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Cooperativity in the counterion catalysis of Morita/Baylis/Hillman reactions promoted by enantioselective trifunctional organocatalysts

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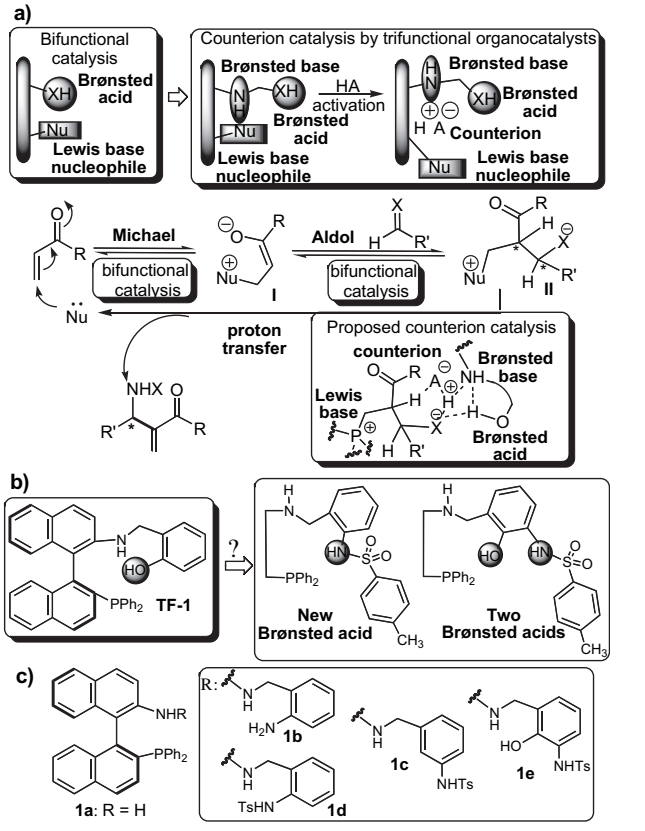
ABSTRACT

New trifunctional organocatalysts with a NHTs Brønsted acid were prepared and tested in their ability to promote the counterion catalysis of generic and aza-Morita/Baylis/Hillman reactions. The cooperativity between the counterion and the NHTs Brønsted acid of the trifunctional catalyst was required for good enantioselectivity and rate enhancement. Better enantioselectivity was observed for aza-MBH reactions at relatively low catalyst loading (2–5 mol %) under facile conditions.

1. Introduction

The Morita/Baylis/Hillman (MBH) reaction is an atom-economic carbon–carbon bond forming reaction between an aldehyde, or imine, and an enone to generate a highly functionalized secondary chiral alcohol or amine. It has great potential in diversity oriented and convergent synthesis but can be limited by (1) slow reaction rates (often days) and (2) capricious substrate scope, primarily due to the complex mechanistic nature of this multi-step reaction.[1,2] Many asymmetric bifunctional organocatalysts have been developed to successfully catalyze several versions of the MBH reaction with high enantioselectivity, although the rate of conversion is still typically in the days range with low-temperature reaction conditions as a requirement.[3]

Extending from the bifunctional approaches that utilize a Lewis base nucleophile and a Brønsted acid for H-bonding interactions, we have made the first demonstration of a strategy of trifunctional organocatalyst induced counterion catalysis[4] for facile and asymmetric aza-MBH reactions with very fast rates (86–96% isolated yields in 3–24 h) and good enantioselectivity (59–92% ee) even at ambient temperature (Scheme 1a).[5] This trifunctional system, while catalytically inactive by itself, employs an additional Brønsted base that serves as the activity switch in response to activation by a strong external Brønsted acid. The installation of the third functionality, nitrogen Brønsted base, effectively changes the bifunctional pathway (slower and less enantioselective) to the trifunctional pathway (faster and more enantioselective).[5] The acid activation conferred by the Brønsted base, combined with the known functions of the Lewis base for initiating the Michael addition and the Brønsted acid for H-bonding interactions, are the



Scheme 1. A trifunctional approach to facile asymmetric MBH reactions at ambient temperature.

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three required catalytic functions to achieve this rate and enantioselectivity enhancement simultaneously. Comprehensive bifunctional controls of the this system were also constructed and tested, along with examination of solvent effects, which showed that each of the three functionalities of **1** was essential for switching to the trifunctional catalysis, that is, dependent on ion-pairing.[5] Second generation catalysts, in which the acidity of the Brønsted acid on the catalyst is enhanced, showed further improvement in reaction rates (0.5–16 h) and expanded substrate scope.[6] Notably, the trifunctional system is again applicable under facile conditions without the need to lower the reaction temperature and raises an interesting prospect of further process-related improvement using this approach. The rapid assembly strategy behind the synthesis of this trifunctional series offers the opportunity to explore the catalytic effect of new types of Brønsted acids that can be installed onto the catalyst scaffold (Scheme 1b). The phenolic Brønsted acid in early generations of the trifunctional catalysts such as **TF-1** can be replaced by a NHTs Brønsted acid. Furthermore, more than one Brønsted acid can be added onto the catalyst scaffold to create new trifunctional and bivalent organocatalysts such as **1e**. Herein reported is a new series of such trifunctional organocatalysts **1b**–**e** (Scheme 1c) that demonstrate further improvement in the rate of conversion in asymmetric aza-MBH reactions at as low as 2–5 mol % loading under facile conditions with good enantioselectivity. In addition, this system displays a new counterion catalysis profile unlike that observed with previous generations of trifunctional catalysts.

