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Enantioselective Trifunctional Organocatalysts for Rate-Enhanced Aza-Morita–Baylis–Hillman Reactions at Room Temperature

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Abstract: A Brønsted acid-activated trifunctional organocatalyst, based on the BINAP scaffold, was used for the first time to catalyze aza-Morita-Baylis–Hillman reactions between *N*-tosylimines and methyl vinyl ketone with fast reaction rates and good enantioselectivity at room temperature. This trifunctional catalyst, containing a Lewis base, a Brønsted base, and a Brønsted acid, required acid activation to confer its enantioselectivity and rate improvement for both electron-rich and electron-deficient imine substrates. The role of the amino Lewis base of **1a** was investigated and found to be the activity switch in response to an acid additive. The counterion of the acid additive was found to influence not only the excess ratio but also the sense of asymmetric induction.

Keywords: asymmetric catalysis; aza-Morita–Baylis–Hillman reaction; chiral amine protonation; cooperative effects; ion pairs

Asymmetric organocatalysis has in recent years seen accelerated growth in its application in synthesis.[1] Given the existing conceptual framework, bifunctional catalysts have evolved to promote highly enantioselective catalytic reactions and underpin further elaboration in catalyst developement.[2] Herein reported is a trifunctional approach, developed from known bifunctional leads, for catalyzing aza-Morita-Baylis–Hillman (azaMBH) reactions with good enantioselectivity and rate enhancement at room temperature.

The azaMBH reaction, similar to its generic counterpart, is an atom-economic carbon-carbon bond forming reaction between an imine and an enone with great potential in diversity oriented and convergent synthesis.[3] A generally accepted mechanism of the generic MBH or azaMBH proceeds *via* a Michael-aldol-proton transfer sequence. The current limitations of these reactions in asymmetric organocatalysis have manifested in their slow reaction rate of days and capricious substrate scope, primarily due to the complex mechanistic intricacies typical of multi-step reactions.[4]

Key advances have recently been reported for catalyzing enantioselective azaMBH reactions using a variety of strategies,[5] two of which appealed to the trifunctional approach here. One is a bifunctional approach to catalyzing the MBH between imines and methyl vinyl ketone (MVK). A BINAP-phosphine serves as the Lewis base to initiate the Michael step, with a phenolic Brønsted acid for polar H-bonding interactions to confer enantioselecivity at low temperatures.[6] Several variations on this theme, in which the required H-bonding interactions could be relayed by multiple Brønsted acids[6j,k] or enabled by additives,[6l] have led to good or high enantioselectivities for some substrates even at room temperature. The completion time of these azaMBH reactions is typically around 10 h for most of the imine substrates, while for some selected substrates, this strategy has led to highly enantioselective azaMBH reactions that reached completion within a day at 0 °C with as little as 1 mol% catalyst loading.[6k] The other strategy extended beyond the bifunctional framework and employed a co-catalytic, trifunctional system.[7] This approach uses an alkylphosphine as the Lewis base to initiate the Michael step and a separate bifunctional chiral borate salt as the medium to confer good enantioselectivity *via* a counterion strategy[8] and H-bonding interactions.[9] These two catalytic models taken together raised the possibility of developing a trifunctional organocatalyst[10] for the azaMBH reaction with motifs of Lewis nucleophilicity, a Brønsted base for ion pairing, and a Brønsted acid for H-bonding interactions all incorporated into one chiral platform (Figure 1 **a**).

