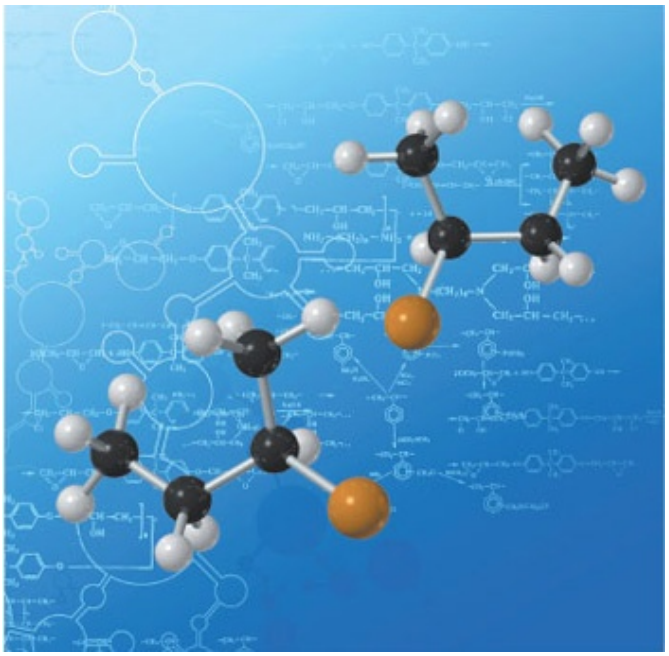

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PAPER

The aza-Morita–Baylis–Hillman reaction of electronically and sterically deactivated substrates†‡

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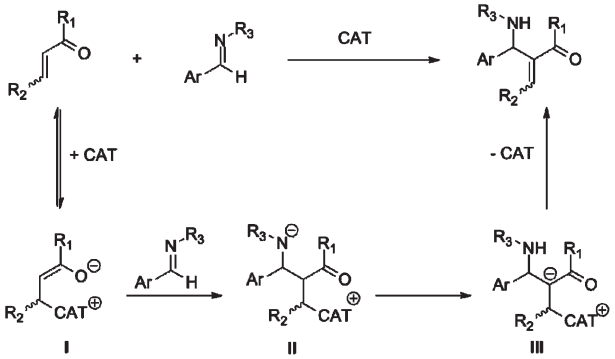
The aza-Morita–Baylis–Hillman (azaMBH) reaction has been studied for electronically and sterically deactivated Michael acceptors. It is found that electronically deactivated systems can be converted with electron-rich phosphanes and pyridines as catalysts equally well. For sterically deactivated systems clearly better catalytic turnover can be achieved with pyridine catalysts. This is in accordance with the calculated affinities of the catalysts towards different Michael-acceptors.

Introduction

The aza-Morita–Baylis–Hillman (azaMBH) reaction is a synthetically useful C–C bond forming reaction involving the coupling of imines with Michael acceptors to form highly functionalized amines (Scheme 1).[1–3,8] Despite the impressive development of various protocols for the enantioselective azaMBH reaction involving either chiral Lewis bases or combinations of achiral Lewis bases with chiral protic co-catalysts,[4–7] the effective transformation of sterically and/or electronically deactivated Michael acceptors still provides an ambitious challenge.

The azaMBH reaction is currently considered to involve initial attack of the Lewis base catalyst on the Michael acceptor,[3c,d,4,9,10] followed by addition of the resulting zwitterionic enolate **I** to the imine substrate. Subsequent intramolecular proton transfer within zwitterionic intermediate **II** and elimination of the nucleophilic catalyst close the catalytic cycle. Previous kinetic studies by Lloyd-Jones *et al.*[11] indicate that reaction rates are most likely limited by the imine addition and/or the subsequent proton transfer step. The step most strongly affected by deactivated Michael acceptors is the initial nucleophilic addition step, and sluggish reaction rates for this class of substrates may simply derive from the reduced preequilibrium formation of zwitterionic enolate **I**. This implies that the use of Lewis base catalysts with increased carbon basicity will predictably lead to higher turnover rates. In the following we show that this is indeed the case.



Scheme 1 The mechanism of the aza-Morita–Baylis–Hillman (azaMBH) reaction of imines with Michael acceptors.

Results and discussion

Initial experiments were performed for the reaction of *p*-chlorotosylimine **1a** with methyl vinyl ketone (**2a**) using the nucleophilic catalysts depicted in Fig. 2 in $CDCl_3$ as the solvent (Scheme 2, Table 1). Methyl vinyl ketone (**2a**) has been selected here as a reference Michael acceptor of known high reactivity.

The reaction was conveniently monitored by ^1H NMR spectroscopy following the signals of imine **1a** and amine product **3aa**. Turnover curves were fitted using a simple kinetic scheme involving pre-equilibrium formation of zwitterionic enolate **I** and the follow-up addition/rearrangement step with imine. This kinetic model involving only three rate constants as variable parameters is closely similar to that used in previous studies,[11] but does not include any type of co-catalysis by product molecules or other protic additives. More complex models involving a larger number of steps have also been explored, but not found to perform substantially better (see ESI† for further details). An example for the turnover curve with catalyst **4d** is depicted in Fig. 1.

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‡ Electronic supplementary information (ESI) available: Details of the kinetic measurements, synthesis and theoretical calculations. See DOI: 10.1039/c2ob07058h

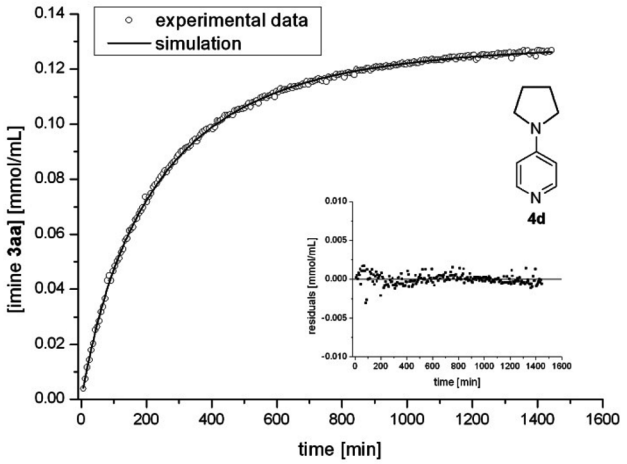


Fig. 1 Results for the reaction of MVK (**2a**) with imine **1a** catalyzed by 10 mol% **4d** in $CDCl_3$.