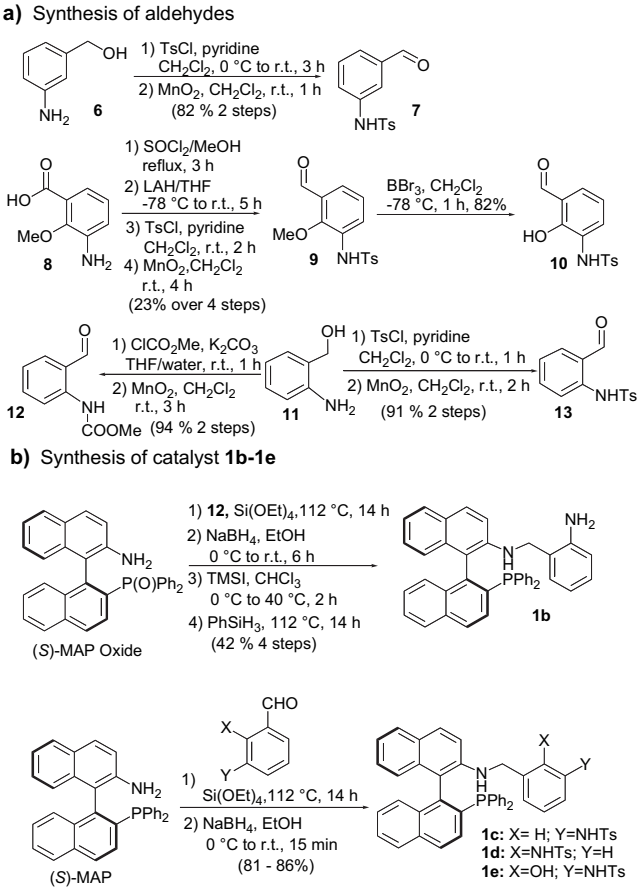
2. Results and discussion

The installation of a new NHTs Brønsted acid moiety on the chiral BINAP backbone to make new trifunctional catalysts required preparation of substituted aryl aldehydes **7**, **10**, **12**, and **13** (Scheme 2). 2-*N*-Tosylbenzaldehyde **13** and 3-*N*-tosylbenzaldehyde **7** were prepared from their commercially available amino alcohols, **11** and **6**, in 91% and 82% yield over two steps, respectively using a modified procedure by Konig[7] (Scheme 2a). The tosylation of **6** or **11** proceeded smoothly under the reported conditions. The more stable and environmentally friendly manganese dioxide was used for benzylic oxidation instead of the reported PCC.

2-Hydroxy-3-*N*-tosylbenzaldehyde **10** was prepared from the commercially available 2-methoxy-3-aminobenzoic acid **8** (Scheme 2a). The amino acid **8** was reduced to the alcohol using a procedure reported by O'Hare.[8] The corresponding amino alcohol was then *N*-tosylated and oxidized to furnish aldehyde **9** using the same reagents as described above. *O*-Methoxy deprotection with boron tribromide provided the desired aldehyde **10** in 20% yield over five steps.

With the required aldehydes in hand, the synthesis of catalysts **1b**–**e** proceeded from (***S***)-**MAP** as described previously.[5,9] Reductive amination of aldehydes **7**, **10**, and **13** with (***S***)-**MAP** yielded multifunctional catalysts **1c**, **1d**, and **1e** in 84%, 86%, and 81% yield over two steps from (***S***)-**MAP**, respectively (Scheme 2b). The synthesis of **1b** was more elaborate as direct reductive amination with (***S***)-**MAP** and 2-amino benzaldehyde gave a complex reaction mixture, probably due to the instability of this aldehyde at high temperatures. Alternatively, 2-*N*-methylcarbamate benzaldehyde **12** was prepared over two steps in 94% yield from **11** as reported by Yoshiharu[10] (Scheme 2a). Aldehyde **12** was then subjected to reductive amination with (***S***)-**MAP** oxide, followed by trimethylsilyl iodide (TMSI) deprotection of the *N*-methylcarbamate and phosphine oxide reduction in neat phenylsilane to give the multifunctional catalyst **1b** over four steps in 41% yield (Scheme 2b).