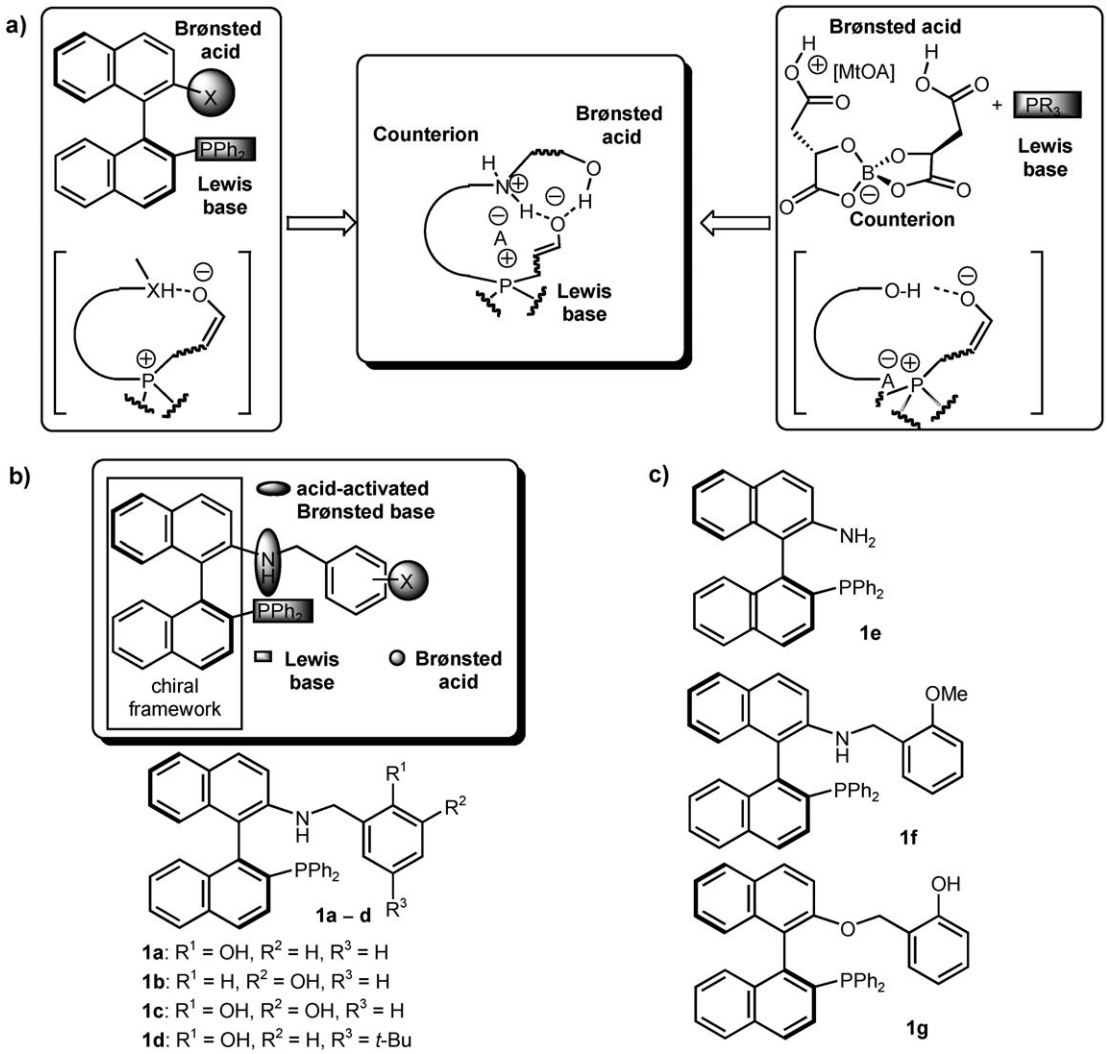
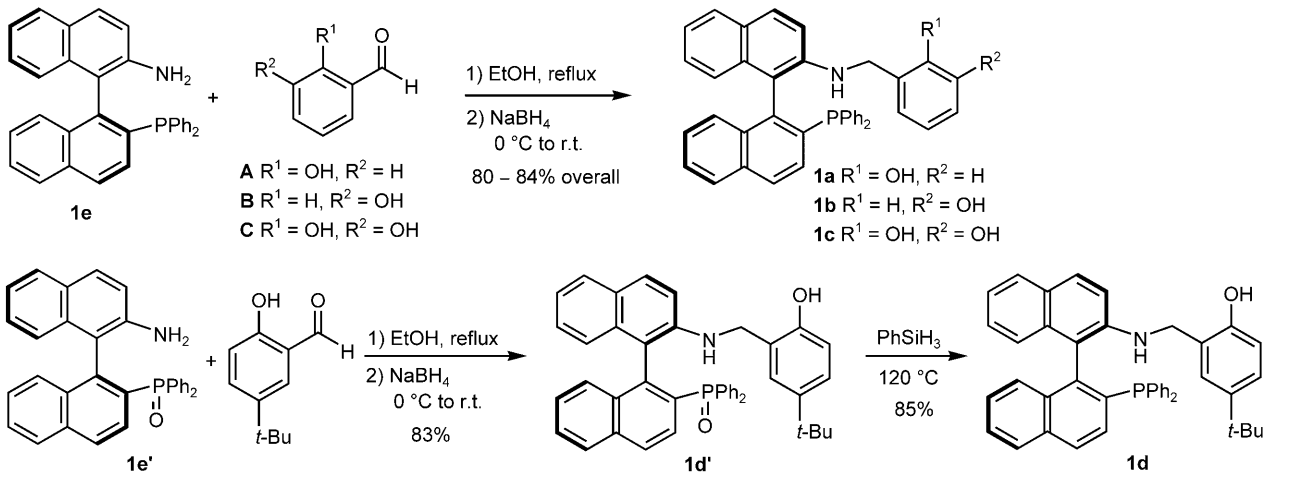


Figure 1. a) A trifunctional catalytic scheme proposed from existing bifunctional systems. **b)** Structures of catalysts **1a–e. c)** Structures of bifunctional catalysts as controls.

All of these themes are mechanistically relevant to the azaMBH and may lead to improved catalytic scope and outcomes in practical terms.

To answer the question if a trifunctional system, rooted in existing bifunctional leads, can be engineered to enhance the catalytic rate as well as enantioselectivity in the azaMBH reaction, a new series of BINAP-based phosphine catalysts were prepared (Figure 1 **b**). Consistent with the parent bifunctional examples, the Lewis nucleophile used for initiation of the azaMBH was a BINAP-based arylphosphine, and the H-bonding functionality an aromatic phenol. In addition, an amino group was installed as the Brønsted base for protonation with a Brønsted acid in order to provide the chiral secondary ammonium salt.[11] An ancillary advantage, in addition to a chiral ion pair, is electrostatic interaction or ion H-bonding interactions that may help with stabilizing zwitterionic intermediates of the MBH reaction.[12] Three bifunctional catalysts (Figure 1 **c**), **1e**, **1f** and **1g**, in which either the amino Brønsted base or the phenolic Brønsted acid was removed, were also prepared as controls (see Supporting Information). By comparing directly the catalytic activities of **1a**–**g**, with or without a Brønsted acid activator, it would be possible to investigate if the addition of a Brønsted base could allow this system to switch from bifunctional to trifunctional as reflected by changes in reaction rates and enantioselectivity.