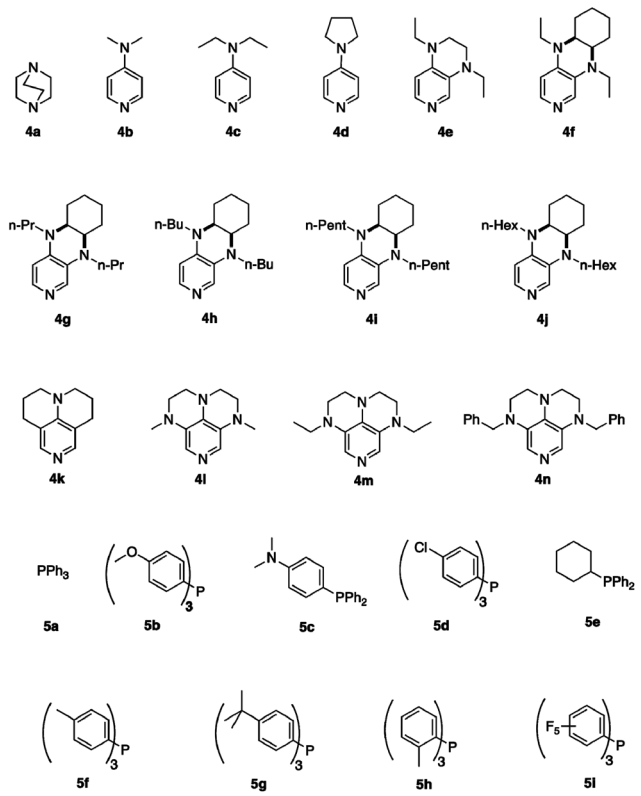


Fig. 2 Catalysts used in the azaMBH reactions.

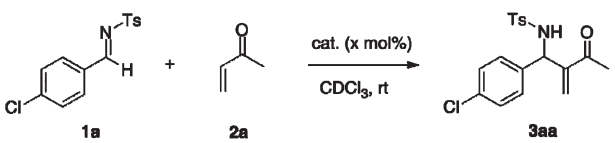
The reaction half-life time $t_{1/2}$ listed in Table 1 as the most relevant kinetic parameter corresponds to the time required for 50% conversion of the initially used imine substrate and is obtained from the simulated turnover curve. Methyl cation affinity (MCA) values are available for most of the catalysts shown in Fig. 2 and reflect the Lewis basicity of these species towards the methyl cation as the smallest carbon electrophile (Table 1).[14]

In the group of nitrogen-based catalysts the reaction is rather sluggish in the presence of catalysts of low Lewis basicity such as DABCO (**4a**), yielding only 8% turnover after 10 h reaction

Table 1 Results for the azaMBH reaction with MVK (**2a**) shown in Scheme 2

Entry	Catalyst	Time [h]	Conversion[ac] [%]	$t_{1/2}$[c] [min]	MCA [kJ mol^{-1}]
Using 10 mol% catalyst					
1	DABCO (**4a**)	10	8	3750[f]	+562.2
2	DMAP (**4b**)	10	56	475	+581.2
3	**4c**	10	83	193	+589.1
4	PPY (**4d**)	10	86	146	+590.1
5	**4n**[g]	8	93	72	+636.8
6	**4e**	5	98	41	+609.0
7	**4m**[g]	4	96	26	+621.6
8	**4l**[g]	4	99	25	+618.7
9	**4f**	3	99(98)[b]	23	+616.0
10	**4k**	3	98	20	+602.7
11	**5i**	–	–	nc[e]	+494.1
12	**5h**	–	–	nc[e]	+643.9
13	**5d**	34	95	271[d]	+586.5
14	PPh_3 (**5a**)	4	99	35	+618.4
15	**5b**	3	98	32	+651.0
16	**5f**	3	99	27	+637.2
17	**5e**	2	98	26	+630.2
18	**5c**	3	99	25	+646.7
19	**5g**	2	99	22	+643.9
Using 5 mol% catalyst					
20	**4e**	10	97	75	+609.0
21	**4j**	10	99	55	–
22	**4h**	10	99	53	–
23	**4i**	10	99	53	–
24	**4f**	10	99(92)[b]	53	+616.0
25	**4g**	10	99	49	–
26	**4k**	5	99	40	+602.7
27	PPh_3 (**5a**)	8	98	69	+618.4
28	**5c**	7	98	64	+646.7
29	**5b**	9	95	60	+651.0
30	**5f**	5	99	46	+637.2
31	**5e**	4	99	45	+630.2
32	**5g**	4	99	41	+643.9
Using 2.5 mol% catalyst					
33	PPh_3 (**5a**)	13	95	146	+618.4
34	**5g**	10	92	80	+643.9
35	**4k**	10	96	77	+602.7
36	**5f**	10	95	76	+637.2

[a] Determined by ^{1}H NMR. [b] Isolated yield. [c] 0.125 M imine, 1.2 eq. MVK. [d] 20% catalyst. [e] No conversion. [f] Extrapolated value. [g] Ref. 12



Scheme 2 The azaMBH reaction of *N*-tosylimine **1a** with MVK (**2a**) in $CDCl_3$.

time. Extrapolating this rate in a linear fashion to 50% turnover yields an approximate half-life time of 3750 minutes. Significantly higher rates are observed for pyridine catalysts such as DMAP (**4b**) and PPY (**4d**). Best results are obtained with the recently developed 3,4-diaminopyridine catalysts such as **4f**, with the tricyclic aminopyridine **4k**,[13] or with some of the phosphanes based on the PPh_3 motif. In all these latter cases complete turnover is achieved after 4 h. For catalyst **4f** it has been

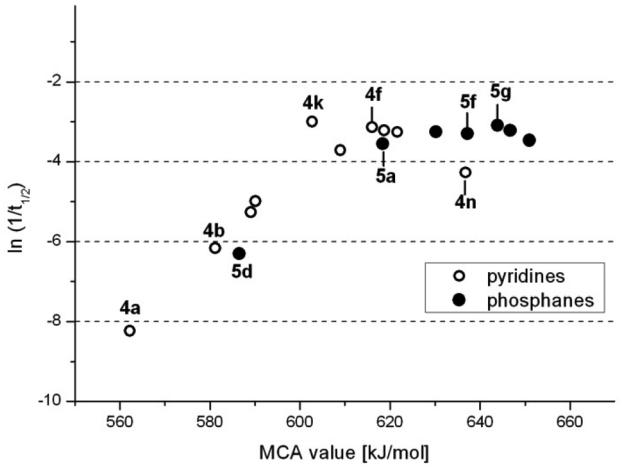


Fig. 3 Correlation of reaction rates *vs.* MCA values for the reaction of MVK (**2a**) and **1a** with 10 mol% catalyst.