The activity of catalysts **1b**–**e**, along with catalysts from earlier generations (**TF-1** and **1a**) were then investigated in both the generic (aldehydes as electrophiles) and aza-MBH (imines as



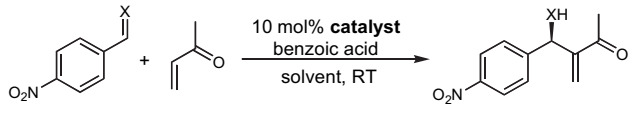
Scheme 2. Catalyst synthesis.

electrophiles) test reactions (Table 1). The effect of acid activation on these new trifunctional catalysts were also examined.

The first point to note is that all of the new trifunctional catalysts **1c**–**e** required acid activation, the lack of which resulted in reduction of both rate and enantioselectivity (Table 1, entries 12–27). This concomitant rise of both the rate and enantioselectivity is the hallmark of the trifunctional catalytic pathway and consistent with the observation on early generations of trifunctional catalysts such as **TF-1** that required the Brønsted base functionality for acid activation.[5] The bifunctional catalyst **1a**, which is used as a control (Table 1, entries 4–7), demonstrates that acid activation is sufficient for enhancing the rate of catalysis, but the enantioselectivity of this catalysis is poor without the third NHTs Brønsted functionality. Catalyst **1b** (Table 1, entries 8–11), which is different from **1d** by missing the NHTs Brønsted acid, exhibited poor response to acid activation with little enantioselectivity and revealed the important role of the NHTs Brønsted acid in conferring the required cooperativity between the catalyst and the acid additive.

The second point to note is that the new trifunctional organocatalysts **1c** and **1d** have significantly different catalytic profiles compared to those of earlier generations. Catalyst **1d**, compared to **TF-1**, is more active, exhibiting a faster rate of catalysis with a similar level of enantioselectivity in both the generic and aza-MBH test reactions (Table 1, entries 1 and 3 vs entries 16 and 21). Catalyst **1c** is also a more active catalyst compared to **TF-1** (Table 1, entries 1 and 3 vs entries 12 and 14). For catalysts **1c** and **1d**, ether, not dichloromethane, was found to be the best solvent for the generic MBH reaction. Catalyst **1e** is a trifunctional catalyst with two Brønsted acid interaction sites (Table 1, entries 24–27). It has a comparable catalytic profile to that of **1c** and **1d** but is a slower catalyst. This suggests that the position of the Brønsted acid

Table 1
Initial catalysis examination of catalysts **1** in test MBH reactions



2a: X = NTs
4a: X = O

3a: X = NTs
5a: X = O

Entry	Cat.	Loading [mol %]	PhCOOH [mol %]	X	Solvent	Time [h]	Conv(ee)[a,b] [%]
1	**TF-1**	10	10	NTs	CH_2Cl_2	3	>95(80)[c]
2	**TF-1**	10	0	NTs	CH_2Cl_2	3	16(0)[c]
3	**TF-1**	10	10	O	CH_2Cl_2	24	no conversion
4	**1a**	10	10	NTs	CH_2Cl_2	3	60(10)
5	**1a**	10	0	NTs	CH_2Cl_2	3	14(0)
6	**1a**	10	10	O	Ether	6	81(33)
7	**1a**	10	0	O	Ether	6	6(n.d.)
8	**1b**	10	10	NTs	CH_2Cl_2	0.5	28(40)
9	**1b**	10	0	NTs	CH_2Cl_2	0.5	9(32)
10	**1b**	10	10	O	Ether	24	38(24)
11	**1b**	10	0	O	Ether	24	33(24)
12	**1c**	5	5	NTs	CH_2Cl_2	0.5	>95(40)
13	**1c**	5	0	NTs	CH_2Cl_2	0.5	34(0)
14	**1c**	10	10	O	Ether	6	95(54)
15	**1c**	10	0	O	Ether	6	30(0)
16	**1d**	10	10	NTs	CH_2Cl_2	0.5	>95(82)
17	**1d**	10	0	NTs	CH_2Cl_2	0.5	37(51)
18	**1d**	10	10	NTs	Ether	0.5	>81(76)
19	**1d**	10	10	NTs	Toluene	0.5	>95(66)
20	**1d**	10	10	O	CH_2Cl_2	3	<5(n.d.)
21	**1d**	10	10	O	Ether	3	73(47)
22	**1d**	10	0	O	Ether	3	9(n.d.)
23	**1d**	10	10	O	Toluene	3	43(50)
24	**1e**	5	5	NTs	CH_2Cl_2	0.5	40(88)
25	**1e**	5	0	NTs	CH_2Cl_2	0.5	17(0)
26	**1e**	10	10	O	Ether	24	75(48)
27	**1e**	10	0	O	Ether	24	36(21)

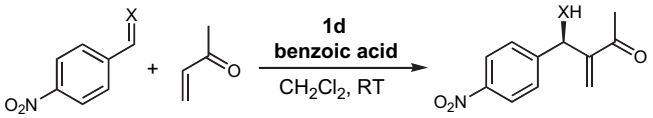
[a] Calculated by ^{1}H NMR spectroscopy.
[b] Determined by chiral HPLC analysis.
[c] Data from Ref. 5.

functionality *ortho* to the Brønsted base functionality is crucial for catalysis with minimal enhancement from the functionality at the *meta* position.