The synthesis of **1a**–**d** revolved around a facile reductive amination reaction to rapidly assemble the required functional groups onto the BINAP chiral scaffold from a known phosphine amine, **1e** (Scheme 1). The preparation of **1e**, following a well-established route from commercially available starting materials,[13] was accomplished on a gram scale. The reductive amination reaction between **1e** and an aldehyde ensued to furnish the final catalysts in one-pot in very



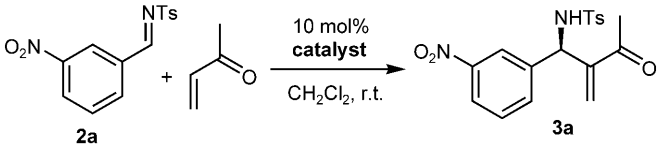
Scheme 1. Synthesis of catalysts **1a–d**.

good yield. This sequence was amenable to all examples except **1d**, in which case the phosphine oxide of **1e** was subjected to the reductive amination first, followed by chemospecific reduction of the phosphine oxide with phenylsilane. The stability of these catalysts was sufficient to resist oxidation during purification except for **1c**, which was partially oxidized during column chromatography.

Phosphines **1a–d** were first tested using a known azaMBH reaction between an imine and MVK at room temperature (25–27 °C) in dichloromethane (DCM) with 10 mol% catalyst loading in the presence or absence of benzoic acid (Table 1). For comparison, triphenylphosphine, **1e′**, and **1e** were also tested. Triphenylphosphine resulted in complex mixtures with or without benzoic acid (entries 1 and 2). The absence of any catalytic activity without a Lewis nucleophile, as seen in the case of **1e′**, confirmed the existing mechanistic interpretation of the MBH in requiring a Lewis nucleophile for initiation (entries 2 and 3). With the necessary phosphine nucleophile, **1e** was able to catalyze the formation of **3a**, independent of benzoic acid activation, although with little enantioselectivity in both cases (entries 5 and 6).

For **1a, 1b** and **1d**, both the rate of reaction and enantioselectivity were very poor in the absence of benzoic acid (entries 7, 8 and 10). Catalyst **1c** was notable in that both the rate of reaction and enantioselectivity were considerably higher even without Brønsted acid activation (entry 9). This characteristic is reminiscent of that from prior bifunctional examples where multiple phenol groups (multivalent H-bonding interactions from Brønsted acids) showed enhanced catalytic performance.[6j,k] However, due to the low stability of this catalyst toward oxidation, its investigation was not pursued further. Catalysts **1a**, **1b**, and **1d** were then subjected to the same test reaction with Brønsted acid activation (entries 11–13). For

Table 1. Aza-MBH reactions of *N*-(arylmethylidene)arylsulfonamide **2a** (1.0 equiv.) with MVK (2.0 equiv.) in the presence of catalysts PPh_3 and **1a–1e** (10 mol%) with and without benzoic acid.



Entry	Catalyst	Benzoic acid [%]	Time [h]	Yield **3a** [%][a]	*ee* [%][b]
1	PPh_3	0	3	–[c]	–
2	PPh_3	10	3	–[c]	–
3	**1e′**	0	3	–	–
4	**1e′**	10	3	–	–
5	**1e**	0	3	63	*rac.*
6	**1e**	10	3	60	10
7	**1a**	0	3	16	*rac.*
8	**1b**	0	15	63	24
9	**1c**	0	3	39	69
10	**1d**	0	3	13	*rac.*
11	**1a**	10	3	>95	82
12	**1b**	10	15	77	38
13	**1d**	10	3	>95	77

[a] Calculated by ^{1}H NMR spectroscopy.
[b] Determined by chiral HPLC analysis.
[c] Complex mixture of products without **3a**.

1a and **1d**, the rate of reaction dramatically improved, and the yield changed from under 20% to nearly quantitative (>95% given the detection limit of proton NMR spectroscopy) in three hours at room temperature.[14] The enantioselectivity in these two cases also significantly improved from none to good (77–82% *ee*). For **1b**, the catalytic rate and enantioselectivity were also consistently low without benzoic acid, and the reaction time was extended to 15 h

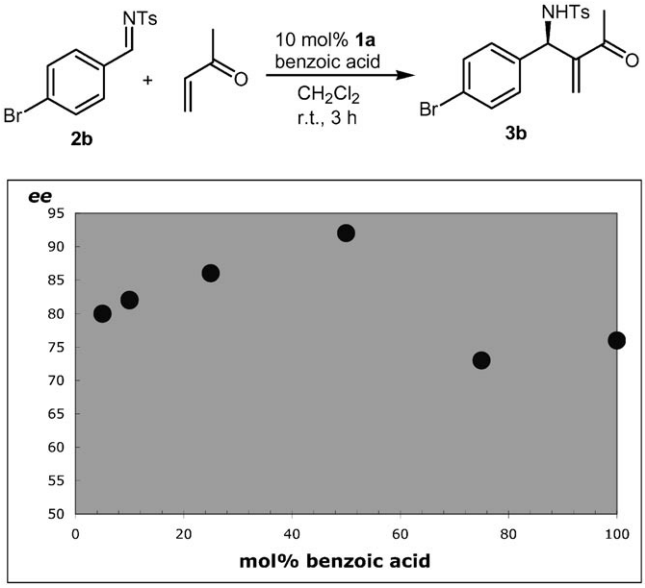


Figure 2. Effect of benzoic acid loading on the azaMBH reactions of *N*-(4-bromophenylmethylidene)arylsulfonamide **2b** (1.0 equiv.) with MVK (2.0 equiv.) in the presence of catalyst **1a** (10 mol%).

