Mechanistic investigations of multidentate organocatalyst-promoted counterion catalysis for fast and enantioselective aza-Morita–Baylis–Hillman reactions at ambient temperature

Christopher Anstiss, Jean-Marc Garnier and Fei Liu*

Received 30th April 2010, Accepted 22nd June 2010
DOI: 10.1039/c0ob00069h

Kinetic experiments were performed on the catalytic cycle of a trifunctional organocatalyst-promoted counterion catalysis of asymmetric aza-Morita–Baylis–Hillman reactions. The catalysis was found to be first order in the trifunctional catalyst with the Michael addition as the rate-limiting step. Temperature variation changed the rate of catalysis but not the enantioselectivity of the reaction.

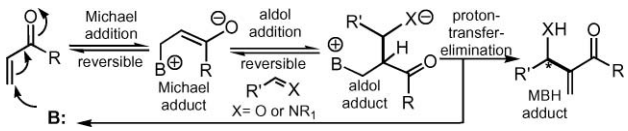
Introduction

Rapid advances in asymmetric organocatalysis have presented new opportunities for the development of enantioselective multidentate organocatalysts as potential enzyme mimics.[1–3] The interest in this approach is multifaceted and underpinned by the efficacy of organocatalysts as green alternatives to traditional approaches. In addition, these small, multifunctional systems can be used as potential models for understanding more complex enzymatic mechanisms and creating novel catalytic modes and motifs that have no natural counterparts.

The recent emergence of trifunctional organocatalysts[4] has demonstrated that it is possible to instigate positive cooperativity in systems with higher organization to approach the level of complexity and proficiency seen in enzyme catalysis. On the other hand, multifunctional systems, while potentially more versatile and efficient, are inherently more prone to competition from lower order or uncooperative catalysis, a problem that places a much higher demand on the mechanistic understanding of the catalyst. This challenge has led to careful definitions of the catalytic role of trifunctional systems by functional studies[4a–d] and, in some instances, mechanistic studies to confirm the likely catalytic pathways in transesterification reactions using a racemic trifunctional organocatalyst.[4a]

We have used the aza-Morita–Baylis–Hillman (azaMBH) as a model system for exploring multifunctional or multidentate organocatalysis that is not only rate enhancing but also capable of a high level of asymmetric induction.[4c–d] The MBH reaction is a multistep carbon–carbon bond-forming reaction that couples an enone and an aldehyde (or an imine in the azaMBH reaction) with the concurrent generation of one chiral alcohol or amine (Scheme 1). This reaction is initiated by the conjugate addition between a Lewis base catalyst with an enone to generate a zwitterionic Michael adduct, which is followed by an aldol addition between the Michael adduct and an electrophile (either aldehyde or imine) to generate another zwitterionic aldol adduct. The final proton transfer step, which is irreversible, eliminates the Lewis base catalyst and furnishes the MBH or azaMBH adduct.

Department of Chemistry & Biomolecular Sciences, Macquarie University, Sydney, NSW, 2109, Australia. E-mail: fliu@alchemist.chem.mq.edu.au; Fax: 61-2-9850-8313; Tel: 61-2-9850-8312

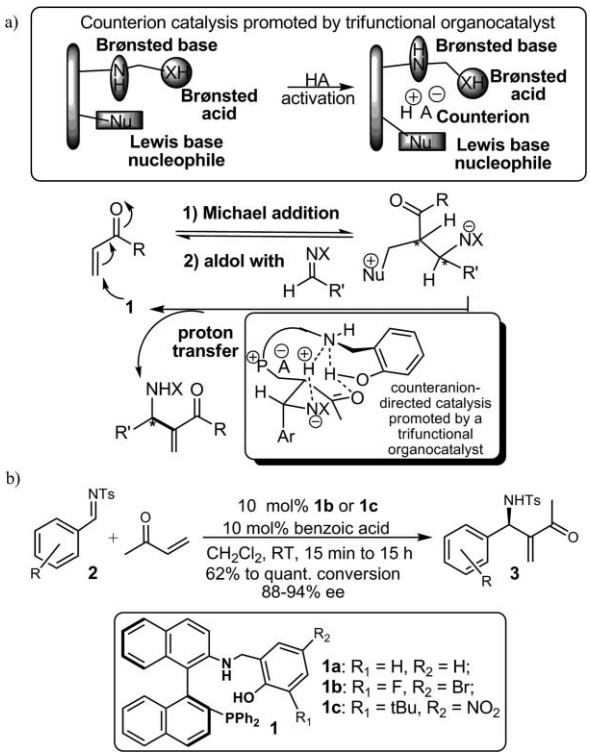


Scheme 1 A general catalytic cycle of the MBH or azaMBH reaction.

This atom-economic reaction, given its well recognized synthetic utility, receives unabated attention but also has long standing problems of slow reaction rates of days and capricious substrate scope.[5] This limits the process prospect of this important carbon–carbon bond forming reaction, especially in the asymmetric sense.

Bifunctional asymmetric organocatalysts have been developed for the MBH or azaMBH reaction.[6] In the bifunctional approach, a Lewis base and a Brønsted acid can be crafted onto one chiral backbone to act cooperatively in the MBH reaction cycle. The Lewis base functionality serves to initiate the Michael addition step of the reaction, and the Brønsted acidity is thought to stabilize the zwitterionic intermediates and promote the subsequent aldol and proton-transfer-elimination step. The bifunctional strategy has been very successful in addressing some of the scope issues, while the solution to rate enhancement without loss of enantioselectivity remains elusive.