The loading effect of the most effective catalyst **1d** in response to acid activation was investigated next (Table 2). In both the generic and aza-MBH test reactions, excess amount of acid additive resulted in reduction of the rate of catalysis (Table 2, entries 1, 2, and 12), although the enantioselectivity was reduced only in the aza-MBH test reaction (Table 2, entries 1 and 2). In both test reactions, a lower catalyst loading with correspondingly lower amount of acid additive improved the enantioselectivity of the catalysis up to a limit (Table 2, entries 9 and 17). For the aza-MBH test reaction, a lower catalyst loading did not affect the rate of catalysis significantly (Table 2, entries 4–7), while for the generic MBH test reaction, the rate of catalysis was faster at a higher catalyst loading (Table 2, entries 13–18). In general, the ratio of 1:1 catalyst to acid additive provided the best balanced outcomes in rate improvement and enantioselectivity.

With the earlier generations of trifunctional catalysts such as **TF-1**, the counterion from the acid additive was found to control the sense of the asymmetric induction.[5] The counterion effect of this new type of trifunctional catalysts was therefore examined using catalyst **1d** (Table 3). Contrary to the varying counterion effect observed with **TF-1**, **1d** exhibited a higher level of consistency in the sense of asymmetric induction. No reversal of the sense of asymmetric induction was observed with different counterions tested, and benzoic acid was again identified as the best additive for enantioselectivity with more generality (Table 3, entries 6 and 10). Also, in the case of **1d**, the generic MBH and aza-MBH reactions

Table 2
The effect of catalyst loading using **1d**



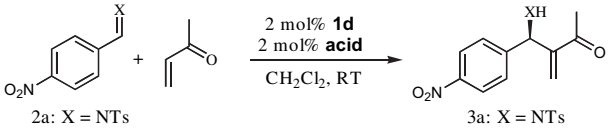
2a: X = NTs
4a: X = O

3a: X = NTs
5a: X = O

Entry	X	**1d** (mol %)	Acid (mol %)	Time [h]	Conv.[a] [%]	ee[b] [%]
1	NTs	**10**	50	0.5	29	71
2	NTs	**10**	20	0.5	48	76
3	NTs	**10**	10	0.5	>95	82
4	NTs	**10**	1	0.5	>95	88
5	NTs	**10**	0.5	0.5	>95	85
6	NTs	**5**	5	0.5	>95	88
7	NTs	**5**	1	0.5	75	91
8	NTs	**2**	2	0.5	36[c]	90
9	*NTs*	***2***	*2*	*0.5*	*89*	*90*
10	NTs	**2**	0.4	0.5	34	88
11	NTs	**1**	1	0.5	0	n.d.
12	O[c]	**10**	20	3	31	52
13	O[c]	**10**	10	3	71	47
14	O[c]	**10**	5	3	77	44
15	O[c]	**10**	1	3	11	n.d.
16	O[c]	**10**	1	24	89	41
17	O[c]	**5**	5	3	21	54
18	O[c]	**5**	10	3	65	48

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

Table 3
The effect of the counterion using catalyst **1d**



2a: X = NTs
4a: X = O

3a: X = NTs
5a: X = O

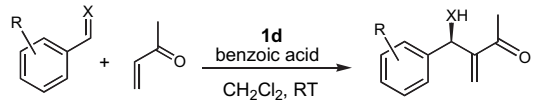
Entry	X	Acid	Conv.[a] [%]	ee[b] [%]
1	NTs	Acetic acid	20	−60[d]
2	NTs	Acetic acid	21	78
3	NTs	Phenylphosphinic acid[e]	82	60
4	NTs	2-Naphtholic acid	20	89
5	NTs	2-Fluorobenzoic acid	34	88
6	NTs	Benzoic acid	36	90
7	O[c]	Acetic acid	33	49
8	O[c]	Phenylphosphinic acid	0	n.d.
9	O[c]	2-Naphtholic acid	42	46
10	O[c]	Benzoic acid	21	54

[a] Calculated by ^{1}H NMR spectroscopy after 30 min of reaction.
[b] Determined by chiral HPLC analysis.
[c] The loading of the catalyst was 5 mol % with 5 mol % acid additive in ether for 3 h.
[d] Reaction time was 3 h with **TF-1** as the catalyst at 10 mol % with 10 mol % acid additive.
[e] Reaction time was 24 h.

showed disparate levels of sensitivity to the counterion variation. The counterion variation displayed less effect on enantioselectivity in the generic MBH reaction than its aza counterpart. This observation suggests that for this trifunctional approach, the cooperativity between the catalyst and the counterion is crucial for enantioselectivity and highly dependent on the nature of the Brønsted acid of the trifunctional catalyst.