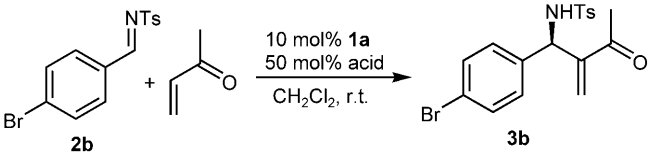
(entry 8). However, the addition of benzoic acid had a minor improvement in rate and enantioselectivity (entry 12). The position of the Brønsted acid phenol appeared to be a determinant in whether the enabling effect of the acid activation on the catalyst could eventuate. This suggests that the catalytically productive form by acid activation was influenced by the phenol through likely H-bonding interactions.

The effect of benzoic acid equivalence was next examined using **1a** and a test azaMBH reaction between a bromoaryl imine and MVK (Figure 2). The loading of catalyst **1a** was maintained at 10 mol% while that of benzoic acid was varied from 5 mol% to 100 mol%. When the benzoic acid loading was 5 mol%, the reaction rate was slightly lower, leading to 85% yield in three hours. The reaction rate appeared to saturate at 10 mol% benzoic acid loading, with all yields being quantitative in three hours for the remaining loading variations. The *ee* continued to improve with more benzoic acid and peaked at 50 mol% benzoic acid loading, after which point the *ee* was lower. The reaction rate was not affected by the amount of benzoic acid after the saturation point of 10 mol%. This characteristic is to the contrary of that seen in bifunctional catalysts where the reaction yield was severely compromised with more than 20 mol% acid additive.[15] The tolerance of excess benzoic acid here suggests that the Brønsted base, upon protonation, may have prevented the protonation of the Lewis base in the presence of excess benzoic acid.

With the optimized activation conditions, the roles of the amino group and the phenolic group were investigated next by comparing the activities of **1a**, **1f**, and **1g** in the absence or presence of benzoic acid (Table 2). Catalyst **1f**, in which the phenolic proton is replaced with a methyl group, exhibited rate improvement upon acid activation, as seen with **1a**, but the enantioselectivity had only a marginal response to acid activation (entries 1 and 2). Catalyst **1g**, in which the Brønsted base is replaced by an isoelectronic oxygen, exhibited the standard bifunctional catalysis where acid activation is not required. Furthermore, the addition of benzoic acid reduced the level of enantioselectivity from 71% to 42% (entries 3 and 4). Only in the case of **1a** was the improvement of both the rate of catalysis and enantioselectivity observed in a coordinated manner (entries 5 and 6). This suggests that the amino Brønsted base provides the switch point from bifunctional to trifunctional catalysis in response to acid activation. Given the essential role of the phosphine Lewis base in reaction initiation, and the importance of an appropriately positioned phenolic Brønsted acid, all three functional groups are required for the activity of **1a**.

The next question then became the catalytic significance of a protonated Brønsted base. An immediate consequence is the formation of a secondary ammonium salt that may help with stabilizing zwitterionic in-

Table 2. Aza-MBH reactions of *N*-(arylmethylidene)arylsulfonamide **2b** (1.0 equiv.) with MVK (2.0 equiv.) in the presence of catalysts **1a**, **1f**, and **1g** (10 mol%) with or without acid additives.



Entry	Catalyst	Acid additive	Time [h]	Yield [%][a]	*ee* [%][b]
1	**1f**	–[c]	6	49	17
2	**1f**	benzoic acid	4	81	46
3	**1g**	–[c]	6	66	71
4	**1g**	benzoic acid	6	78	42
5	**1a**	–[c]	3	10	*rac.*
6	**1a**	benzoic acid	3	>95	92
7	**1a**	acetic acid	3	20	−60[e]
8	**1a**	phosphoric acid	2	31 (71[d])	−28[e]
9	**1a**	pyridinium chloride	23	–[f]	–
10	**1a**	pyridinium bromide	23	–[f]	–

[a] Calculated by ^{1}H NMR spectroscopy.
[b] Determined by chiral HPLC analysis.
[c] No additive.
[d] Obtained after 6 h.
[e] Opposite enantioselectivity observed.
[f] Starting imine recovered.

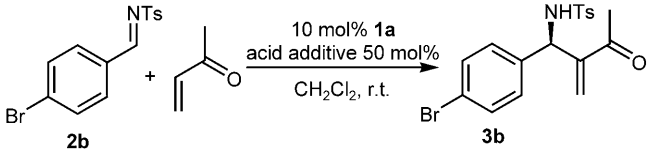
termediates of the MBH during the reversible Michael and aldol steps. The role of the counterion of this chiral ammonium salt as a conjugate base could also be catalytically relevant and therefore was investigated. In addition to benzoic acid, other acids such as acetic acid, phosphoric acid, pyridinium chloride and pyridinium bromide were also examined (Table 2, entries 7–10). Changing the counterion changed the rate of catalysis significantly. Acetic acid did not provide much activation (entry 7). The activation by phosphoric acid was stronger yet still lower than that from benzoic acid (entry 8). In addition, the sense of asymmetric induction was reversed in both cases to prefer the opposite enantiomer. Catalysis was lost with pyridinium chloride or pyridinium bromide (entries 9 and 10). These observations, taken together, suggest that the counterion of the ammonium salt may play a critical role in the irreversible proton-transfer step, as reflected by the dependence of the rate and the the sense of asymmetric induction on the conjugate base.

The performance dependence of **1a** on benzoic acid additive prompted further investigation of other aryl carboxylic acid additives with varying pK_a values and shapes. Both the reaction rate and enantioselectivity were adversely affected compared to the case with benzoic acid (Table 3). In some cases where the pK_a of the acid additive was varied, with approximate shape conservation, the reduction in reaction rate and enantioselectivity was not as severe (entries 2–4 and 7–9). Large substituents at the *meta* position on the acid additive resulted in loss of catalysis (entries 5 and 6). This is consistent with earlier observations where the counterion greatly influenced the catalytic rate and enantioselectivity. In this series of aryl carboxylic acid additives, no change in the the sense of asymmetric induction was observed.