Equipped with the design insight from bifunctional systems, we have made the initial demonstration of a trifunctional organocatalyst-promoted counterion catalysis for this reaction to address the rate issue without loss of enantioselectivity (Scheme 2a).[4c] In this trifunctional system **1**, a third functionality, in the form of a nitrogen Brønsted base, is installed as an activity switch in response to an additional Brønsted acid. This activation elevates the catalysis from bifunctional to trifunctional with significant rate enhancement. Unlike bifunctional catalysis, where the reaction rate and enantioselectivity vary independently, this trifunctional strategy has a unique catalytic profile in that the rate of reaction and enantioselectivity arise in a coordinated fashion when **1** becomes activated. Catalyst screening established the optimal spatial orientation and electronic characteristics of the three functionalities, and led to fast rates and good enantioselectivity without the need to lower the reaction temperature (Scheme 2b).[4c–d] Compared to the existing enantioselective bifunctional counterparts that, in general, require half a day to days for good conversion at lower temperatures, the trifunctional



Scheme 2 A trifunctional organocatalyst-promoted asymmetric counterion-directed catalysis of azaMBH reactions.

catalysts **1** can reach completion within hours, and in some cases, minutes, with no reduction in enantioselectivity. Comprehensive bifunctional controls of the this system were also constructed and tested, which showed that each of the three functionalities of **1** was essential for switching to the trifunctional catalysis.[4c] An investigation of the solvent effect found that the trifunctional catalysis and asymmetric induction remained largely tolerant of nonpolar aprotic solvents, but were both severely reduced in polar or protic solvents, which suggested the requirement of a tight ion-pair for this trifunctional catalysis.[4c] Various counterions were also investigated to reveal that benzoic acid provided the fastest rate with the highest enantioselectivity while, in general, aryl carboxylates performed better in trifunctional catalysis than acetates and phosphonates.[4c]

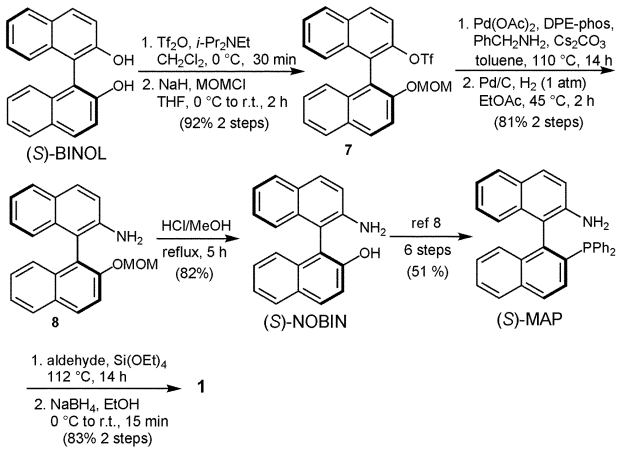
Due to the multifunctional nature of **1**, several questions emerged after the initial functional studies of this system. The first and foremost is on the molecularity of the trifunctional catalysis. While functionally we have established the positive cooperativity of the phosphine Lewis base, the nitrogen Brønsted base and the phenolic Brønsted acid, it remains untested if the positive cooperativity is acting *cis* (intramolecularly) and not in *trans* (intermolecularly). Another question relates to the rate-limiting step of this trifunctional catalytic cycle. Also, the effect of temperature on the enantioselectivity and rate of this system remains unclear. Herein reported are experimental mechanistic studies on azaMBH reactions catalyzed by **1**. In this report, kinetic experiments are described to address these questions with additional substrate scope studies to shed light on the likely operating features of **1**. This will allow better design principles for the next generation catalysts to be developed.

Results and discussion

There are no precedents of substantial mechanistic studies on bifunctional or trifunctional organocatalysts for the MBH or azaMBH reactions. Several experimental mechanistic studies, however, have been conducted for MBH or azaMBH reactions with monofunctional Lewis base organocatalysts.[7] Most of the studies employed a nitrogen Lewis base for MBH reactions between enones and aldehydes. One study utilized triphenyl phosphine as the monofunctional Lewis base for azaMBH reactions between an enone nucleophile (methyl vinyl ketone) and an imine electrophile. With the use of initial rate kinetics, this study established that, with an acidic additive, the rate of catalysis was first order with respect to the monofunctional phosphine catalyst, the enone nucleophile, and the imine electrophile.[7c] For system **1** here, initial rate kinetic measurements were likewise performed to examine the rate of catalysis with respect to the trifunctional phosphine catalyst, methyl vinyl ketone, and the imine substrate.

1) Scalable synthesis of catalyst 1.

All of the existing mechanistic studies on the MBH or azaMBH reactions utilized readily available catalysts (*e.g.* DABCO or triphenylphosphine) from commercial sources. The trifunctional system **1** is not commercially available and required optimization for a gram-scale synthesis so that any one rate experiment could be conducted without hindrance and with the same batch of catalyst for each rate plot to maintain consistency in data collection and interpretation. A scalable synthesis of **1** was therefore developed from the cheap and commercially available (*S*)-BINOL (Scheme 3).



Scheme 3 Scalable synthesis of **1** from (*S*)-BINOL.

To access the key intermediate (*S*)-NOBIN, a modified procedure as described by Salinger and Brückner was followed.[8a] Methoxymethyl protection of triflated (*S*)-BINOL for the preparation of 2-methoxymethoxy-2′-trifluoromethanesulfoxy-1,1′-binaphthyl intermediate **7** was found to be sluggish under the reported conditions of phosphorous pentoxide and dimethoxymethane. Alternatively, **7** was prepared using sodium hydride and chloromethyl methyl ether as described by Maruoka and co-workers.[8b] Furthermore, palladium-catalyzed debenzylation, under the Salinger and Brückner conditions, to yield

2-methoxymethoxy-2′-amino-1,1′-binaphthyl intermediate **8** was found to suffer over-reduction. This yielded 14% of a side product with saturated binaphthalene ring at the 6′ and 8′ position as suggested by low resolution ESI mass spectrometry and ^{1}H NMR spectroscopy. The use of 10 mol% palladium on carbon under 1 atm of hydrogen at 45 °C eliminated the formation of this unwanted side reaction to give the free amine **8** in excellent yield without the need for column purification. Overall, 5.0 g of (*S*)-BINOL was converted to 3.1 g of (*S*)-NOBIN over five steps in 62% yield using this modified route. The key amino phosphine compound (*S*)-MAP was then synthesized on gram-scale in six steps and 51% overall yield following the procedure reported by Kocovsky.[9] Catalysts **1** were then prepared from (*S*)-MAP as previously described.[4c–d] The same batch of catalyst was used for each set of experiments for a rate plot with varying concentrations of one reactant.[10]

2) The role of the acid activation in the induction of asymmetry.