The substrate scope of catalyst **1d** was investigated last using a representative set of aryl imines and aryl aldehydes (Table 4). These electrophiles **2** and **4** bear both electron rich and deficient substituents at *ortho*, *meta*, and *para* positions of the aromatic ring.

Table 4
The substrate scope of catalyst **1d** at 2–10 mol % loading



2: X = NTs
4: X = O

3: X = NTs
5: X = O

Entry	R	X	Cat. [mol %]	Time [h]	Yield[a] [%]	ee[b] [%]
1	*p*-NO_2 (**2a**)	NTs	2	2	92 (**3a**)	86[c]
2	*p*-Br (**2b**)	NTs	2	12	92 (**3b**)	81
3	*o*-Cl (**2c**)	NTs	5	12	96 (**3c**)	54
4	*p*-Me (**2d**)	NTs	5	36	93 (**3d**)	70[c]
5	*m*-NO_2 (**2e**)	NTs	2	2	97 (**3e**)	86
6	*o*-OMe (**2f**)	NTs	5	36	91 (**3f**)	60
7	*p*-NO_2 (**4a**)	O	10	6	73[d] (**5a**)	47
8	*p*-Me (**4b**)	O	10	24	—[e]	—

[a] Isolated yield.
[b] Determined by chiral HPLC analysis.
[c] Scale-up reaction at 1 mmol of imine.
[d] Calculated by ^{1}H NMR spectroscopy.
[e] No conversion by ^{1}H NMR spectroscopy.

As **1d** is a very active catalyst, the reactions were performed at 2–5 mol % loading for the aza-MBH reactions and 10 mol % for the generic MBH reactions. In some cases (Table 4, entries 1 and 4), the reactions were performed at a relatively large scale to investigate the process utility of this system. Comparable to the observations made with **TF-1** in the aza-MBH reactions, catalyst **1d** is generally tolerant of substituted aryl imines except the *ortho*-substituted ones (Table 4, entries 3 and 6). The catalyst is robust in scaled-up reactions with excellent isolated yields. However, the enantioselectivity of the scaled up reaction is slightly lower (86% ee vs 90% ee) compared to that in the small-scale test reaction. For the generic MBH reaction, the activity of catalyst **1d** is limited by the reactivity of the aryl aldehyde, as the more electron rich aryl aldehyde did not result in any conversion. It is worth noting that while ineffective, **1d** did not lead to formation of side products, which is markedly more chemospecific compared to other bifunctional catalysts that lead to complex reaction mixtures with electron rich aryl aldehydes.[11]

3. Conclusions

In summary, new enantioselective trifunctional catalysts **1b–e** were synthesized and investigated in generic and aza-MBH reactions. The activity of these catalysts requires acid activation, as seen with previous trifunctional systems.[5,6] In the case of **1d**, a lower loading of catalyst and acid additive unexpectedly improved enantioselectivity for both the generic and aza-MBH test reactions. More importantly, the counterion effect of this new series was found to differ significantly from that in previous series of trifunctional catalyst, suggesting that the counterion effect requires cooperativity from the Brønsted acid functionality for asymmetric induction. This will serve as an important design principle in the development of next generation catalysts. Catalyst **1d** was also amenable to reaction processes on larger scales with low loading levels at 2–5 mol % for the aza-MBH reactions with good enantioselectivity. While its activity for the generic MBH reactions is limited in scope, **1d** exhibited a high level of catalytic chemospecificity without converting the starting material to unwanted products.

4. Experimental section

4.1. 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 F_{254} aluminum 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 parts per million using chloroform as the internal reference (^{1}H, 7.26 ppm, ^{13}C, 77.09 ppm for $CDCl_3$). All spectra were processed using Bruker TOPSPIN (1.4) and MestRec 4.9.9.6. Infrared spectra were taken on a Perkin–Elmer paragon 1000PC FTIR spectrometer. Optical rotations were measured at 21 °C on a P1010 digital polarimeter (Jasco, Japan). High resolution mass analysis was provided by University of Illinois, Urban-Champaign USA.

4.2. General procedure for the preparation of *N*-tosyl aldehydes 7 and 13

To a solution of amino alcohol (500 mg, 4.06 mmol) and pyridine (401 μL) in $CHCl_3$ (15 mL) was slowly added a solution of 4-toluenesulfonyl chloride (860 mg, 4.51 mmol) in $CHCl_3$ (4.3 mL). After stirring at room temperature for 2 h the reaction was concentrated in vacuo, redissolved in EtOAc, and washed with saturated aqueous NH_4Cl. The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo to give the crude (*N*)-sulfonamide alcohol, which was used immediately without further purification. To a solution of crude alcohol in CH_2Cl_2 (20 mL) was added manganese dioxide (2.82 g, 32.5 mmol). After stirring at room temperature for 1 h, the reaction was filtered through a pad of Celite and the filtrate was concentrated in vacuo. The crude product was purified by flash chromatography on silica gel (petroleum ether/EtOAc, 3:1) to afford purified aldehydes **7** and **13**.