The same test reaction was next performed in various solvents (Table 4). It may be difficult to deconvolute the solvent effect on catalysis, as many factors would be altered concurrently by changing the solvent, such as acidity, solubility, conformation, etc. However, in general, organic ammonium ion pairing and H-bonding interactions would be better preserved in non-polar aprotic solvents. Consistent with this premise, the rate of catalysis and enantioselectivity were found to be generally better in non-polar and aprotic environments (entries 1–5), while not evident was a strict correlation between catalytic proficiency and apparent polarity as reflected in solvent permissivities. When a more polar solvent such as acetonitrile was used, the rate of catalysis along with enantioselectivity decreased significantly (entry 6). When a protic polar solvent, such as methanol, was used, catalysis was completely inhibited (entry 7). This confirms that tight ion pairing is essential for catalysis activation of **1a**.

The substrate scope was investigated last using **1a** and benzoic acid (Table 5). Both electron-deficient and electron-rich aryl *N*-tosylimines were amenable to this trifunctional approach. As expected, electron-rich imines required longer reaction times, although

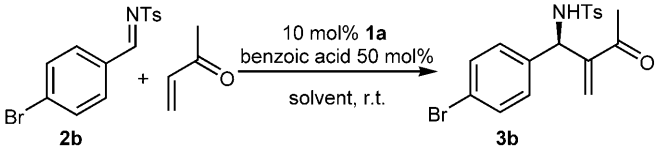
Table 3. Aza-MBH reactions of *N*-(4-bromophenylmethylidene)arylsulfonamide **2b** (1.0 equiv.) with MVK (2.0 equiv.) in DCM with catalyst **1a** (10 mol%) and various additives.



Entry	Additive	Time [h]	Yield [%][a]	*ee* [%][b]
1	benzoic acid	3	>95	92
2	*p*-FC_6H_4COOH	5.5	57	77
3	*o*-FC_6H_4COOH	3	7	n.d.
4	*o*-FC_6H_4COOH	24	87	80
5	(*m*-NO_2)$_2C_6H_3COOH$	3.5	–[c]	–
6	(*m*-MeO)$_2C_6H_3COOH$	3.5	–[c]	–
7	1-naphthoic acid	3	60	n.d.
8	1-naphthoic acid	15	92	72
9	2-naphthoic acid	15	>95	75

[a] Calculated by ^{1}H NMR spectroscopy.
[b] Determined by chiral HPLC analysis.
[c] Starting imine recovered.

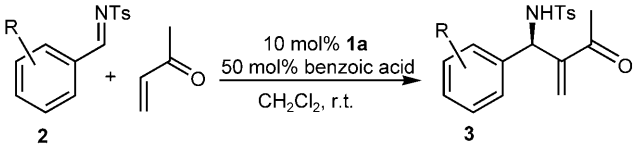
Table 4. Aza-MBH reactions of *N*-(4-bromophenylmethylidene)arylsulfonamide **2b** (1.0 equiv.) with MVK (2.0 equiv.) in various solvents with catalyst **1a** (10 mol%) and benzoic acid (50 mol%).



Entry	Solvent	Time [h]	Yield [%][a]	*ee* [%][b]
1	THF	3	32	70
2	Toluene	2	63	70
3	Et_2O	4	>95	61
4	$CHCl_3$	3	51	78
5	CH_2Cl_2	3	>95	92
6	CH_3CN	21[c]	39	53
7	MeOH	3	–[d]	–

[a] Calculated by ^{1}H NMR spectroscopy.
[b] Determined by chiral HPLC analysis.
[c] Very low conversion in 3 h, and reaction was extended to 21 h.
[d] Starting materials recovered.

Table 5. Aza-Morita-Baylis–Hillman reactions of *N*-(arylmethylidene)arylsulfonamide **2** (1.0 equiv.) with MVK (2.0 equiv.) in DCM with catalyst **1a** (10 mol%) and benzoic acid (50 mol%).



Entry	R	Time [h]	Yield [%][a] of **3**	Isolated Yield [%] of **3**	*ee* [%][b]
1	*m*-$NO_2C_6H_4$, **2a**	3	**3a**, >95	93	82
2	*p*-BrC_6H_4, **2b**	3	**3b**, >95 (39[c])	96	92 (90[c])
3	*p*-ClC_6H_4, **2c**	3	**3c**, 68 (>95[d])	92	80 (79[d])
4	*o*-ClC_6H_4, **2d**	2.5	**3d**, 37 (>95[d])	86	59 (59[d])
5	*p*-FC_6H_4, **2e**	3.5	**3e**, 55 (>95[d])	92	81 (80[d])
6	*p*-$NO_2C_6H_4$, **2f**	3	**3f**, >95	94	80
7	*o*-$NO_2C_6H_4$, **2g**	3	**3g**, >95	90	80
8	*p*-MeC_6H_4, **2h**	5	**3h**, 19 (>95[d])	89	82 (82[d])
9	*o*-$MeOC_6H_4$, **2i**	2.5	**3i**, 39 (>95[d])	91	79 (78[d])
10	*m*-$MeOC_6H_4$, **2j**	5	**3j**, 29 (>95[d])	90	87 (84[d])

[a] Calculated by ^{1}H NMR spectroscopy.
[b] Determined by chiral HPLC analysis.
[c] Reaction performed at 0 °C.
[d] Obtained after 24 h.