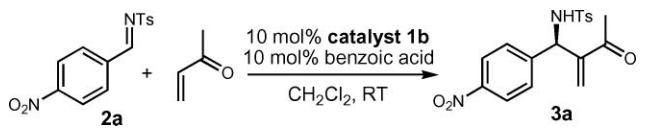
The trifunctional system **1** has two states of activity and switches from the "off" state to the "on" state after acid activation. We have shown in our earlier functional studies that, in the "off" state of **1**, the catalysis is slow and with little enantioselectivity.[4c] Upon the addition of an acid, the reaction improved markedly in rate, and most importantly, proceeded with good to high enantioselectivity. To ensure that the level of asymmetric induction is indeed coupled to acid activation of the trifunctional catalyst, a delayed-activation experiment was performed using catalyst **1b** and a test azaMBH reaction between imine **2a** and MVK (Table 1 scheme).

As shown in Table 1, the trifunctional organocatalyst **1b** could confer little enantioselectivity in the "off" state without acid activation (Table 1, entry 1). Upon acid activation, catalyst **1b** exhibited markedly improved enantioselectivity along with significant rate enhancement (Table 1, entry 2). The test reaction with **1b** reached full conversion in under 30 min with good enantioselectivity maintained (Table 1, entry 3). This suggests that the catalytic pathway with acid activation (highly enantioselective) is distinctly different from that without acid activation (much less enantioselective). It was hypothesized that the enantioselective pathway (with acid activation) would be faster than the non-enantioselective pathway (without acid activation), which was tested by the following delayed acid addition experiment.

When the addition of benzoic acid was delayed by 30 min (Table 1, entry 4), the *ee* is reduced significantly as the competing pathway with lower enantioselectivity received a thirty minute advantage in reaction time. Using the enantiomeric ratios (*e.r.*) for **1b**, the enantioselective pathway with acid activation is estimated to be about three-fold faster than the racemic pathway without acid activation.

As a precaution to a potential dilution effect on catalysis in the delayed-activation experiment, the test reaction from entry 2 was also repeated, with the reaction volume diluted by five-fold after a few minutes of reaction (Table 1, entry 5). Although the reaction rate was slightly reduced, the enantioselectivity remained unchanged. In summary, in the "on" state with acid activation, the trifunctional catalysis is not only enantioselective but also kinetically dominating over competing pathways. With this clear kinetic advantage, the subsequent rate measurements would be reflective primarily of the trifunctional enantioselective pathway.

Table 1 A delayed-activation experiment using *N*-(arylmethylidene)arylsulfonamide **2a** (1.0 equiv.), MVK (2.0 equiv.), **1b** (10 mol%) and benzoic acid (10 mol%) in dichloromethane



Entry	Time/min	Conv. [%][a]	*ee* [%][b]	*e.r.*
1[c]	90	90	16	58 : 42
2	15	91	88	94 : 6
3	30	>95	88	94 : 6
4	60[d]	95	48	74 : 26
5	30	87[e]	88	94 : 6

[a] Calculated by ^{1}H NMR spectroscopy. [b] Determined by chiral HPLC analysis. [c] Without benzoic acid addition. [d] Benzoic acid added with a 30 minute delay after reaction has been initiated by MVK. [e] Reaction mixture was diluted by the addition of 4 reaction volumes of CH_2Cl_2.

3) The reaction is first order with respect to the trifunctional catalyst.

The multifunctional nature of the trifunctional system **1** presents the possibility that the roles of the three functionalities may be fulfilled by more than one catalyst molecule acting in concert. This would not be discernable in functional studies but readily determined *via* measurement of initial rates of the reaction with various concentrations of the trifunctional catalyst. In order to minimize error, a relatively slower azaMBH reaction between 4-bromoaryl imine **2b** and MVK was used with a slower catalyst **1c** to ensure rate measurement could be taken in time using NMR spectroscopy with methyl benzoate as the integration standard for all rate experiments described in sections 2 to 6 (Fig. 1).

The concentration of the catalyst was varied from 12 mM to 24 mM with the concentrations of the enone and imine substrates kept constant at 36 mM. The linear relationship between the initial rate of reaction and the concentration of catalyst **1c** indicates that the trifunctional enantioselective catalytic pathway is first order in the catalyst (Fig. 2). The positive cooperativity of the three functionalities is thus uni-molecular.

4) The reaction is zero order with respect to the imine substrate.

It has been shown that in azaMBH reactions catalyzed by triphenyl phosphine, the reaction is first order with respect to the imine substrate, provided that the proton-transfer-elimination step is accelerated by acidic additives and no longer rate-limiting.[7c] The aldol step between the electrophile and the Michael adduct is the most typical rate-limiting step in either MBH or azaMBH reactions for monofunctional organocatalysts such as DABCO or triphenylphosphine.

Given that in this study only one trifunctional catalyst is responsible for the activation of the azaMBH cascade and remains covalently linked to all intermediates throughout the reaction sequence until the release of the catalyst to complete the catalytic cycle, the next question became which step in this catalytic cycle would be rate-limiting. The reaction order in the imine substrate was thus investigated at a constant concentration of 12 mM

