Trifunctional organocatalyst-promoted counterion catalysis for fast and enantioselective aza-Morita–Baylis–Hillman reactions at ambient temperature†

Jean-Marc Garnier and Fei Liu*

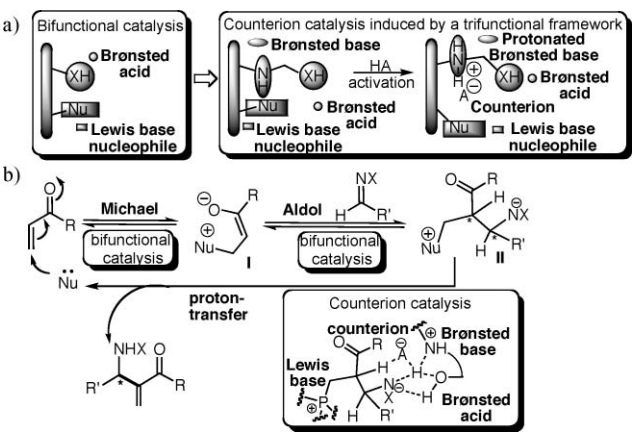
Received 27th January 2009, Accepted 3rd February 2009
First published as an Advance Article on the web 18th February 2009
DOI: 10.1039/b901781j

Fast and enantioselective aza-Morita–Baylis–Hillman reactions between electron-deficient or electron-rich aromatic *N*-tosyl imines and methyl vinyl ketone were achieved at ambient temperature using asymmetric counterion-directed catalysis promoted by trifunctional organocatalysts with a Brønsted base as the activity switch after protonation with benzoic acid.

In the past decade asymmetric organocatalysis has received renewed interest since its initial conceptual demonstration in the last century.[1] Efforts thus far have firmly established this approach as a viable counterpart to existing metal- or enzyme-based catalytic systems.[2] While in scope they have verified advantages, in the sense of catalysis, where rates and enantioselectivity jointly define the catalytic proficiency, organocatalysts still require much improvement to emulate that seen with metal or enzyme catalysts. One strategy is to develop enzyme-mimicking bifunctional or trifunctional organocatalysts,[3] and recently, a biomimetic trifunctional organocatalyst, although without enantioselectivity, has shown remarkable catalytic rates reminiscent of enzyme catalysis in transesterification reactions.[3b] Reported herein is a rational and systematic approach to developing asymmetric trifunctional organocatalysts for fast and facile aza-Morita–Baylis–Hillman reactions in organic solvents using the strategy of counterion-directed catalysis.[4]

The MBH and azaMBH reactions are multi-step carbon–carbon bond-forming reactions with recognized synthetic utility but hampered by the problems of slow rates and limited scope.[5] Enantioselective bifunctional organocatalysts have been developed, with impressive substrate scope, for catalyzing the MBH or azaMBH reactions in nonpolar aprotic solvents with high ee values, although the rate of reaction is generally slow – in the range of hours to days even at 10–20% catalyst loading.[6] However, nonpolar aprotic solvents are necessary for asymmetric catalytic approaches that require preservation of key H-bonding interactions. In selected cases, bifunctional catalysts with multivalent H-bonding donors can achieve higher catalytic turnover without compromising the enantioselectivity, although the rate of reaction is difficult to control due to the typical requirement of low temperatures to maintain high ee.[6e–g] Recently, key mechanistic experiments on the MBH or azaMBH reactions have pointed to the proton transfer as the generally accepted rate-limiting step,[7] which augur well for new asymmetric catalytic strategies targeting the rate-limiting step in order to improve the catalytic proficiency with faster rates and more facile reaction conditions.

We have initiated a new trifunctional organocatalyst-induced counterion catalysis approach using the azaMBH reaction between electron-rich and electron-deficient aromatic *N*-tosyl imines and methyl vinyl ketone (MVK).[8] This led to enhanced rates in these reactions (86–96% isolated yields in 3–24 h) with good enantioselectivity (59–92% ee) without the need to lower the reaction temperature (Scheme 1). Extending from the bifunctional approach that utilises a Lewis base nucleophile and a Brønsted acid for H-bonding interactions, this trifunctional system employs an additional Brønsted base that serves as the activity switch in response to protonation by a strong Brønsted acid (Scheme 1a). The resulting chiral ion-pair becomes catalytically active, with the counterion of the acid additive controlling the ee and the sense of asymmetric induction by selectively "gating" the rate-limiting proton transfer step (Scheme 1b). Unlike bifunctional catalysis where the rate and enantioselectivity vary independently, this counterion strategy has resulted in enantioselective azaMBH reactions where the rate of reaction and enantioselectivity arise in a coordinated fashion.