their *ee* values are comparable to those of the electron-deficient imines. Notably, electron-rich arylimines with *ortho*- or *meta*-methoxy substiutents were able to react to completion within a day.[16] Lowering the reaction temperature only slowed the reaction rate with little effect on enantioselectivity (entry 2). This characteristic is distinctly different from that of bifunctional catalysts that require low temperatures to restrict conformation for high enantioselectivity. Reaction time exhibited no influence on enantioselectivity (entries 3–6 and 8–10), suggesting a catalytic path that is independent of product formation. The isolated yields are comparable to calculated conversion yields for substrates that exhibited fast completion rates. When the reactions rates are slower, as seen with **3d** and **3h** (entries 4 and 8), the isolated yields are 5–10% lower than the conversion yields. This suggests that that as the catalysis of the desired pathway becomes less efficient, there may be more conversion loss to minor competing side reactions.

This trifunctional system was also applied to a generic MBH reaction between MVK and 4-nitrobenzaldehyde, and furnished the desired MBH product in 3 days in 86% yield, although with only 26% *ee*. Triarylphosphines in their monomeric form usually exhibit no catalytic activity in generic MBH reactions.[17] This raises the possibility that tuning the acidity and H-bonding network of this system may lead to improved rate and enantioselectivity for the more difficult generic MBH reactions with MVK. It is also possible that this trifunctional approach can be combined with the strategy of multivalent H-bond donors for further catalysis improvement.[18]

In summary, a Brønsted acid-activated trifunctional organocatalyst **1a** was used for the first time to catalyze azaMBH reactions between *N*-tosylimines and MVK with fast rates and good enantioselectivity at room temperature. The extension of bifunctional catalysis to trifunctional catalysis was achieved by including a Brønsted base that, upon protonation, provides a secondary ammonium ion pair that positively cooperates with the phenolic Brønsted acid after nucleophilic initiation of the reaction. This improved the rate of catalysis for these azaMBH reactions in aprotic solvents with good enantioselectivity without the need to lower the reaction temperature. For the more difficult generic MBH counterpart, this catalyst was able to catalyze a reaction between an aryl aldehyde and MVK in a non-polar aprotic solvent although with low rate and enantioselectivity at this point. A working hypothesis is that activation by benzoic acid after protonation at the nitrogen center, in conjunction with the phenol group, provided an H-bonding network and counterion that are required for the observed catalysis (Figure 3, proposed transition structures). In the disfavoured transition structure, the proton-transfer step would be slow, and the rate of this pathway does not depend on the presence or absence of an ion pair. The pathway through the favoured transition structure, however, is expedited by **1a** only after protonation with benzoic acid to form the required chiral ion pair. The kinetic advantage

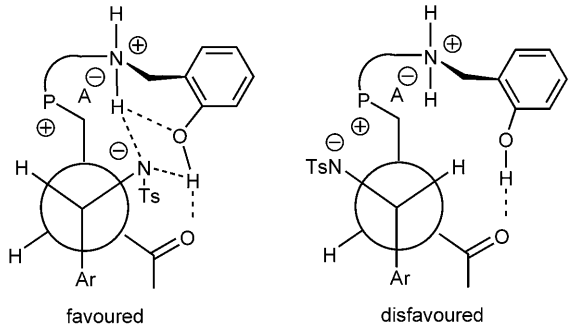


Figure 3. Proposed transition structures for the formation of **3**.

from a counterion-facilitated proton transfer allows the substrates to pass through this pathway faster than other competing pathways, which is consistent with the observation that the rate enhancement and enantioselectivity arise jointly upon acid activation. Without benzoic acid, catalysis by **1a** was much less effective and unable to provide enantioselectivity. As the MBH reaction, particularly the generic version, is a multi-step, complex reaction with many challenges such as autocatalysis, reversibility and racemization, it may be a prerequisite that a generally productive catalytic system will need to negotiate fast turn-over as well as enantioselectivity to out-compete intrinsic complications. This trifunctional approach, when combined with known strategies in the bifunctional framework, may offer new opportunities in addressing the rate and scope problem of this very complex reaction.

Experimental Section

General Procedure for the Preparation of Catalysts 1a–c

To a solution of (*S*)-(+)-2-(diphenylphosphino)-1,1′-binaphthyl-2′-amine **1e** (0.5 mmol) in absolute ethanol (4 mL) was added salicylaldehyde (0.5 mmol) at room temperature, and the reaction mixture was refluxed until completion (followed by TLC). After cooling, CH_3CN (2 mL) was added to solubilize the imine and the reaction mixture was cooled to 0 °C and then $NaBH_4$ (1.5 mmol) was added in one portion and stirred at room temperature for 1 h. The mixture was quenched with H_2O, and the organic phase was extracted with EtOAc (3 times). The combined organic phases were washed with brine, dried over anhydrous magnesium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (eluent petroleum ether/EtOAc) to afford catalysts **1a–c** as off-white solids (characterization data in the Supporting Information).

(*S*)-2-({1-[2-(Diphenylphosphino)naphthalen-1-yl]-naphthalen-2-ylamino}methyl)-4-*tert*-butylphenol oxide (1d′)

To a solution of (*S*)-(+)-2-(diphenylphosphine oxide)-1,1′-binaphthyl-2′-amine (200 mg, 0.442 mmol) **1e′** in absolute ethanol (8 mL) was added 2-hydroxy-5-*tert*-butylbenzaldehyde (83 mg, 0.464 mmol) at room temperature and the reaction mixture was refluxed for 2 h. After cooling, CH_3CN (2 mL) was added to solubilize the imine. The reaction mixture was cooled to 0 °C and then $NaBH_4$ (50 mg, 1.32 mmol) was added in one portion and stirred at room temperature for 1 h. The mixture was quenched with H_2O and the organic phase was extracted with EtOAc (3 times). The combined organic phases were washed with brine, dried over anhydrous magnesium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (eluent petroleum ether/EtOAc: 85/15) to furnish **1d′** as an off-white solid; yield: 230 mg (characterization data in the Supporting Information).