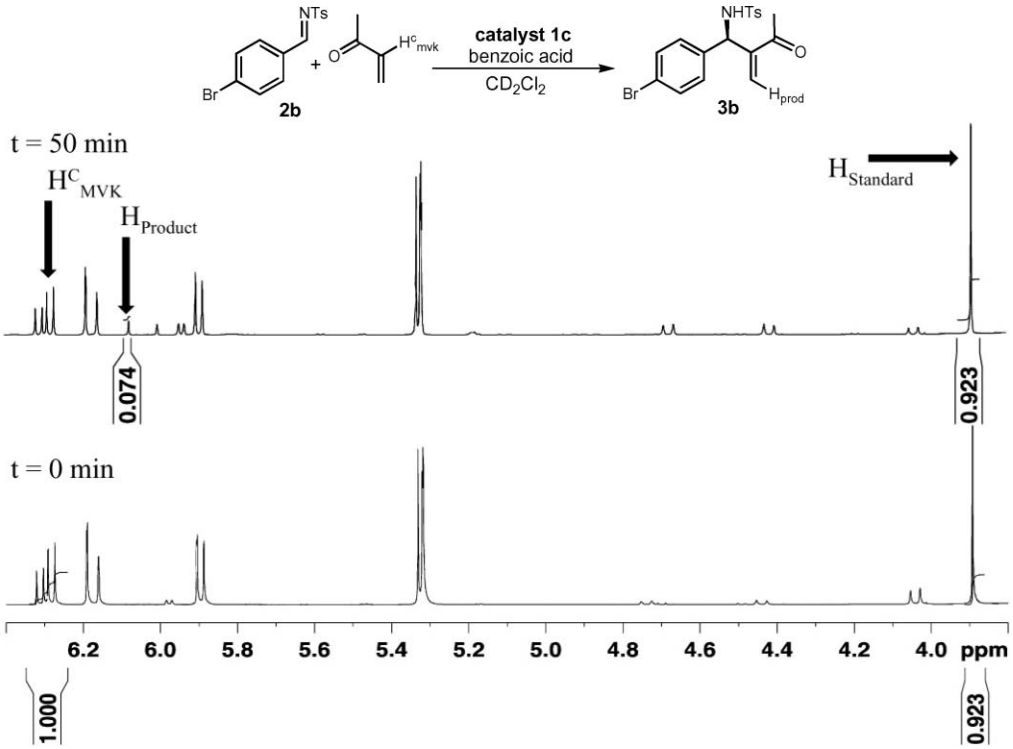


Fig. 1 Representative NMR traces of the reaction between **2b** and MVK.

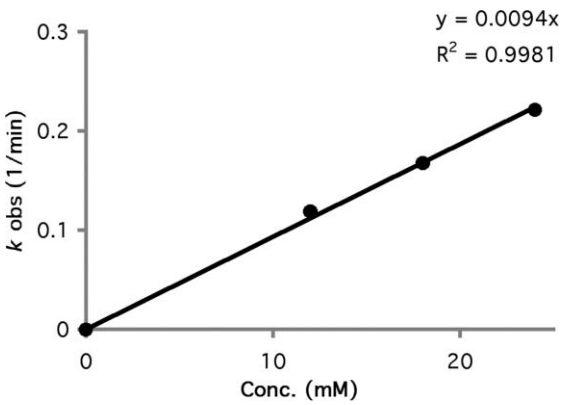


Fig. 2 The reaction cycle promoted by the trifunctional organocatalyst **1c** is first order with respect to the catalyst.

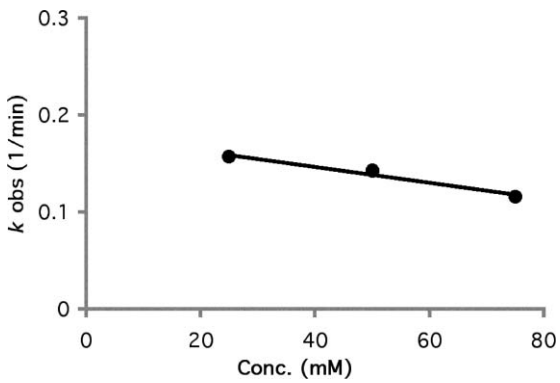


Fig. 3 The catalytic cycle promoted by **1c** is zero order with respect to the imine substrate.

catalyst **1c** and 36 mM MVK with varying concentrations of the imine from 25 mM to 75 mM. The initial rate did not increase but rather decreased slightly at higher imine concentrations (Fig. 3).

The zero order in the imine substrate suggests first that the aldol step involving the imine is not rate-limiting in this trifunctional catalytic cycle. Since the trifunctional catalyst contains a protic component and is therefore capable of catalyzing the proton transfer-elimination step, the hypothesized mode of action of the trifunctional catalyst in promoting the proton transfer step, as suggested earlier,[4c] is consistent with the observed zero order in the imine substrate. It is possible that the aldol step in this catalytic cycle could also be promoted by the action of catalyst **1c**.

Secondly, a slightly faster reaction rate at lower imine concentrations seems to indicate an inhibitory role of excess imine substrate in the rate-determining step of this catalytic cycle. Noncovalent interactions between the catalyst and the imine substrate may reduce slightly the effective concentration of the catalyst at higher imine concentrations and render the reaction slower. Another possibility is that the acid additive could also be sequestered by excess imine, which would lead to less prominence of the enantioselective trifunctional pathway.

The role of the acid additive in this interference was then examined with 60 mM imine at 20 mol% acid additive and 10 mol% loading of catalyst **1c**. Excess acid additive did not rescue the rate of catalysis but again resulted in a reduction of the reaction rate (data not shown). This suggested the possibility of interference from unwanted protonation of the Lewis base of the catalyst by excess acidity. Taken together, the results point to the sensitive nature of the reaction rate to factors early in the catalytic cycle prior to the involvement of the imine substrate, indicating that in this catalytic cycle the Michael addition may be the rate-limiting step. Another

point was that, while required to switch on the catalyst, the amount of the acid additive should be controlled carefully to preserve the activity of the Lewis base on the trifunctional catalyst.

5) The reaction is first order with respect to MVK.

In the studies of monofunctional organocatalysis of MBH or azaMBH reactions, the cycle was invariably found to be first order with respect to the enone nucleophile.[7] The reaction order in the imine or aldehyde electrophile, as discussed earlier, can be either first or second, with the aldol addition step typically as rate-limiting.[7a,b,d] The proton-transfer-elimination step is usually not rate-limiting when acidic additives are used, or the reaction has proceeded long enough to exhibit autocatalysis by the action of the protic MBH adduct.[7d] In the trifunctional case here, with constant catalyst concentration of 12 mM and imine concentration of 36 mM, the reaction order with respect to MVK, varied from 45 mM to 75 mM, was again found to be first order (Fig. 4). Given that the reaction is zero order with respect to the imine substrate, the Michael, not the aldol, addition step is now rate-limiting in the case here. As the Michael step is reversible, the use of the Michael acceptor in large excess can be employed to saturate the rate of Michael addition at the expense of efficiency. The implication here for catalyst design, under economical and practical conditions, is that the nucleophilicity of the phosphine could be enhanced to accelerate further the catalysis to attenuate the use of MVK in large excess.