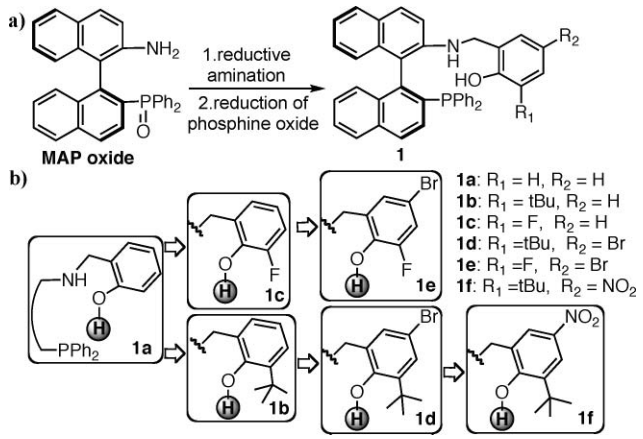
Scheme 1 Counterion catalysis of the azaMBH reaction. (a) Extension from bifunctional catalysis to a trifunctional framework for counterion catalysis. (b) Promoting the proton-transfer step in the azaMBH reaction by counterion catalysis.

The modular nature of this catalytic system presented an opportunity to systematically and rapidly adjust the apparent acidity of the phenolic Brønsted acid group by adding substituents on the phenol ring to investigate its potential effect on further

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

† Electronic supplementary information (ESI) available: Spectra and characterisation data of catalysts **1b–1f** and MBH/azaMBH reaction adducts **3** and **6**. See DOI: 10.1039/b901781j

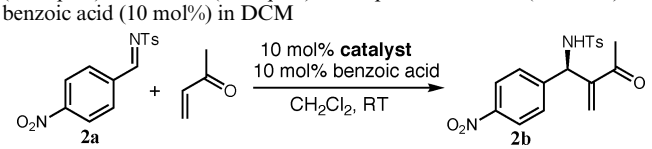
promoting the catalytic proficiency of this counterion strategy (Scheme 2). This acidity tuning of the phenolic Brønsted acid could have a variety of effects for and against the counterion catalysis. A more acidic phenolic Brønsted acid could facilitate the protonation of the Brønsted base and provide a stronger ionic H-bonding network to position the counterion better for catalysis. However, as this trifunctional system contains the bifunctional themes and is capable of bifunctional catalysis in its unprotonated form, the bifunctional catalysis may also escalate, interfering with the counterion catalysis that requires acid activation. Nonetheless, an iterative process was followed to construct catalysts **1b–f** related to the root catalyst **1a**. All catalysts **1a–f** were readily procured with the reductive amination method, followed by silane reduction, starting from MAP oxide[9] and, as triaryl phosphines, displayed good air stability.



Scheme 2 Acidity tuning of the trifunctional organocatalysts. (a) A general synthesis of **1** from MAP oxide. (b) Acidity tuning from the root catalyst **1a**.

Catalysts **1a–f** were tested using the azaMBH reaction between an *N*-tosyl imine and MVK (Table 1).‡ Compared to the root catalyst **1a**, the addition of an electron-rich *tert*-butyl substituent *ortho* to the phenolic Brønsted acid reduced slightly the rate of conversion and ee (entry 2). On the other hand, the addition of an electron–withdrawing fluorine substituent resulted in an initial rate

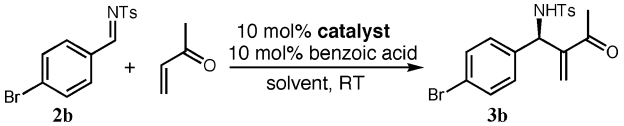
Table 1 AzaMBH reactions of *N*-(arylmethylidene)arylsulfonamide **2a** (1.0 equiv.) with MVK (2.0 equiv.) in the presence of **1a–f** (10 mol%) and benzoic acid (10 mol%) in DCM



Entry	Catalyst	Time/min	Conv. (%)[a]	ee (%)[b]
1	**1a**	15	15 (>95[c])	80
2	**1b**	15	85[c]	73
3	**1c**	15	57 (87)[d]	81
4	**1d**	15	91 (>95)[d]	82
5	**1e**	15	87 (>95)[d]	88
6	**1f**	15	57 (91)[d]	87

[a] Calculated by ^{1}H NMR spectroscopy. [b] Determined by chiral HPLC analysis. [c] Conversion after 180 min. [d] Conversion after 30 min in parentheses.