*4.2.1. 3-N-Tosylbenzaldehyde (**7**).* Yield: 916 mg, 82% over two steps; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.37 (s, 3H), 7.23 (d, J=8.1 Hz, 2H), 7.36 (br s, 1H), 7.42 (m, 2H), 7.57 (m, 1H), 7.61 (t, J=4.3 Hz, 1H), 7.70 (d, J=8.1 Hz, 2H), 9.91 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.0, 121.8, 126.8, 127.1, 127.7, 130.3, 130.5, 136.1, 137.8, 138.2, 144.8, 192.0; IR (KBr, cm^{-1}) 3454, 3167, 3064, 2975, 2924, 2854, 1673, 1586, 1504; HRMS (ESI) [M+H$^+$]: 276.0693, calcd for $(C_{14}H_{14}NO_3S)^+$: 276.0694.

*4.2.2. 2-N-Tosylbenzaldehyde (**13**)*[7]. Yield: 1.016 g, 91% over two steps; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.36 (s, 3H), 7.16 (t, J=7.6 Hz, 1H), 7.24 (d, J=8.5 Hz, 2H), 7.51 (t, J=7.7 Hz, 1H), 7.59 (d, J=7.7 Hz, 1H), 7.69 (d, J=8.4 Hz, 1H), 7.76 (d, J=8.5 Hz, 2H), 9.83 (s, 1H), 10.78 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.0, 118.2, 122.4, 123.3, 125.6, 127.7, 130.2, 136.2, 136.5, 140.4, 144.6, 195.4; APCI [M+H$^+$]: 276, calcd for $(C_{14}H_{14}NO_3S)^+$: 276.

4.3. Preparation of 2-hydroxy-3-*N*-tosyl benzaldehyde 10

To a solution of 3-amino-2-methoxybenzoic acid **8** (1.0 g, 5.98 mmol) in MeOH (10 mL) was added thionyl chloride (1.74 mL) slowly at to 0 °C. After refluxing for 3 h, the reaction was cooled to room temperature, quenched with saturated aqueous $NaHCO_3$, and extracted three times with EtOAc. The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting oil was dissolved in THF (20 mL) and was added to a suspension of lithium aluminum hydride (241 mg, 6.3 mmol) in THF (23 mL) at −78 °C. The reaction was allowed to come to room temperature and left to stir for 4 h. The reaction was quenched with saturated aqueous Na_2SO_4 (1.5 mL) and dried over solid Na_2SO_4 (1 g). The mixture was filtered through a pad of Celite and washed with MeOH (50 mL). The filtrate was concentrated to yield the crude amino alcohol, which was used immediately without further purification of

characterization. This crude amino alcohol was transformed into 3-*N*-tosyl-2-methoxybenzaldehyde **9** as described for the preparation of aldehydes **7** and **13**.

*4.3.1. 3-N-Tosyl-2-methoxybenzaldehyde (**9**).* Yield: 420 mg, 23% over four steps; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.35 (s, 3H), 3.62 (s, 3H), 7.17 (t, J=8.0 Hz, 1H), 7.23 (d, J=8.4 Hz, 2H), 7.51 (dd, J_1=7.8, J_2=1.6 Hz, 1H), 7.71 (d, J=8.4 Hz, 2H), 7.81 (dd, J_1=8.0, J_2=1.6 Hz, 1H), 10.15 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.9, 64.9, 125.4, 125.8, 126.0, 127.6, 129.3, 130.3, 131.8, 136.4, 144.9, 152.4, 189.2; IR (KBr, cm^{-1}) 3455, 3267, 1686, 1592, 1538; HRMS (ESI) [M+H$^+$]: 306.0789, calcd for $(C_{15}H_{16}NO_4S)^+$: 306.0800.

To a solution of 3-*N*-tosyl-2-methoxybenzaldehyde **9** (100 mg, 0.326 mmol) in CH_2Cl_2 (8 mL) was added boron tribromide (307 μL, 3.26 mmol) dropwise at −78 °C. After stirring at −78 °C for 1 h, the reaction was diluted with ether, warmed to room temperature, and quenched with H_2O. The product was extracted with EtOAc. The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (petroleum ether/EtOAc, 2:1) to afford 3-*N*-tosyl-2-hydroxybenzaldehyde **10**.

*4.3.2. 2-Hydroxy-3-N-tosyl benzaldehyde (**10**).* Yield: 77.8 mg, 82%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.34 (s, 3H), 6.96 (t, J=7.7 Hz, 1H), 7.04 (br s, 1H), 7.18 (d, J=8.2 Hz, 2H), 7.29 (d, J=8.0 Hz, 1H), 7.66 (d, J=8.2 Hz, 2H), 7.82 (d, J=8.2 Hz, 2H), 9.78 (s, 1H), 11.12 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.9, 120.5, 120.6, 126.2, 127.6, 127.9, 130.0, 136.4, 144.5, 151.7, 196.8; IR (KBr, cm^{-1}) 3339, 3258, 3050, 1666, 1594; HRMS (ESI) [M+H$^+$]: 292.0634, calcd for $(C_{14}H_{14}NO_4S)^+$: 292.0644.