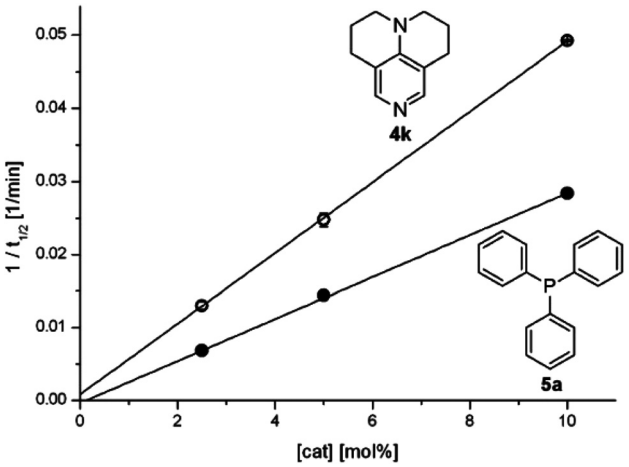
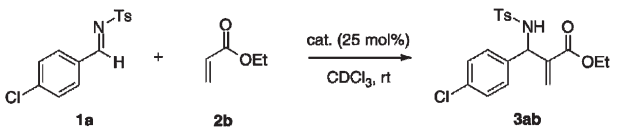


Fig. 4 Correlation of the rates of reaction of MVK (**2a**) with **1a** *vs.* the concentration of the catalysts **4k** and **5a**.

verified that this translates into an isolated yield of 98% after product isolation and purification. With respect to $t_{1/2}$ values the tricyclic pyridine **4k** is found to be the fastest catalyst, closely followed by pyridine **4f**. This closely parallels recent results for the Lewis base-catalyzed acylation of tertiary alcohols.[16] Phosphane **5g** is the most active phosphane catalyst studied here, but is only moderately faster than other triarylphosphanes carrying electron-donating substituents in *para* position such as **5c**. Replacing one of the phenyl groups in PPh_3 (**5a**) by a cycloalkyl substituent as in **5e** also enhances the catalytic activity, but also leads to a notable increase in phosphane oxidation (and thus deactivation). Rather poor results are obtained for phosphanes with electron-withdrawing substituents (such as **5i**) or with sterically demanding substituents in *ortho* position (as in **5h**).

With rate data for a larger number of systems in hand we can test for a possible quantitative correlation between catalyst basicity as quantified by MCA values and reaction rate. As can be seen in Fig. 3 a linear correlation between basicity and reaction rate exists for catalysts of low Lewis basicity (that is, with MCA values less than 610 kJ mol^{-1}). For more Lewis basic compounds a saturation of the reaction rate at high level is found. The only catalyst not following this general trend is sterically hindered phosphane **5h**, whose rather large MCA value of 643.9 kJ mol^{-1} equals that of the most active phosphane **5g**, but whose very low reactivity did not allow for determining the reaction rate quantitatively. The intrinsically good Lewis basicity of catalyst **5h** is thus completely compensated by steric effects in reactions involving the substrate pair **1a**/**2a**.

The absolute reaction rates obtained for electron-rich pyridines and phosphanes are somewhat too large at catalyst loadings of 10 mol% to obtain a precise picture of catalytic performance. To this end several of the reactions have been reinvestigated with a lower catalyst loading of 5 mol% (Table 1), now also including derivatives of catalyst **4f** with alkyl sidechains of variable lengths. The largely similar $t_{1/2}$ values determined for 3,4-diaminopyridines **4f–4j** imply, however, that the increasingly longer alkyl side chains in these compounds do not lead to an enhancement of the electron density of the pyridine ring (and thus not to an increase in catalytic performance). Tricyclic



Scheme 3 The azaMBH reaction of *N*-tosylimine **1a** with ethyl acrylate (**2b**) in $CDCl_3$.

pyridine **4k** thus remains the most effective catalyst found here, closely followed by phosphane **5g**.

For selected catalysts the reaction was also investigated at a loading of 2.5 mol%. Together with the results obtained at higher loadings this allows for an approximate analysis of the dependence of the reaction rate on the catalyst loading (Fig. 4). Measurements at even lower loadings were accompanied by oxidation of the phosphane catalysts in a significant manner and were thus not pursued any further (see ESI† for details). The results for the most stable catalysts, *e.g.* **4k** and **5a** indicate that reaction rates vary linearly with the catalyst concentration (*cf.* Fig. 4). In mechanistic terms this implies the involvement of a single catalyst molecule in the rate limiting step. For both of these catalysts the interpolation curve is observed to pass through the intercept, reflecting minimal background reactivity. This latter point is also in line with rate measurements performed in the absence of catalysts.

Tosylimine **1a** was also used in benchmark reactions with ethyl acrylate (**2b**) as the Michael acceptor. Due to the much lower reactivity of this latter compound, reasonable turnover times require higher substrate concentrations and a catalyst loading of 25 mol% (Scheme 3, Table 2).

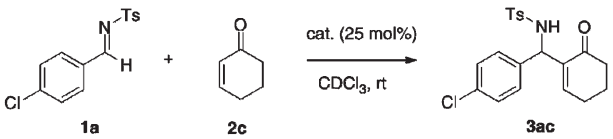
With these reaction conditions full conversion can be obtained after a maximum of five days. The phosphane catalyst **5f** turned out to be the most effective choice in this series with complete turnover after two days, although pyridine **4k** is almost equally active. The half-life time of triphenylphosphane **5a** is more than two times longer than the two best catalysts.

In order to explore the effects of steric hindrance on the catalytic efficiency of pyridine and phosphane catalysts, the azaMBH reaction of cyclohexenone (**2c**) was studied under the same conditions used for acrylate **2b** (Scheme 4, Table 3).

Table 2 Results for the azaMBH reaction with ethyl acrylate (**2b**) using 25 mol% catalyst as shown in Scheme 3

Entry	Catalyst	Time [d]	Conversion[ab] [%]	$t_{1/2}$ [min]
1	**5a**	5	99	1384
2	**4f**	4	99	747
3	**4k**	3	99	612
4	**5f**	2	99	595

[a] Determined by ^{1}H NMR. [b] 0.25 M imine, 4.0 eq. **2b**.



Scheme 4 The azaMBH reaction of *N*-tosylimine **1a** with cyclohexenone (**2c**) in $CDCl_3$.

Table 3 Results for the azaMBH reaction with cyclohexenone (**2c**) using 25 mol% catalyst as shown in Scheme 4

Entry	Catalyst	Time [h]	Conversion[ac] [%]	$t_{1/2}$[c] [min]
1	DABCO (**4a**)	40	4	—
2	Quinuclidine	40	25	—
3	DMAP (**4b**)	40	36	—
4	PPY (**4d**)	30	43	—
5	**4f**	30	99(98)[b]	264
6	**4k**	30	98	242
7	**4l**	40	95	456
8	**4m**	72	98	581
9	**4n**	72	97	758
10	PPh_3 (**5a**)	40	<3	—
11	**5f**	40	<3	—

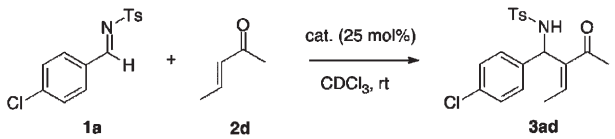
[a] Determined by ^{1}H NMR. [b] Isolated yield. [c] 0.25 M imine, 4 eq. **2c**.