Table 2 AzaMBH reactions of *N*-(arylmethylidene)arylsulfonamide **2b** (1.0 equiv.) with MVK (2.0 equiv.) in the presence of **1d** or **1f** (10 mol%) and benzoic acid (10 mol%) in various solvents



		1d		**1f**	
Entry	Solvent	Conv. (%)[a]	ee (%)[b]	Conv. (%)[c]	ee (%)[b]
1	THF	>95	80	70	79
2	Toluene	>95	86	>95	87
3	Et_2O	>95	87	87	86
4	$CHCl_3$	>95	86	>95	88
5	CH_2Cl_2	>95	90	>95	92

[a] Calculated by ^{1}H NMR spectroscopy after 30 min of reaction. [b] Determined by chiral HPLC analysis. [c] Calculated by ^{1}H NMR spectroscopy after 60 min of reaction.

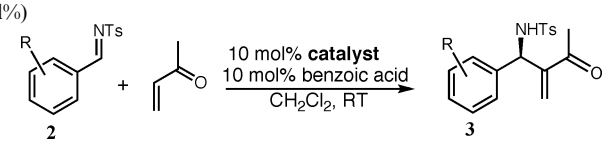
enhancement of about 4-fold with comparable ee (entry 3). This suggested that increasing the acidity of the phenolic Brønsted acid might have an overall positive effect on promoting the counterion catalysis. The addition of a second electron-withdrawing bromo group in the *para* position, as seen in catalysts **1d** and **1e** (entries 4 and 5), improved the conversion to 87–91% in 15 min with improved enantioselectivity. An even more electron-withdrawing nitro group at the *para* position, however, resulted in slight reduction of catalytic proficiency. In summary, a more acidic phenolic Brønsted acid improved the catalytic proficiency of the counterion catalysis, up to a limit.

Catalysts **1d** and **1f** were next examined in various solvents using a test azaMBH reaction (Table 2). As expected, nonpolar aprotic solvents generally preserved the required tight-ion pairing for catalysis, with dichloromethane providing the best ee values for both **1d** and **1f**.

The substrate scope was also investigated using **1d** and **1f** (Table 3). In general, **1d** delivered faster rates (for both electron-deficient and electron-rich aromatic *N*-tosyl imine substrates) with slightly lower ee. It is possible that, in **1f**, the bulky *tert*-butyl group *ortho* to the phenolic Brønsted acid may provide some barrier to the competing monofunctional or bifunctional catalysis of the acidified phenolic proton, resulting in a more consistent enantioselectivity range (87–94% ee), compared to that of **1d** (72–93% ee), without the need to lower the reaction temperature.

The scope of this trifunctional organocatalyst-promoted counterion strategy was further tested in the more difficult generic MBH reaction or the azaMBH reaction with acrylate esters (Table 4). Triaryl phosphines are generally poor catalysts for these reactions with little activity, although attempts have been made to use more nucleophilic chiral alkyl phosphines to catalyse these reactions with moderate ee.[10] Upon acid activation, **1f** exhibited good rates of reaction for these test cases, while **1a** showed no activity even with benzoic acid activation. In the generic MBH reaction between an aldehyde and MVK (entry 1, Table 4), the rate of conversion and ee were both reduced compared to those seen with the its aza counterpart (entry 6, Table 3). For the azaMBH reaction between electron-deficient *N*-tosyl imines and phenyl acrylate (entries 2–4, Table 4), the rate of conversion is also significantly slower compared to those with MVK. For these

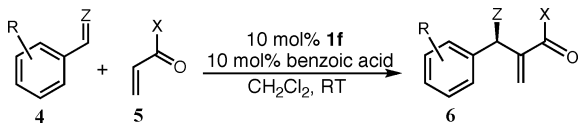
Table 3 Aza-Morita–Baylis–Hillman reactions of *N*-(arylmethylidene)arylsulfonamide **2** (1.0 equiv.) with MVK (2.0 equiv.) in DCM with catalyst **1d** or **1f** (10 mol%) and benzoic acid (10 mol%)