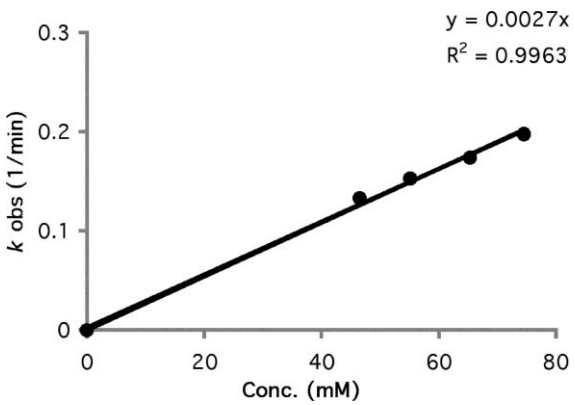


Fig. 4 The catalytic cycle promoted by **1c** is first order with respect to the enone substrate MVK.

6) The effect of temperature on the rate and enantioselectivity of the catalysis.

Bifunctional organocatalysts for the MBH reaction typically require the use of lower temperatures to access higher levels of enantioselectivity. The effects of temperature on catalysis are difficult to resolve, as temperature variations can change conformational arrangement, apparent acidities, and kinetic preferences for intermediates. Generally, however, enantioselectivity tends to improve at lower temperatures. The disadvantage of this is that the reaction is less facile as the rate of reaction is compromised for enantioselectivity, which limits the utility of the catalyst.

In the trifunctional system here, the dependence of the enantioselectivity and rate of reaction on temperature was investigated from 0 °C to 40 °C. The reaction conversion was monitored with respect to time, and *ee* analysis was performed at the starting and finishing stages of the reaction for all temperatures. As the reaction is first-order with respect to the catalyst **1c**, which is kept constant, the rate of reaction should follow a first order mechanism with respect to MVK. This is supported by the apparent first-order kinetic analysis at all four temperatures (Fig. 5 and Table 2).

Table 2 Parameters from rate plots from Fig. 3 indicating the reaction is likely to be first order

Entry	*T*/K	Rate/hr^{-1}	R^2	*ee* [%][a]	*ee* [%][b]
1	313	0.23	0.9905	93	90
2	303	0.10	0.9972	94	90
3	293	0.041	0.9397	94	90
4	273	0.0051	0.9954	94	91

[a] Measured at 5–10% conversion by chiral HPLC analysis. [b] Measured at >90% conversion by chiral HPLC analysis.

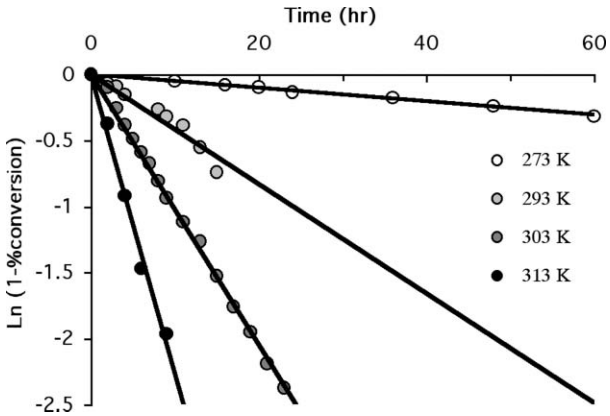
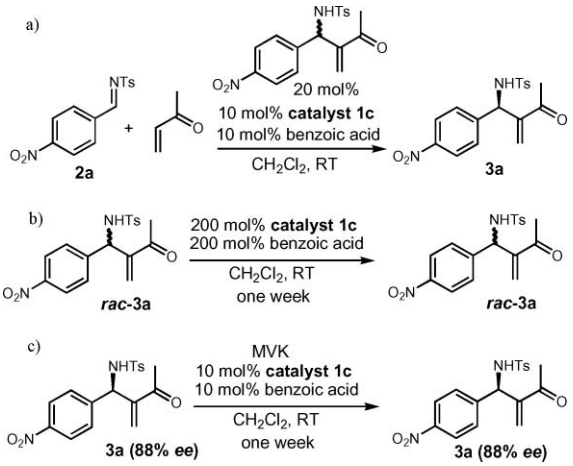


Fig. 5 The first order plot of the reaction at various temperatures from 0 °C to 40 °C.

While the rate of reaction was lower at lower temperatures as expected, the enantioselectivity of the reaction intriguingly was found to be completely insensitive to temperature variation (Table 2). There was, however, a slight reduction in enantioselectivity at higher conversions of the reaction (Table 2, last two columns). This leakage at higher conversions could be due to a larger presence of the MBH product that is itself a Brønsted acid. This may interfere with hydrogen bonding interactions with the catalyst that are important in conferring enantioselectivity. Alternatively, the enantioselectively formed product may be racemized by other pathways as previously suggested.[7c]

7) The role of the azaMBH adduct in catalysis.

One of the mechanistic intricacies of the MBH reaction is the autocatalysis from the protic MBH product, which becomes more evident as the reaction proceeds.[7d] In order to investigate the possible role of autocatalysis in the trifunctional organocatalyst-promoted azaMBH reaction, a test azaMBH reaction was performed using **2a** and MVK with **1c** as the catalyst at 10 mol% loading (Scheme 4a). This test reaction is one of the fastest azaMBH reactions, with completion under one hour, and therefore used to minimize effects from other potential racemization pathways that may be more pronounced at longer reaction times. The reaction was spiked with 20 mol% racemic azaMBH adduct **3a** at the



Scheme 4 The effect the azaMBH adduct on the trifunctional catalytic cycle.

start to examine if this would result in reduced enantioselectivity due to the protic product interference from the start. If product interference, from either enantiomer, were significant, then a considerable drop in enantioselectivity would manifest, with a possible change in reaction rate as well. The rate of reaction in this case was found to be unaffected, and the final apparent *ee* at completion was 70%. Given the initial spike of 20 mol% of racemic product, the expected apparent *ee* would be 71% if the enantioselective catalytic pathway was immune to the spike. This indicates that product interference is an unlikely or negligible event in this catalytic cycle.