The reaction of cyclic ketone **2c** with DABCO (**4a**) as catalyst shows almost no conversion. For the pyridine catalysts, in contrast, good turnover can be observed in particular for the 3,4-diaminopyridine catalyst **4f** and the tricyclic pyridine **4k**. With these catalysts, essentially complete turnover is achieved after 30 h reaction time, which translates into an isolated yield of adduct **3ac** of 98% for **4f**. In surprising contrast to the result obtained for the acyclic Michael acceptors **2a** and **2b**, there is practically no turnover when using any of the phosphane catalysts for reaction with cyclohexenone **2c**. This unexpected result may indicate a generally larger sensitivity of triarylphosphanes to steric demands of the Michael acceptor, or may alternatively indicate the presence of stabilizing contacts between phosphane catalyst and carbonyl oxygen atom in the zwitterionic enolates **I** formed in the initial addition steps (see Scheme 1). As indicated in Scheme 1 this latter type of interaction is only possible in acyclic Michael acceptors for geometric reasons. In order to differentiate between these two effects, additional measurements have been performed for acyclic Michael acceptor *trans*-3-penten-2-one (**2d**), in which the center of attack also carries an alkyl substituent.

Table 4 Results for the azaMBH reaction with *trans*-3-penten-2-one (**2d**) using 25 mol% catalyst as shown in Scheme 5

Entry	Catalyst	Time [d]	Conversion[ac] [%]	$t_{1/2}$[c] [h]
1	**4f**	29	92	164
2	**4k**	29	98(93)[b]	120
3	PPh_3 (**5a**)	5	<2	—
4	**5f**	5	<2	—

[a] Determined by ^{1}H NMR. [b] Isolated yield. [c] 0.125 M imine, 4 eq. **2d**.



Scheme 5 The azaMBH reaction of *N*-tosylimine **1a** with *trans*-3-penten-2-one (**2d**) in $CDCl_3$ solution.

Although the reaction of the sterically hindered ketone **2d** is the slowest of the four investigated azaMBH reactions, full conversion can be obtained for pyridine catalysts **4f** and **4k** after 29 days. Product isolation and characterization indicates formation of a single stereoisomer **3ad** with (*E*)-configuration according to NOE experiments and X-ray analysis. In contrast to the two pyridine catalysts **4f** and **4k**, there is no significant turnover for triarylphosphanes **5a** or **5f**. Since the acyclic nature of alkene **2d** does allow for contacts between carbonyl oxygen and phosphane catalysts in zwitterionic intermediate **I**, this latter result implies that triaryl phosphane catalysts are intrinsically more sensitive to the steric demands of Michael acceptors than pyridine catalysts.

The largely different reactivities of the four Michael acceptors **2a–2d** are already apparent from the conversion data in Tables 1–4. It was nevertheless desirable to compare the catalytic properties of the best catalysts **4k** and **5f** in transformations with these four substrates under strictly identical conditions. To this end, an additional set of rate measurements was performed using tosylimine **1a** at 0.25 M concentration in combination with 4.0 eq. Michael acceptor and 25 mol% catalyst. As can be seen from the turnover plot for catalysts **4k** and **5a** in Fig. 5, the reaction is now so fast for MVK (**2a**) as the substrate that the reaction is essentially complete within 3 minutes (**4k**) and 20 minutes (**5a**) respectively.

For the azaMBH reaction with MVK (**2a**) and **4k** as catalyst, the reaction half-life time is roughly one minute. The half-life times are dramatically increased for the electronically deactivated Michael acceptor **2b** (612 minutes), as well as for sterically hindered Michael acceptors (**2c**, 242 minutes; **2d**, 1890 minutes). The difference in the reactions of MVK (**2a**) and acrylate **2b** of 1 : 612 is significantly larger as compared to the ratio of 1 : 38 found in kinetic studies for the addition of DMAP (**4b**) to MVK and methyl acrylate in aqueous solution.[24] The half-life time in the case of phosphane **5a** as catalyst (*cf*. Fig. 5) is four minutes (MVK (**2a**)) and 1384 minutes (ethyl acrylate (**2b**)) respectively. As already mentioned above the phosphanes are not catalytically active in the case of sterically hindered Michael-acceptors (**2c** and **2d**).

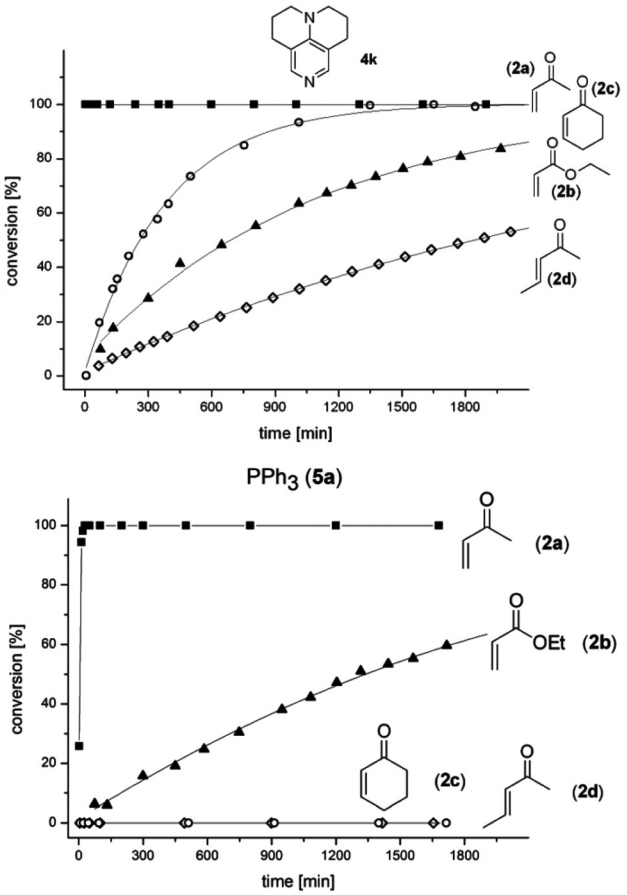
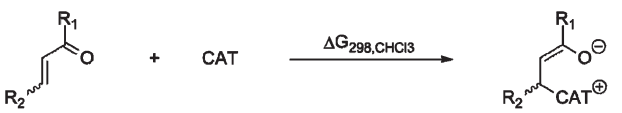


Fig. 5 Turnover curves for **4k** (top) and **5a** (bottom) for the azaMBH reactions of tosylimine **1a** (0.25 M) with 4 eq. of Michael acceptors **2a** (filled squares), **2b** (filled triangles), **2c** (empty circles) or **2d** (empty diamonds).