4.4. Preparation of 2-*N*-methylcarbamate benzaldehyde 12

To a solution of 2-aminobenzyl alcohol **11** (500 mg, 4.06 mmol) and potassium carbonate (5.6 g, 40.6 mmol) in THF/H_2O (20 mL, 2:1 v/v) was added methyl chloroformate (470 μL, 6.09 mmol) dropwise at 0 °C. After stirring at room temperature for 1 h, the reaction was quenched with H_2O, extracted with EtOAc, and washed with brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo to give the crude *N*-protected alcohol, which was used without further purification. To a solution of crude alcohol in CH_2Cl_2 (20 mL) was added manganese dioxide (2.82 g, 32.5 mmol). After stirring at room temperature for 2 h, the reaction was filtered through a pad of Celite, washed with EtOAc. The filtrate was concentrated in vacuo and the crude aldehyde was purified by flash chromatography on silica gel (petroleum ether/EtOAc, 1:2) to afford 2-*N*-methylcarbamate benzaldehyde **12**.

*4.4.1. 2-N-Methylcarbamate benzaldehyde (**12**)*[10]. Yield: 669 mg, 92%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.80 (s, 3H), 7.16 (t, J=7.7 Hz, 1H), 7.59 (t, J=8.3, 1H), 7.64 (d, J=7.4 Hz, 1H), 8.45 (d, J=8.5 Hz, 1H), 9.90 (s, 1H), 10.60 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 52.8, 118.7, 121.8, 122.4, 136.4, 141.7, 154.6, 195.5; APCI [M+H$^+$]: 180, calcd for $(C_9H_{10}NO_3)^+$: 180.

4.5. Preparation of catalyst 1b

To a mixture of (***S***)-**MAP** oxide (0.1 mmol) and **12** (0.1 mmol) was added tetraethylortho silicate (200 μL) at room temperature. The reaction mixture was refluxed overnight (14 h), cooled, and diluted with absolute ethanol/acetonitrile (1 mL; 1:1). The solution was cooled to 0 °C and then $NaBH_4$ (1 mmol) was added in three portions and stirred at room temperature for 6 h. The mixture was quenched with dropwise addition of water, and the organic phase was extracted with ethyl acetate (three times). The combined organic phases were washed with brine, dried over anhydrous magnesium sulfate, and concentrated under vacuum. This crude product was redissolved in chloroform (1 mL), cooled to 0 °C, and treated with dropwise addition of TMSI (0.1 mmol). The reaction was warmed to 40 °C and stirred for 2 h, quenched with methanol (1 mL), and diluted with dichloromethane (5 mL). The organic phase was washed with water and brine, dried over anhydrous magnesium sulfate, and concentrated under vacuum. This crude phosphine oxide was reduced as previously reported[5] to give catalyst **1b** as a white foam.

*4.5.1. Catalyst **1b**.* Yield: 25 mg, 42% over four steps; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.27 (t, J=5.4 Hz, 1H), 3.74 (br s, 2H), 4.02 (d, J=13.5 Hz, 2H), 6.49 (d, J=8.0 Hz, 1H), 6.57 (d, J=8.5 Hz, 1H), 6.62 (t, J=7.5 Hz, 2H), 6.89 (d, J=7.4 Hz, 1H), 6.94 (t, J=7.7 Hz, 1H), 6.98–7.05 (m, 3H), 7.09–7.19 (m, 5H), 7.23–7.36 (m, 6H), 7.43 (d, J=8.5 Hz, 1H), 7.48 (t, J=7.3 Hz, 1H), 7.77 (d, J=8.0 Hz, 1H), 7.83–7.93 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 47.4, 114.3, 116.2, 117.7, 118.5, 122.4, 123.4, 124.7, 126.5, 126.6, 127.2, 127.5, 127.9, 128.2, 128.5, 128.6, 128.7, 128.9, 129.0, 129.1, 130.1, 130.2, 130.9, 133.4, 133.7, 134.0, 134.1, 134.4, 134.6, 137.7, 138.4, 142.0, 144.1; ^{31}P NMR (162 MHz, $CDCl_3$) δ −11.7; IR (KBr, cm^{-1}) 3428, 3370, 3049, 2852, 1619, 1596; ESI [M+H$^+$]: 588.2081, calcd for $(C_{39}H_{31}N_2P)^+$: 588.2092; $[\alpha]_D^{21}$ −6.8 (*c* 1.0; $CHCl_3$).