		1d			1f		
Entry	R	Time/min	Conv. (%)[a]	ee (%)[b]	Time/min	Conv. (%)[a]	ee (%)[b]
1	*m*-NO_2 **2a**	30	>95	84	60	89	87
2	*p*-Br **2b**	60	>95	90	60	41 (>95)[c]	92
3	*p*-Cl **2c**	60	91	90	120	71	94
4	*o*-Cl, **2d**	180	>95	72	180	39 (72)[d]	89
5	*p*-F, **2e**	60	71	88	180	87	90
6	*p*-NO_2 **2f**	30	>95	82	30	>95	87
7	*o*-NO_2 **2g**	30	59	78	60	42 (>95)[c]	88
8	*p*-Me **2h**	180	78	93	900	62	93
9	*o*-OMe **2i**	180	43 (82)[d]	76	900	64	88
10	*m*-OMe **2j**	150	93	91	120	31 (81)[d]	94

[a] Calculated by ^{1}H NMR spectroscopy. [b] Determined by chiral HPLC analysis. [c] Conversion after 180 min. [d] Conversion after 360 min.

Table 4 Generic or azaMBH reactions of an electrophile **4** (1.0 equiv.) with an enone **5** (2.0 equiv.) in DCM with catalyst **1f** (10 mol%) and benzoic acid (10 mol%)



Entry	R	Z	X	Time/h	Conv. (%)[a]	ee (%)[b]
1	*p*-NO_2	O	Me	24	95 (**6a**)	52
2	*p*-NO_2	NTs	OPh	16	53 (**6b**)	40
3	*p*-Br	NTs	OPh	16	41 (**6c**)	77
4	*p*-Cl	NTs	OPh	60	48 (**6d**)	70

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

less reactive substrates, the proton-transfer step is, as expected, slower compared to that of more reactive substrates such as *N*-tosyl imines with MVK. This would lead to retardation of the counterion-catalysed proton-transfer pathway, resulting in leakage of enantioselectivity to competing pathways. A variable due to the significantly different enolate geometry, in addition to a slower proton-transfer step, was also introduced in the azaMBH reactions with the use of an acrylate ester. This may also be part of the basis to the significantly reduced rates observed in these cases, as the position of the counterion could also be significantly altered.

The persistent scope issue of the MBH reaction has limited the development of a generally effective catalytic system. This is attributed to the complex nature of this reaction, where the geometry of the highly unstable Michael adduct, the reversibility of the Michael-aldol step, and the autocatalysis by the adduct itself all converge to render the rate and enantioselectivity difficult to attain concurrently with generality.[7b–d] While bifunctional organocatalysts for the MBH or azaMBH reaction will continue to improve in scope, the rates for these systems tend to be slower, as lower temperatures are generally required to maintain enantioselectivity by conformational locking. The trifunctional organocatalyst-promoted counterion strategy here (Fig. 1) offers a different avenue by promoting the rate-limiting proton-transfer step, which can be combined with the steric-based strategies to afford a catalytic system with improved scope by expediting a particular proton-transfer pathway while hindering spatially the competing pathways without the low temperature prerequisite. Effort towards a generally proficient system using this trifunctional organocatalyst-promoted counterion strategy for fast and enantioselective MBH reactions under facile conditions is currently underway and will be reported in due course.

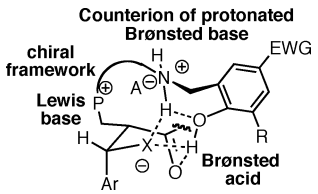


Fig. 1 Proposed transition structure for the counterion catalysis promoted by a trifunctional organocatalyst.

Acknowledgements

This work is supported by an Australian Research Council Discovery Grant (ARC-DP055068).

Notes and references

‡ Typical reaction procedure for generic or azaMBH reaction catalyzed by phosphines **1a–e**: An imine or aldehyde (0.5 mmol), phosphine catalyst (10 mol%, 0.05 mmol) and benzoic acid (10 mol%, 0.05 mmol) were combined under N_2. DCM (0.1 mL per mg of catalyst) was added, followed by the purified enone (2 equiv.) dropwise. The reaction was stirred at room temperature until completion. The solvent was evaporated and the crude mixture was immediately subjected to the chiral HPLC for the ee analysis.

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