Scheme 6 Formation of adducts between catalyst and Michael-acceptors.

Suspecting that the largely different reaction rates for Michael acceptors **2a–2c** are, at least in part, due to the energetics of the first step of the catalytic cycle shown in Scheme 6, the reaction free energies for this step in $CHCl_3$ solution have been calculated for catalysts **4f** and **5a** using a theoretical protocol optimized for the description of zwitterionic species in organocatalytic reactions (Fig. 6).[21]

The reaction free energies for the addition of catalysts **4f** and **5a** to alkenes **2a–2c** are all large and positive, implying a rather unfavorable position of the preequilibrium. In qualitative agreement with the measured rate data, the most stable intermediate is calculated for the addition of **4f** to MVK (**2a**), closely followed by the adduct formed from the same alkene with **5a**. The zwitterionic intermediates **I** formed through reaction with the electronically deactivated acrylate **2b** are less favourable for both catalysts, again with a small preference for catalyst **4f**. This is again in agreement with available rate data. For sterically

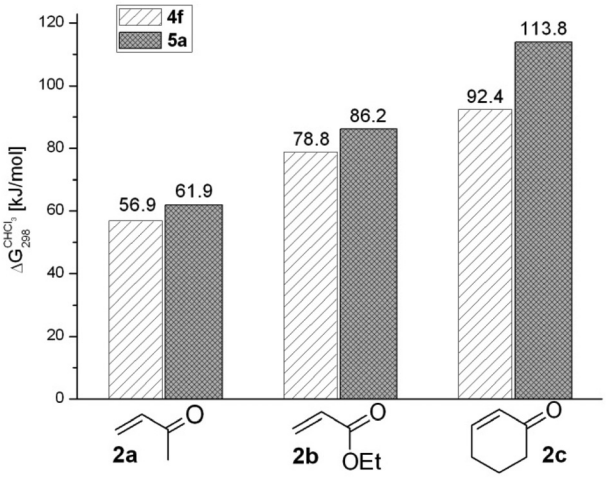


Fig. 6 Reaction free energies $\Delta G_{298,CHCl_3}$ for the formation of zwitterionic enolates **I** involving catalysts **4f** and PPh_3 (**5a**) and different Michael acceptors (**2a–2c**).

hindered alkene **2c** the agreement between calculated stabilities and measured rate data are less satisfactory in that the (comparatively fast) reaction with catalyst **4f** is not compatible with the very low calculated stability of the respective intermediate **I**. The least stable intermediate studied here is the adduct formed through reaction of alkene **2c** with phosphane **5a**, which is again in satisfactory agreement with the non-observation of product formation. The energetically best conformations of the MVK-adducts with **4f** and **5a** are depicted in Fig. 7.

In both structures we can identify a close contact between the enolate oxygen atom and one of the catalyst C–H bonds. In catalyst **4f** this interaction involves the α-C–H bond of the pyridine ring. This is closely similar to interactions identified between acylpyridinium ions and carboxylate counter ions in pyridine-catalyzed acylation reactions.[22,23] In the adduct formed with PPh_3 (**5a**) the enolate oxygen atom is in direct contact with one of the phenyl *ortho*-C–H bonds.

In order to explore the synthetic scope of the protocols developed above, the reactions with MVK (**2a**) as the Michael acceptor were repeated with 3,4-diaminopyridine catalyst **4f** at 5 mol% loading for a number of different tosylimines (Scheme 7, Table 5). The entries in Table 5 are ordered by σ_{para} parameters.[20,25]

It is gratifyingly found that catalyst **4f** used at 5 mol% loading yields acceptable turnover times and good synthetic yields even for deactivated tosylimines carrying donor substituents such as **1h**. Reaction times are, of course, much shorter for acceptor substituted imines such as **1b** and **1c**. The latter are the fastest imines which can also be found by their σ_{para} parameters. We note in passing that the variations in reaction times and yields observed here are fully compatible with, at least partially, rate-limiting addition of zwitterionic intermediates **I** to the imine substrates. A completely analogous set of experiments was performed with catalyst **4f** for the sterically hindered Michael acceptor cyclohexenone **2c** (Scheme 8, Table 6).

Reactions with sterically hindered Michael acceptor **2c** are, even at the much higher catalyst and substrate concentrations used now, significantly slower as compared to those involving

MVK (**2a**). After sufficiently long reaction times the corresponding azaMBH products **3** can, however, be isolated in good to excellent yields in all cases.

Conclusion

An effective protocol for the azaMBH reaction could be developed for all four Michael acceptors studied here. MVK (**2a**) is the most reactive of the studied substrates. Having no background reaction MVK (**2a**) and the tosylimine (**1a**) can be converted to the azaMBH product quantitatively in minutes. Most pyridine and phosphane catalysts tested in this reaction lead to full conversion in a short time. Using deactivated substrates, the necessary reaction times for full conversion are significantly increased. For the electronically deactivated Michael acceptor (**2b**) pyridines as well as phosphanes can be used. In the case of sterically hindered substrates (**2c** and **2d**) only pyridines are catalytically active, which illustrates the synthetic value of this class of catalysts. All results found here are compatible with a reaction mechanism involving preequilibrium formation of zwitterionic intermediates from Michael acceptors and catalysts, and subsequent rate-limiting addition to the imine (followed by intramolecular proton transfer and elimination of catalyst). The high sensitivity of the azaMBH reaction rates to the steric and the electronic properties of the Michael acceptor substrate found here for the reaction in chloroform solution are, however, also compatible with a partially rate-limiting first addition step.

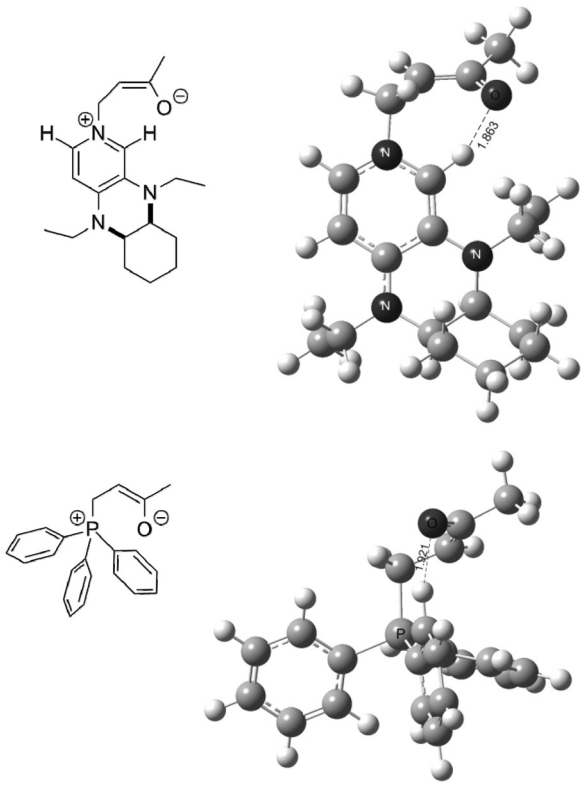
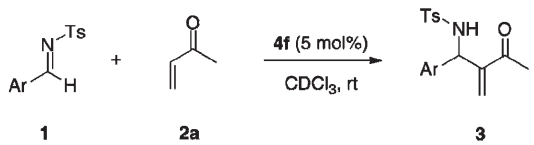