(*S*)-2-({1-[2-(Diphenylphosphino)naphthalen-1-yl]-naphthalen-2-ylamino}methyl)-4-*tert*-butylphenol (1d)

Phosphine oxide **1e′** (207 mg, 0.328 mmol) was combined with $PhSiH_3$ (2 mL) in a sealed tube. The reaction mixture was heated at 120 °C for 15 h and then cooled to room temperature. The $PhSiH_3$ was flushed with N_2 for 10 min and the residue was quickly purified by flash chromatography on silica gel (eluent petroleum ether/EtOAc: 90/10) to afford **1e** as an off-white solid; yield: 171 mg (characterization data in the Supporting Information).

Typical Reaction Procedure for Phosphines 1a–e-Catalyzed Aza-Baylis–Hillman Reaction of *N*-Tosylimines 2a–j with MVK

N-Tosylimine (0.5 mmol), phosphine (10 mol%, 0.05 mmol) and benzoic acid (50 mol%, 0.25 mmol) were combined under N_2. DCM (0.1 mL per mg of catalyst) was added followed by distilled methyl vinyl ketone (MVK) (1.0 mmol) dropwise. The reaction mixture was stirred until completion. The solvent was evaporated and the crude mixture was subjected to chiral HPLC for the *ee* analysis and purified by silica gel flash column chromatography.

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References

[1] For a general overview, see A. Berkessel, H. Gröger, *Asymmetric Organocatalysis*, VCH, Weinheim, **2005**.
[2] For a general definition of acid and base organocatalysis, see: J. Seayad, B. List, *Org. Biomol. Chem.* **2005**, *3*, 719–724. For a recent review on Lewis base catalysis,