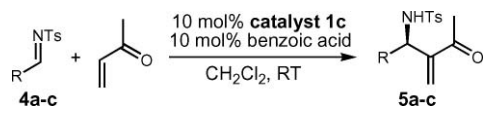
As the azaMBH adduct contains an enone moiety, there exists the possibility of the trifunctional catalyst reacting with the product and initiating a reversal of the azaMBH reaction. The reversibility of this catalytic cycle of the azaMBH reaction was examined using the same azaMBH adduct **3a** (Scheme 4b). The racemic adduct **3a** was treated with only catalyst **1c** and benzoic acid. In order to maximize any potential effect for observation, the catalyst and benzoic acid were used in excess at 2 equiv. of the adduct **3a**. The reaction was allowed to stand for one week and found to remain completely unchanged in composition. Enantio-enriched **3a** (88% *ee*) was also incubated under catalysis conditions (without the imine substrate to stop conversion of MVK to the MBH product) for one week and found to retain its *ee* (Scheme 4c).

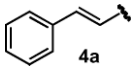
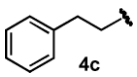
The absence of any observable effect of the azaMBH product during the catalytic time course suggests that the mild reduction in enantioselectivity over the course of the reaction may be due to racemization pathways but not due to product interference of the catalytic cycle itself.

8) Substrate scope profile.

This trifunctional catalytic system has been found to be particularly effective for a wide range of aryl imines, regardless of the electronic nature or position of the substituent on the aromatic ring of the imine. Given the kinetic profile of the catalytic cycle implicating the role of the catalyst in promoting the proton transfer step, it would be important to assess the sensitivity of the catalytic outcome with respect to the substrate. Three additional imine substrates **4a–c** were prepared as previously described.[11] Compared to the control reaction with an aryl imine substrate

Table 3 Generic or azaMBH reactions of electrophiles **4** (1.0 equiv.) with MVK (2.0 equiv.) in dichloromethane with catalyst **1c** (10 mol%) and benzoic acid (10 mol%)



Entry	R	Time/hr	Conv. [%][a]	*ee* [%][b]
1	*p*-bromophenyl	3	95	94
2	 4a	16	44	77
3	 4b	16	—[c]	—
4	 4c	16	—[c]	—

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

(Table 3, entry 1),[4d] these substrates are less reactive and sterically more demanding (Table 3, entries 2 to 4).

In the case of a less reactive substrate that still contains the α-sp^2 carbon characteristic with comparable steric bulk, the catalyst was able to produce the product at a slower rate and reduced level of enantioselectivity (Table 3, entry 2). With alkyl imine substrates that are weaker electrophiles and also bulkier, the catalyst was not able to convert the substrate to the desired product (Table 3, entries 3 and 4). Interestingly, these alkyl imines remained intact during the reaction, which is contrary to the reported instability of these alkyl imines in bifunctional catalysis of the azaMBH reaction.[12] In general, alkyl imines are known to be less reactive substrates compared to the aryl imines in the azaMBH pathway, and this low activity can render these imines more susceptible to the competing hydrolysis pathway, especially in the presence of basic reactive species. However, in this trifunctional catalysis, the low activity of the imine substrate was not accompanied by the usual hydrolysis bleed-off. The absence of the unwanted hydrolysis of the imine substrates in this system suggests that, unlike the bifunctional counterparts, the activity of the trifunctional catalyst may be restricted to the MBH reaction pathway. The higher level of catalytic chemospecificity here in turn may also hint that the activity of the trifunctional catalyst in the MBH pathway may depend on more stringent molecular recognition of the imine substrate by the catalyst.

Conclusions

The complex nature of the MBH reaction with competing auto-catalysis has made the rate enhancement and enantioselectivity difficult to attain concurrently for this reaction with generality in substrate scope. The trifunctional organocatalytic approach has shown some success in achieving more proficient catalysis with good enantioselectivity for subclasses of substrates, from which new generations of catalysts can be developed to expand its substrate scope. Mechanistic investigations here attribute the positive cooperativity of the three functionalities to only

one catalyst molecule. With the molecularity of the catalysis ascertained, future structural and computational studies will be able to shed light on the likely transition structures for an improved design of this new catalytic system. The need for a rational approach is evident as the possibilities for catalyst modification are vast with multiple functionalities. This study also suggests that, for some substrates, the rate of the Michael addition could be enhanced to shunt more of the imine substrate into the faster enantioselective catalytic cycle, provided that the subsequent steps after the Michael addition are not rate limiting by the action of the catalyst. For less reactive imine substrates that are not recognised by the current generation of trifunctional catalysts, the limitation may also be due to an uncatalyzed proton transfer step. This suggests that modification of the Brønsted acid moiety, and its associated counterion, may be important to enable proper molecular recognition at the aldol and proton transfer stages for future generations of catalysts.

Experimental

General

Unless otherwise stated, all chemicals and reagents were received from Sigma Aldrich, Castle Hill, NSW Australia and used without further purification. Reactions were performed under a nitrogen atmosphere. Reactions were magnetically stirred and monitored by thin-layer chromatography (TLC) using silica gel 60 F254 aluminium pre-coated plates from Merck (0.25 mm). Flash column chromatography was performed on silica gel (60 Å 0.06–0.2 mm, 400 mesh from Scharlau). ^{1}H NMR and ^{13}C NMR spectra were obtained in dry $CDCl_3$ on a Bruker Avance DPX 400 MHz spectrometer. Chemical shifts were reported in ppm using chloroform or dichloromethane as the internal reference (^{1}H, 7.26 ppm, ^{13}C, 77.09 ppm for $CDCl_3$ and ^{1}H, 5.25 ppm, ^{13}C, 53.8 ppm for CD_2Cl_2). All spectra were processed using Bruker TOPSPIN (1.4) and MestRec 4.9.9.6. Kinetics experiments were performed under dry conditions in a sealed NMR tube on a Bruker Avance DPX400 or DRX600 NMR spectrometers without mechanical agitation. Infrared spectra were taken on a Perkin Elmer paragon 1000PC FTIR spectrometer. Optical rotations were measured at 23 °C on a P1010 digital polarimeter (Jasco, Japan). High resolution mass analysis was provided by University of Illinois, Urban-Champaign USA.