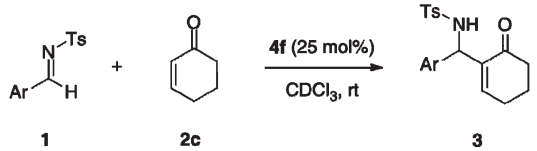
Fig. 7 Structures of the best conformations of zwitterionic enolates **I** formed in the reaction of catalysts **4f** and **5a** with MVK (**2a**).

Experimental

All air and water sensitive manipulations were carried out under a nitrogen atmosphere using standard Schlenk techniques. Calibrated flasks for kinetic measurements were dried in the oven at 120 °C for at least 12 h prior to use and then assembled quickly while still hot, cooled under a nitrogen stream and sealed with a rubber septum. All commercial chemicals were of reagent grade and were used as received unless otherwise noted. $CDCl_3$ was refluxed for at least one hour over CaH_2 and subsequently distilled. ^1H and ^{13}C NMR spectra were recorded on Varian 300 or Varian INOVA 400 machines at room temperature. All ^1H chemical shifts are reported in ppm (δ) relative to TMS (0.00); ^{13}C chemical shifts are reported in ppm (δ) relative to $CDCl_3$ (77.16). ^1H NMR kinetic data were measured on a Varian Mercury 200 MHz spectrometer at 23 °C. HRMS spectra (ESI-MS) were carried out using a Thermo Finnigan LTQ FT



Scheme 7 The azaMBH reaction of MVK (**2a**) with various tosylimines and catalyst **4f** in $CDCl_3$ solution.



Scheme 8 The azaMBH reaction of cyclohexenone (**2c**) with various tosylimines and catalyst **4f** in $CDCl_3$ solution.

Table 5 Results for the azaMBH reaction with MVK (**2a**) using 5 mol% catalyst **4f** and selected tosylimines as shown in Scheme 7

Entry	Ar	Tosylimine	Time [h]	Yield[ac] [%]	Conv.[bc] [%]	Prod.
1	*p*-NO_2-C_6H_4	**1c**	1.5	90	99	**3ca**
2	*p*-NC-C_6H_4	**1b**	1.5	94	99	**3ba**
3	*p*-Br-C_6H_4	**1e**	14	86	93	**3ea**
4	*p*-Cl-C_6H_4	**1a**	10	92	99	**3aa**
5	C_6H_5	**1f**	15	73	99	**3fa**
6	*p*-Me-C_6H_4	**1g**	20	80	89	**3ga**
7	*p*-MeO-C_6H_4	**1h**	48	74	85	**3ha**

[a] Isolated yield. [b] Determined by ^1H NMR. [c] 0.125 M imine, 1.2 eq. MVK.

instrument. IR spectra were measured on a Perkin-Elmer FT-IR BX spectrometer mounting ATR technology. All kinetic measurements with reaction times longer than 24 h were mechanically shaken; for each reaction the rotation speed was set at 480 turns per minute. Analytical TLC was carried out using aluminium sheets silica gel Si 60 F254.

General procedure (I) for benchmark reactions of MVK 2a with 10%/5% catalyst

0.5 mL from 5.0 mL of stock solution I (**1a** (220 mg, 0.75 mmol), MVK **2a** (63 mg, 0.90 mmol) and trimethoxybenzene (27 mg)) and 0.1 mL from 2 mL of stock solution II (0.15 mmol/0.075 mmol of catalyst) were mixed in a NMR-tube and sealed.

General procedure (II) for benchmark reactions of 2b and 2c with 25% catalyst

0.5 mL from 5.0 mL of stock solution I (**1a** (441 mg, 1.50 mmol), **2b**/**2c** (6.0 mmol) and trimethoxybenzene (67.2 mg)) and 0.1 mL from 2 mL of stock solution II (0.375 mmol of catalyst) were mixed in a NMR-tube and flame-sealed.

General procedure (III) for benchmark reactions of 2d with 25% catalyst

0.5 mL from 5.0 mL of stock solution I (**1a** (220 mg, 0.75 mmol), **2d** (252 mg, 3.0 mmol) and trimethoxybenzene (67.2 mg)) and 0.1 mL from 2 mL of stock solution II (0.1875 mmol of catalyst) were mixed in a NMR-tube and flame-sealed. The reaction mixture was directly subjected to silica gel column chromatography and eluted with ethyl acetate to give the corresponding azaMBH product.

3d: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.91 (3H, d, J = 9.4 Hz, CH_3), 2.02 (3H, s, CH_3), 2.39 (3H, s, CH_3), 5.47 (1H, d, J = 10.3 Hz), 6.39 (1H, d, J = 10.4 Hz, NH), 6.74 (1H, q, J = 7.1 Hz), 7.02–7.33 (6H, m, Ar), 7.62 (2H, d, J = 8.4 Hz, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.79, 21.46, 25.93, 53.32, 126.40, 126.94, 127.31, 128.46, 129.37, 129.65, 133.05, 137.68, 138.14, 139.94, 142.80, 143.27, 199.65. MS (EI): *m*/*z* 91, 155, 222, 223, 224, 225, 296, 297, 298, 334, 344, 346. HRMS (ESI) $[M - H]^+$ calc. for $C_{19}H_{20}NO_3SCl$: requires 378.0925, found: 378.0927.

IR [cm^{-1}]: $\tilde{\nu}$ = 3331 (NH), 2954, 1975, 1659, 1598, 1548, 1492, 1415, 1334, 1291, 1162, 1092, 1014, 903, 723, 670.

General procedure (IV) for the reaction of different imines with MVK (2a) (*cf.* Table 5)

Methyl vinyl ketone (**2a**, 1.2 eq.), tosylimine (**1b–i**, 1.0 eq.) and **4f** (5 mol%) as a catalyst were mixed in chloroform. The reaction was monitored by ^{1}H NMR until the disappearance of the tosylimine was observed. The reaction mixture was directly subjected to silica gel column chromatography and eluted with ethyl acetate–isohexane = 1 : 4 to give the corresponding azaMBH product.