see: S. E. Denmark, G. L. Beunter. *Angew. Chem.* **2008**, *120*, 2–82; *Angew. Chem. Int. Ed.* **2008**, *47*, 2–81.
[3] For a recent review on the MBH in general, see: a) D. Basavaiah, A. J. Rao, T. Satyanarayana, *Chem. Rev.* **2003**, *103*, 811–891. For a recent review on the azaMBH, see: b) Y.-L. Shi, M. Shi, *Eur. J. Org. Chem.* **2007**, 18, 2905–2916.
[4] For initial mechanistic work: a) J. S. Hill, N. S. Issacs, *J. Phys. Org. Chem.* **1990**, *3*, 285–288. For recent mechanistic investigation, see: b) L. S. Santos, C. H. Pavam, W. P. Almeida, F. Coelho, M. N. Eberlin, *Angew. Chem.* **2004**, *116*, 4430–4433; *Angew. Chem. Int. Ed.* **2004**, *43*, 4330–4333; c) K. E. Price, S. J. Broadwater, H. M. Jung, D. T McQuade, *Org. Lett.* **2005**, *7*, 147–150; d) K. E. Price, S. J. Broadwater, D. T. McQuade, *J. Org. Chem.* **2005**, *70*, 3980–3987; e) P. Buskens, J. Klankermayer, W. Leitner, *J. Am. Chem. Soc.* **2005**, *127*, 16762–16763; f) V. K. Aggarwal, S. Y. Fulford, G. C. Lloyd-Jones, *Angew. Chem.* **2005**, *117*, 1734–1736; *Angew. Chem. Int. Ed.* **2005**, *44*, 1706–1708; g) I. T. Raheem, E. N. Jacobsen, *Adv. Synth. Catal.* **2005**, *347*, 1701–1708; h) R. Robiette, V. K. Aggarwal, J. N. Harvey, *J. Am. Chem. Soc.* **2007**, *129*, 15513–15525.
[5] For a review on enantioselective MBH reactions, see: G. Masson, C. Housseman, J. Zhu, *Angew. Chem.* **2007**, *119*, 4698–4712; *Angew. Chem. Int. Ed.* **2007**, *46*, 4614–4628.
[6] Representative BINAP phosphine-based bifunctional organocatalysis of the azaMBH: a) M. Shi, L.-H. Chen, *Chem. Commun.* **2003**, 1310–1311; b) M. Shi, G.-L. Zhao, *Adv. Synth. Catal.* **2004**, *346*, 1205–1219; c) M. Shi, L.-H. Chen, *J. Am. Chem. Soc.* **2005**, *127*, 3790–3800; d) K. Matsui, S. Takizawa, H. Sasai, *J. Am. Chem. Soc.* **2005**, *127*, 3680–3681; e) M. Shi, C.-Q. Li, *Tetrahedron: Asymmetry* **2005**, *16*, 1385–1391; f) M. Shi, L.-H. Chen, W-D. Teng, *Adv. Synth. Catal.* **2005**, *347*, 1781–1789; g) M. Shi, L.-H. Chen, *Pure Appl. Chem.* **2005**, *77*, 2105–2110; h) K. Matsui, K. Tanaka, A. Horri, S. Takizawa, H. Sasai. *Tetrahedron: Asymmetry* **2006**, *17*, 578–583; i) K. Matsui, S. Takizawa, H. Sasai, *Synlett* **2006**, *5*, 761–765; j) Y-H. Liu, L.-H. Chen, M. Shi, *Adv. Synth. Catal.* **2006**, *348*, 973–979; k) K. Ito, K. Nishida, T. Gotanda, *Tetrahedron Lett.* **2007**, *48*, 6147–6149; l) Y-L. Shi, M. Shi, *Adv. Synth. Catal.* **2007**, *349*, 2129–2135; m) M. Shi, G.-N. Ma, J. Gao, *J. Org. Chem.* **2007**, *72*, 9779–9781; n) M.-J. Qi, T. Ai, M. Shi, G. Li, *Tetrahedron* **2008**, *64*, 1181–1186; o) Y-H. Liu, M. Shi, *Adv. Synth. Catal.* **2008**, *350*, 122–128; p) X.-Y. Guan, Y.-Q. Jiang, M. Shi, *Eur. J. Org. Chem.* **2008**, *12*, 2150–2155.
[7] Phosphine-based trifunctional co-catalysis of the azaMBH: a) S. Luo, X. Mi, L. Zhang, S. Liu, H. Xu, J-P. Cheng, *Angew. Chem.* **2006**, *118*, 3165–3169; *Angew. Chem. Int. Ed.* **2006**, *45*, 3093–3097; b) R. Gausepohl, P. Buskens, J. Kleinen, A. Bruckmann, C. W. Lehmann, J. Klankermayer, W. Leitner, *Angew. Chem.* **2006**, *118*, 3772–3775; *Angew. Chem. Int. Ed.* **2006**, *45*, 3689–3692.
[8] a) S. Mayer, B. List, *Angew. Chem.* **2006**, *118*, 4299–4301; *Angew. Chem. Int. Ed.* **2006**, *45*, 4193–4196. For a recent highlight on counterion catalysis, see: b) J. Lacour, D. Linder, *Science* **2007**, *317*, 462–463.
[9] For recent reviews: a) M. S. Taylor, E. N. Jacobsen, *Angew. Chem.* **2006**, *118*, 1550–1573; *Angew. Chem. Int. Ed.* **2006**, *45*, 1520–1543; b) A. G. Doyle, E. N. Jacobsen, *Chem. Rev.* **2007**, *107*, 5713–5743.
[10] For the first biomimetic trifunctional organocatalyst, see: a) T. Ema, D. Tanida, T. Matsukawa, T. Sakai, *Chem. Commun.* **2008**, 957–958. For a recent example of acid activated, enantioselective trifuntional organocatalyst for a Michael addition, see b) D.-Q. Xu, L.-P. Wang, S.-P. Luo, Y.-F. Wang, S. Zhang, Z.-Y. Xu, *Eur. J. Org. Chem.* **2008**, *12*, 1049–1053.
[11] For representative examples of asymmetric ammonium salt catalysis, see: epoxidation-a) M. F. A. Adamo, V. K. Aggarwal, *J. Am. Chem. Soc.* **2000**, *122*, 8317–8318; b) V. K. Aggarwal, C. Lopin, F. Sandrinelli, *J. Am. Chem. Soc.* **2003**, *125*, 7596–7601; c) X. Wang, B. List, *Angew. Chem.* **2008**, *120*, 1135–1138; *Angew. Chem. Int. Ed.* **2008**, *47*, 1119–1122. Michael addition: d) Y. Xiong, Y. Wen, F. Wang, B. Gao, X. Liu, X. Huang, X. Feng, *Adv. Synth. Catal.* **2007**, *349*, 2156–2166. Aldol reactions: e) S. Luo, H. Xu, L. Zhang, J. Li, J.-P. Cheng, *Org Lett.* **2008**, *10*, 653–656. For a recent review on protonated chiral catalysts, see: f) C. Bolm, T. Rantanen, I. Schiffers, L. Zani, *Angew. Chem.* **2005**, *117*, 1788–1793; *Angew. Chem. Int. Ed.* **2005**, *44*, 1758–1763.
[12] For a recent review on organic ammonium salt and ion hydrogen bonding, see: K. Sada, T. Tani, S. Shinkai, *Synlett* **2006**, *15*, 2364–2374.
[13] a) P. Kocovsky, S. Vyskocil, M, Smrcina, *Chem. Rev.* **2003**, *103*, 3213–3245; b) S. Vyskocil, M. Smrcina, V. Hanus, M. Polasek, P. Kocovsky, *J. Org. Chem.* **1998**, *63*, 7738–7748; c) M. Smrcina, M. Lorenc, V. Hanus, P. Sedmera, P. Kocovsky, *J. Org. Chem.* **1992**, *57*, 1917–1920.
[14] For catalyst **1a**, the yields of product **3a** in one and two hours were 65% and 90%, respectively.
[15] 20–50 mol% benzoic acid additive could result in yield reduction to as low as 11%. See ref.[6]
[16] Reaction times for electron rich imine substrates under comparable conditions can be as long as 3 days, see ref.[6]
[17] Polymeric triarylphosphines can catalyze generic MBH reactions in moderate to good yield in 3–5 days at room or elevated temperatures; see: C. Kwong, R. Huang, M. Zhang, M. Shi, P. H. Toy, *Chem. Eur. J.* **2007**, *13*, 2369–2376.
[18] It has just been reported that a partially racimized chiral alkyl(diaryl)phosphine-based on the BINAP scaffold can lead to completion of azaMBH reactions in 1 to 5 h between electron-rich and -deficient imines and MVK; see: Z. Lei, G. Ma, M. Shi, *Eur. J. Org. Chem.* **2008**, *22*, 3817–3820.