General information for the kinetics experiments.

Unless otherwise stated, all kinetics experiments were performed under dry conditions in a sealed NMR tube on a Bruker Avance DRX600 Cryoprobe NMR spectrometer without mechanical agitation at 301 K. The receiver gain and relaxation time were set to 128 and 5 s, respectively. Dichloromethane-d_2 was pre-treated by filtering through a plug of activated basic alumina. Freshly distilled methyl benzoate was used as a standard, with its integration normalized internally against the concentration of imine and MVK. Liquid transfer technique from stock solutions was employed for quantities less than 10 mg.

Synthesis of catalysts 1

The synthesis of (*S*)-NOBIN followed literature procedures with modifications for synthesizing **7** and **8**. The procedure for the preparation of 2-methoxymethoxy-2′-trifluoromethanesulfoxy-1,1′-binaphthyl intermediate **7** is as follows: to a suspension of sodium hydride (455 mg, 18.9 mmol) in THF (80 mL) at 0 °C was slowly added the precursor 2-hydroxy-2′-trifluoromethanesulfoxy-1,1′-binaphthyl (7.15 g, 17.1 mmol) under nitrogen and stirred for 30 min. To this yellow mixture chloromethyl methyl ether (1.43 mL, 18.9 mmol) was added dropwise. The reaction was stirred at room temperature for 2 h, quenched carefully with water and extracted with ethyl acetate. The extracts were washed once with brine, dried over sodium sulfate and concentrated to produce a viscous oil purified by column chromatography on silica gel with petroleum ether–ethyl acetate (9 : 1) to give **7** (7.46 g, 16.1 mmol, 94%). The procedure for the preparation of 2-methoxymethoxy-2′-amino-1,1′-binaphthyl intermediate **8** is as follows: to a solution of 2-*N*-benzyl-2′-trifluoromethanesulfoxy-1,1′-binaphthyl (5.82 g, 13.8 mmol) in ethyl acetate (30 mL) was added palladium (10% on carbon, 1.41 g, 1.38 mmol). The reaction was heated at 45 °C under H_2 (1 atm) for 3 h. After filtration through Celite the solvent was removed to produce **8** (4.3 g, 12.9 mmol; 94%), which was used without further purification. The preparation of (*S*)-MAP and catalysts **1** followed the procedures as previously described without change.[4c]

Reaction procedures

azaMBH reactions. An imine (0.015 mmol), phosphine catalyst (10 mol%, 0.0015 mmol) and benzoic acid (10 mol%, 0.0015 mmol) were combined under N_2. Dichloromethane (0.1 mL per mg of catalyst) was added, followed by distilled methyl vinyl ketone (2 equiv.) dropwise. The reaction was stirred at room temperature until completion. The reaction mixture was evaporated to dryness, and the crude mixture was immediately subjected to chiral HPLC analysis.

General procedure for the experiments on the catalyst order. Catalyst **1c** (4.0–8.0 mg, 6.1–12.1 μmol, 12.1–24.2 mM), benzoic acid (1 equiv. to the catalyst), methyl benzoate (0.64 mg, 5.6 μmol, 11.2 mM) and 4-bromo-*N*-tosyl imine (6.2 mg, 18.3 μmol, 36.6 mM) were dissolved in dichloromethane-d_2 to afford a total reaction volume of 0.5 mL. Freshly distilled methyl vinyl ketone (1.27 mg, 18.1 μmol, 36.3 mM) was added and the solution was transferred to an NMR tube. The tube was sealed and the time course of the reaction was followed by ^{1}H NMR spectroscopy.

General procedure for the experiments on the imine order. 4-bromo-*N*-tosyl imine **2b** (4.2–12.7 mg, 12.4–37.6 μmol, 24.8–75.1 mM), catalyst **1c** (4.0 mg, 6.1 μmol, 12.1 mM), benzoic acid (1 equiv. to the catalyst) and methyl benzoate (0.61 mg, 5.3 μmol, 10.6 mM) were combined and dissolved in dichloromethane-d_2 to afford a total reaction volume of 0.5 mL Freshly distilled methyl vinyl ketone (1.27 mg, 18.1 μmol, 36.3 mM) was added and the solution was transferred to an NMR tube. The tube was sealed and the time course of the reaction was followed by ^{1}H NMR spectroscopy.

General procedure for the experiments on the methyl vinyl ketone order. Catalyst **1c** (4.0 mg, 6.1 μmol, 12.1 mM), benzoic acid (1 equiv. to the catalyst), methyl benzoate (0.61 mg, 5.3 μmol, 10.6 mM) and 4-bromo-*N*-tosyl imine (6.2 mg, 18.3 μmol, 36.6 mM) were combined and dissolved in dichloromethane-d_2 to afford a total reaction volume of 0.5 mL. Freshly distilled methyl

vinyl ketone (1.69–2.64 mg, 24.1–37.6 μmol, 48.2–75.2 mM was added and the solution was transferred to an NMR tube. The tube was sealed and the time course of the reaction was followed by ^{1}H NMR spectroscopy.

General procedure for the experiments on the rate and enantioselectivity dependence on temperature. Catalyst **1c** (1 mg, 1.5 μmol, 3 mM), benzoic acid (1 equiv. to the catalyst), methyl benzoate (0.64 mg, 5.6 μmol, 11.2 mM) and 4-bromo-*N*-tosyl imine (5.1 mg, 15.1 μmol, 110 mM) were combined and dissolved in 0.5 mL dichloromethane-d_2. The solution was transferred to an NMR tube and freshly distilled methyl vinyl ketone (2.65 mg, 37.8 μmol, 275 mM) was added. The tube was sealed and the time course of the reaction was followed by ^{1}H NMR spectroscopy at 273–303 K. Sample aliquots at each temperature were taken at approximately 10% and >90% conversions and subjected to chiral HPLC for enantioselectivity analysis.