General procedure (V) for the reaction of different imines with 2c (*cf.* Table 6)

Cyclohexenone (**2b**, 4.0 eq.), tosylimine (**1b–i**, 1.0 eq.) and **4f** (25 mol%) as a catalyst were mixed in chloroform. The reaction was monitored by ^{1}H-NMR until the disappearance of the tosylimine was observed. The reaction mixture was directly subjected to silica gel column chromatography and eluted with ethyl acetate–isohexane = 1 : 4 to give the corresponding azaMBH product.

3aa: ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.12 (3H, s, Me), 2.40 (3H, s, Me), 5.21 (1H, d, J = 8Hz, NH), 5.72 (1H, d, J = 8.4 Hz, CH), 6.04 (1H, s), 6.08 (1H, s,), 7.03 (2H, d, J = 8.7Hz, Ar), 7.19 (4H, m, Ar), 7.62 (2H, d, J = 8.0Hz, Ar) (in line with published data).[7d]

3ba: ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.14 (3H, s, Me), 2.40 (3H, s, Me), 5.26 (1H, d, J = 9.2 Hz), 5.83 (1H, d, J = 8.7Hz), 6.04 (1H, s), 6.10 (1H, s), 7.25 (4H, m, Ar), 7.49 (2H, d, J = 6.7 Hz, Ar), 7.63 (2H, d, J = 7.2 Hz, Ar) (in line with published data).[6b]

3ca: ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.15 (3H, s, Me), 2.42 (3H, s, Me), 5.32 (1H, d, J = 9.4 Hz), 5.91 (1H, d, J = 9.4 Hz), 6.08 (1H, s), 6.13 (1H, s), 7.30 (4H, m, Ar), 7.64 (2H, d, J = 8.3 Hz, Ar), 8.06 (2H, d, J = 8.7 Hz) (in line with published data).[26]

3ea: ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.13 (3H, s, Me), 2.41 (3H, s, Me), 5.24 (1H, d, J = 9.1 Hz), 6.00 (1H, s), 6.05 (1H, s), 6.08 (1H, s), 7.21 (2H, d, J = 7.8 Hz), 7.30 (4H, m, Ar), 7.61 (2H, J = 7.8 Hz) (in line with published data).[27]

3fa: ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.17 (3H, s, Me), 2.42 (3H, s, Me), 5.29 (1H, d, J = 8.6 Hz), 5.66 (1H, d, J = 8.6 Hz), 6.09 (1H, s), 6.11 (1H, s), 7.11 (2H, m, Ar), 7.21–7.27 (5H, m, Ar), 7.67 (2H, d, J = 8.1 Hz, Ar) (in line with published data).[28]

3ga: ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.15 (3H, s, Me), 2.26 (3H, s, Me), 2.41 (3H, s, Me), 5.26 (1H, d, J = 8.4 Hz), 5.73 (1H, d, J = 8.4 Hz), 6.09 (2H, d, J = 1.0Hz), 6.86–7.03 (4H, m, Ar), 7.24 (2H, m, Ar), 7.63 (2H, d, J = 8.0 Hz, Ar) (in line with published data).[7d]

3ha: ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.16 (3H, s, Me), 2.42 (3H, s, Me), 3.74 (3H, s, Me), 5.24 (1H, d, J = 8.4 Hz, NH), 5.60 (1H, d, J = 8.4 Hz, CH), 6.09 (2H, m), 6.72 (2H, d, J = 8.2 Hz, Ar), 6.99 (2H, d, J = 8.8 Hz, Ar), 7.25 (2H, d, J = 8.0 Hz, Ar), 7.65 (2H, d, J = 8.2 Hz, Ar) (in line with published data).[7d]

3ac: ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 1.62–1.74 (1H, m), 1.77–1.90 (1H, m), 2.03–2.17 (2H, m, CH_2), 2.20–2.35 (2H, m, CH_2), 2.40 (3H, s, Me), 5.05 (1H, d, J = 9.4 Hz), 5.96 (1H, d, J = 9.6 Hz), 6.80 (1H, t, J = 4.4 Hz), 7.09–7.25 (6H, m, Ar), 7.61 (2H, d, J = 7.6 Hz, Ar) (in line with published data).[29]

3bc: ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.64–1.74 (1H, m, CH_2), 1.76–1.79 (1H, m, CH_2), 2.05–2.17 (2H, m, CH_2), 2.22–2.30 (2H, m, CH_2), 2.41 (3H, s, Me), 5.09 (1H, s), 6.02 (1H, s), 6.81 (1H, t, J = 3.0 Hz), 7.25 (2H, d, J = 9.0 Hz, Ar), 7.34 (2H, d, J = 9.0 Hz, Ar), 7.51 (2H, d, J = 6.0 Hz, Ar), 7.63 (2H, d, J = 6.0 Hz, Ar). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 21.49, 21.87, 25.84, 38.24, 59.50, 111.27, 118.53, 126.98, 127.23, 129.52, 132.14, 136.07, 137.69, 143.52, 144.64, 150.09, 151.07. MS (EI): *m*/*z* 331, 281, 253, 207, 155 ($MePhSO_2^+$), 91 ($MePh^+$). HRMS (ESI) $[M - H]^+$ calc. for $C_{21}H_{19}N_2O_3S$: requires 379.1116, found: 379.1123. IR [cm^{-1}]: 3265 (NH), 3300, 2954, 2924, 2225, 1662 (C═O), 1606, 1598, 1501, 1495, 1423, 1396,

Table 6 Results for the azaMBH reaction with cyclohexenone (**2c**) using 25 mol% catalyst **4f** and selected tosylimines as shown in Scheme 8

Entry	Ar	Tosylimine	Time [h]	Yield[ac] [%]	Conv.[bc] [%]	Prod.
1	*p*-NO_2-C_6H_4	**1c**	24	85	99	**3cc**
2	*p*-NC-C_6H_4	**1b**	24	88	99	**3bc**
3	*p*-Br-C_6H_4	**1e**	60	90	99	**3ec**
4	*p*-Cl-C_6H_4	**1a**	30	98	99	**3ac**
5	C_6H_5	**1f**	60	83	95	**3fc**
6	*p*-MeO-C_6H_4	**1h**	120	69	90	**3hc**
7	*o*-Cl-C_6H_4	**1d**	48	84	95	**3dc**
8	*trans*-Ph-CH=CH	**1i**	54	87	96	**3ic**

[a] Isolated yield. [b] Determined by ^{1}H NMR. [c] 0.25 M imine, 4.0 eq. ketone **2c**.

1330, 1305, 1287, 1248, 1160, 1094, 1079, 1043, 1018, 980, 927, 906, 876, 865, 826, 811, 733, 706.

3cc: ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 1.63–1.70 (1H, m), 1.79–1.87 (1H, m), 2.04–2.13 (2H, m CH_2), 2.20–2.36 (2H, m, CH_2), 2.40 (3H, s, Me), 5.14 (1H, d, J = 9.4 Hz), 6.09 (1H, d, J = 9.4 Hz), 6.83 (1H, t, J = 4.2 Hz), 7.25 (2H, d, J = 6.8 Hz, Ar), 7.39 (2H, d, J = 8.8 Hz, Ar), 7.63 (2H, d, J = 8.4 Hz, Ar), 8.05 (2H, d, J = 7.0 Hz, Ar) (in line with published data).[29]

3dc: ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.75–1.83 (2H, m, CH_2), 2.16–2.30 (4H, m, CH_2), 2.36 (1H, s, Me), 5.53 (1H, d, J = 6.0 Hz), 6.13 (1H, d, J = 6.0 Hz), 7.02–7.33 (6H, m), 7.42–7.44 (1H, m, Ar), 7.62 (2H, d, J = 6.0 Hz, Ar). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 21.44, 21.51, 25.83, 38.47, 56.24, 126.44, 126.71, 127.23, 128.52, 129.21, 129.31, 129.48, 129.68, 132.42, 135.77, 136.38, 143.13, 150.14, 199.0. HRMS (ESI) $[M + Na]^+$ calc. for $C_{20}H_{20}ClNNaO_3S$: requires 412.0750, found: 412.0743. IR [cm^{-1}]: 3260 (NH), 2953, 2922, 2854, 1675, 1594, 1575, 1494, 1472, 1438, 1379, 1328, 1306, 1286, 1258, 1154, 1136, 1088, 1078, 1037, 980, 952, 913, 854, 815, 756, 744, 715, 705, 699, 608.

3ec: ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.61–1.74 (1H, m, CH_2), 1.78–1.88 (1H, m, CH_2), 2.07–2.10 (2H, m, CH_2), 2.20–2.28 (2H, m, CH_2), 2.41 (3H, s, Me), 5.03 (1H, d, J = 6.9 Hz), 5.99 (1H, d, J = 6.9 Hz), 6.80 (1H, t, J = 3.3 Hz), 7.06 (2H, d, J = 6.3 Hz, Ar), 7.23 (2H, d, J = 6.3 Hz, Ar), 7.33 (2H, d, J = 6.3 Hz, Ar), 7.61 (2H, d, J = 6.3 Hz, Ar). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 21.48, 21.93, 25.80, 38.33, 59.15, 121.372, 127.26, 128.02,129.44, 131.40, 136.49, 137.72, 138.38, 143.31, 149, 33, 198.87. MS (EI): *m/z* 334, 281, 207, 183 ($MePhSO_2NHCH_2^+$), 171 ($MePhSO_2NH_2^+$), 155 ($MePhSO_2^+$), 91 ($MePh^+$). HRMS (ESI) $[M]^+$ calc. for $C_{20}H_{24}O_3N_2BrS$: requires 451.0691, found: 451.0687. IR [cm^{-1}]: 3356 (NH), 3259, 3187, 2925, 2865, 1668 (C=O), 1597, 1527, 1486, 1454, 1423, 1387, 1335, 1303, 1286, 1158, 1092, 1078, 1051, 1007, 980, 957, 933, 917, 905, 814, 797, 736, 708, 688, 660, 633.

3fc: ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 1.61–1.69 (1H, m), 1.77–1.85 (1H, m), 2.02–2.13 (2H, m, CH_2), 2.20–2.32 (2H, m, CH_2), 2.39 (3H, s, Me), 5.11 (1H, d, J = 9.2 Hz), 5.98 (1H, d, J = 9.4 Hz), 6.79 (1H, t, J = 4.2 Hz), 7.15–7.22 (6H, m, Ar), 7.62 (2H, d, J = 8.6 Hz, Ar) (in line with published data).[29]

3hc: ^{1}H NMR ($CDCl_3$, 600 MHz): δ = 1.62–1.69 (1H, m), 1.78–1.85 (1H, m), 2.03–2.13 (2H, m, CH_2), 2.21–2.32 (2H, m, CH_2), 2.40 (3H, s, Me), 3.74 (3H, s, Me), 5.06 (1H, d, J = 9.2 Hz), 5.89 (1H, d, J = 9.4 Hz), 6.72–6.78 (2H, m), 6.82 (1H, s), 7.06 (2H, d, J = 6.8 Hz), 7.22 (2H, d, J = 8.6 Hz, Ar), 7.62 (2H, d, J = 8.2 Hz, Ar) (in line with published data).[29]

3ic: ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.66–1.78 (1H, m), 1.79–1.93 (1H, m), 2.08–2.22 (2H, m, CH_2), 2.23–2.33 (2H, m, CH_2), 2.35 (3H, s, Me), 4.64 (1H, t, J = 6.0 Hz), 5.85 (1H, d, J = 9.0 Hz), 6.08 (1H, dd, J = 9.0 Hz, J = 6.0 Hz), 6.33 (1H, d, J = 18 Hz), 6.79 (1H, t, J = 6.0 Hz), 7.19–7.28 (6H, m, Ar), 7.69 (2H, d, J = 9.0 Hz, Ar). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 21.40, 22.03, 25.77, 38.37, 59.19, 126.45, 126.48, 127.38, 127.80, 128.40, 129.41, 131.53, 136.15, 143.13, 148.53, 199.11. HRMS (ESI) $(M + Na)^+$ calc. for $C_{22}H_{23}NNaO_3S$: requires 404.1296, found: 404.1291. IR [cm^{-1}]: 3288 (NH), 3026, 2955, 2924, 2867, 1732, 1660, 1596, 1493, 1447, 1426, 1385, 1326, 1304, 1250, 1213, 1160, 1151, 1090, 1028, 974, 914, 883, 841, 815, 757, 747, 698, 632.

Theoretical procedures

Calculation of reaction free energies $\Delta G_{298}(CHCl_3)$ for the addition of catalysts **4k** and **5a** to Michael acceptors **2a–2c** involve geometry optimization of reactants and products at the MPW1K/6-31+G(d) level of theory. Thermal corrections to 289.15 K and 1 atm were calculated using the rigid rotor/harmonic oscillator model at the same level of theory. Single point calculations were subsequently performed at MP2(FC)/6-31+G(2d, p) level of theory and combined with the DFT results to obtain reaction free energies. Solvation free energies were obtained for all species through single point calculations with the PCM model in combination with UAHF radii at the RHF/6-31G(d) level. Combination of the gas phase free energies with these solvation energies yield, after correcting for the solution standard state of 1 mol l^{-1}, the free energies in solution at 298.15 K shown in Fig. 6.[17–19] All calculations have been performed using Gaussian 03, Rev. D.91.[15]

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