Spectroscopic data

(*E*)-4-Methyl-*N*-(4-methylene-5-oxo-1-phenylhex-1-en-3-yl)benzenesulfonamide (**5a**). The spectroscopic data of the compound was found to match those in a previous report.[13] ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.17 (s, 3H); 2.31 (s, 3H); 4.80 (dd, *J1* = 9.0 Hz, *J2* = 7.8 Hz, 1H); 5.70 (d, *J* = 9.0 Hz, 1H); 6.98 (m, 3H); 6.28 (d, *J* = 15.9 Hz, 1H); 7.14–7.27 (m, 7H), 7.69 (d, *J* = 8.1 Hz, 2H). **ESI** [M+Na$^+$]: found 378.1138, calcd for $(C_{20}H_{21}NO_3SNa)^+$: 378.1140. Chiral HPLC analysis: eluent: hexane–isopropanol = 80 : 20; flow rate: 0.7 mL min^{-1}; t_{major} = 12.8 min, t_{minor} = 14.6 min.

Acknowledgements

C. A. is supported by an Australian Postgraduate Award.

References

1 For an overview of asymmetric organocatalysis, see A. Berkessel and H. Gröger, *Asymmetric Organocatalysis: from Biomimetic Concepts to Applications in Asymmetric Synthesis*, Wiley-VCH, Weinheim, 2005.
2 (*a*) For recent reviews of asymmetric organocatalysis, see: D. Enders and A. Narine, *J. Org. Chem.*, 2008, **73**, 7857–7870; (*b*) A. Dondoni and A. Massi, *Angew. Chem., Int. Ed.*, 2008, **47**, 4638–4660.
3 For a proper definition of bifunctional organocatalysis, see: J. Seayad and B. List, *Org. Biomol. Chem.*, 2005, **3**, 719–724.
4 (*a*) For recent examples of trifunctional organocatalysts: T. Ema, D. Tanida, T. Matsukawa and T. Sakai, *Chem. Commun.*, 2008, 957–958; (*b*) W. Chen, W. Du, Y-Z. Duan, Y. Wu, S-Y Yang and Y-C Chen, *Angew. Chem., Int. Ed.*, 2007, **46**, 7667–7670; (*c*) J-M. Garnier, C. Anstiss and F. Liu, *Adv. Synth. Catal.*, 2009, **351**, 331–338; (*d*) J-M. Garnier and F. Liu, *Org. Biomol. Chem.*, 2009, **7**, 1272–1275; (*e*) D-Q. Xu, L-P. Wang, S-P. Luo, Y-F. Wang, S. Zhang and Z-Y. Xu, *Eur. J. Org. Chem.*, 2008, 1049–1053; (*f*) C-J. Wang, Z-H. Zhang, X-Q. Dong and X-J. Wu, *Chem. Commun.*, 2008, 1431–1433.
5 (*a*) Recent representative reviews on the MBH reaction: D. Basavaiah, A. J. Rao and T. Satyanarayana, *Chem. Rev.*, 2003, **103**, 811–891; (*b*) D. Basavaiah, K. V. Rao and R. J. Reddy, *Chem. Soc. Rev.*, 2007, **36**, 1581–1588; (*c*) V. Declerck, J. Martinez and F. Lamaty, *Chem. Rev.*, 2009, **109**, 1–48.
6 (*a*) Y-L. Shi and M. Shi, *Eur. J. Org. Chem.*, 2007, **18**, 2905–2916; (*b*) G. Masson, C. Housseman and J. Zhu, *Angew. Chem., Int. Ed.*, 2007, **46**, 4614–4628; (*c*) C. Menozzi and P. I. Dalko, *Enantioselective Organocatalysis*, Wiley-VCH, Weinheim, 2007, 151–187.
7 (*a*) Recent experimental mechanistic studies on the MBH or azaMBH reaction: K. E. Price, S. J. Broadwater, H. M. Jung and D. T. McQuade, *Org. Lett.*, 2005, **7**, 147–150; (*b*) K. E. Price, S. J. Broadwater, B. J. Walker and D. T. McQuade, *J. Org. Chem.*, 2005, **70**, 3980–3987; (*c*) P. Buskens, J. Klankermayer and W. Leitner, *J. Am. Chem. Soc.*, 2005, **127**, 16762–16763; (*d*) V. K. Aggarwal, S. Y. Fulford and G. C. Lloyd-Jones, *Angew. Chem., Int. Ed.*, 2005, **44**, 1706–1708; (*e*) I. T. Raheem and E. N. Jacobsen, *Adv. Synth. Catal.*, 2005, **347**, 1701–1708; (*f*) M. E. Krafft, T. F. N. Haxell, K. A. Seibert and K. A. Abboud, *J. Am. Chem. Soc.*, 2006, **128**, 4174–4175; (*g*) G. W. Amarante, H. M. S. Milagre, B. G. Vaz, B. R. Vilacha Ferreira, M. N. Eberlin and F. Coelho, *J. Org. Chem.*, 2009, **74**, 3031–3037; (*h*) L. S. Santos, C. H. Pavam, W. P. Almeida, F. Coelho and M. N. Eberlin, *Angew. Chem., Int. Ed.*, 2004, **43**, 4330–4333.
8 (*a*) D. Salinger and R. Brückner, *Synlett*, 2009, 109–111; (*b*) T. Ooi, K. Ohmatsu and K. Maruoka, *J. Am. Chem. Soc.*, 2007, **129**, 2410–2411.
9 S. Vyskocil, M. Smrcina, V. Hanus, M. Polasek and P. Kocovsky, *J. Org. Chem.*, 1998, **63**, 7738–7748.
10 Overall two batches of catalysts **1c** were used. Both batches of the catalyst were found to be identical in activity in control reactions.
11 A. Solladié-Cavallo, M. Roje, R. Welter and V. Sunjic, *J. Org. Chem.*, 2004, **69**, 1409–1412.
12 M. Shi, Y-M. Xu and Y-L. Shi, *Chem.–Eur. J.*, 2005, **11**, 1794–1802.
13 M. Shi, L-H. Chen and C-Q Li, *J. Am. Chem. Soc.*, 2005, **127**, 3790–3800.