4.6. General procedure for the preparation of catalysts 1c–e

To a mixture of (***S***)-**MAP** (0.1 mmol) and aldehyde (0.1 mmol) was added tetraethylortho silicate (200 μL) at room temperature. The reaction mixture was refluxed overnight (14 h), cooled, and diluted with absolute ethanol/acetonitrile (1 mL; 1:1). The solution was cooled to 0 °C and then $NaBH_4$ (0.15 mmol) was added in one portion and stirred at room temperature for 1 h. The mixture was quenched with dropwise addition of water, and the organic phase was extracted with ethyl acetate (three times). The combined organic phases were washed with brine, dried over anhydrous magnesium sulfate, and concentrated under vacuum. Catalysts **1c** and **1d** were subject to flash chromatography on silica gel (eluent petroleum ether/ethyl acetate) and catalyst **1e** preparative TLC to afford purified catalysts **1c**–**e** as off-white solids.

*4.6.1. Catalyst **1c**.* Yield: 60 mg, 84%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.22 (s, 3H), 3.65 (t, J=5.9 Hz, 1H), 3.96 (d, J=16.5 Hz, 2H), 6.16 (br s, 1H), 6.59 (s, 1H), 6.65 (d, J=8.4 Hz, 1H), 6.81 (t, J=9.1 Hz, 2H), 6.93–7.33 (m, 18H), 7.44–7.55 (m, 4H), 7.73 (d, J=8.7 Hz, 2H), 7.90 (dd, J=8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.8, 47.5, 113.8, 116.7, 116.8, 119.7, 120.3, 122.2, 123.8, 124.6, 126.6, 126.8, 126.9, 127.3, 127.5, 127.7, 128.2, 128.5, 128.6, 128.7, 128.8, 128.9, 129.0, 129.8, 129.9, 130.0, 131.2, 133.2 133.3, 133.7, 133.8, 133.9, 134.0, 134.5, 134.6, 134.7, 136.5, 137.2, 137.8, 137.9, 138.0, 138.5, 138.6, 142.0, 142.3, 143.7, 144.1; ^{31}P NMR (162 MHz, $CDCl_3$) δ −12.0; IR (KBr, cm^{-1}) 3424, 3050, 2923, 2854, 2284, 1597, 1511; ESI [M+H$^+$]: 713.2393, calcd for $(C_{46}H_{37}N_2O_2PS)^+$: 712.2392; $[\alpha]_D^{21}$ −31.9 (*c* 1.0; $CHCl_3$).

*4.6.2. Catalyst **1d**.* Yield: 61 mg, 86%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.40 (s, 3H), 3.26 (t, J=4.3 Hz, 1H), 3.58 (dd, J_1=13.4, J_2=4.3 Hz, 2H), 6.68 (d, J=8.5 Hz, 1H), 6.82 (d, J=7.5 Hz, 1H), 6.94–7.07 (m, 5H), 7.10–7.45 (m, 18H), 7.54 (t, J=8.3 Hz, 1H), 7.78 (d, J=8.3 Hz 1H), 7.86–7.98 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.0, 47.8, 114.7, 119.5, 119.6, 123.2, 124.0, 125.0, 125.6, 126.4, 127.0, 127.3, 127.8, 128.1, 128.3, 128.6, 129.0, 129.1, 129.2, 129.8, 130.0, 130.3, 130.6, 133.3, 133.4, 133.7, 133.9, 134.0, 134.2, 134.3, 134.5, 136.8, 137.4, 137.5, 137.7, 137.8; ^{31}P NMR (162 MHz, $CDCl_3$) δ −12.1; IR (KBr, cm^{-1}) 3419, 3052, 2923, 2854, 1620, 1597, 1512; ESI [M+H$^+$]: 713.2388, calcd for $(C_{46}H_{37}N_2O_2PS)^+$: 713.2392; $[\alpha]_D^{21}$ −15.6 (*c* 1.0; $CHCl_3$).

*4.6.3. Catalyst **1e**.* Yield: 59 mg, 81%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.00 (s, 3H), 3.35 (br s, 1H), 3.71, (s, 2H), 6.67 (d, J=7.8 Hz, 1H), 6.75

(t, J=7.8 Hz, 1H), 6.81 (d, J=8.5 Hz, 1H), 6.94–7.02 (m, 6H), 7.09–7.40 (m, 13H), 7.42 (dd, J_1=8.5, J_2=2.7 Hz, 1H), 7.49–7.57 (m, 3H), 7.83 (t, J=7.8 Hz, 2H), 7.93 (d, J=8.2 Hz, 2H), 8.84 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.3, 48.8, 115.1, 120.0, 121.3, 123.0, 123.8, 124.4, 125.0, 125.3, 125.5, 125.6, 126.9, 127.0, 127.1, 127.5, 127.6, 128.0, 128.4, 128.5, 128.6, 128.7, 129.0, 129.1, 129.2, 129.3, 129.5, 129.6, 130.1, 130.3, 132.9, 133.0, 133.2, 133.4, 133.5, 134.1, 134.2, 136.5, 142.7, 143.6, 147.5, 147.8, 153.7, 157.9, 165.5; ^{31}P NMR (162 MHz, $CDCl_3$) δ −12.5; IR (KBr, cm^{-1}) 3424, 3050, 2922, 2853, 2284, 1618, 1596, 1512; ESI [M+H$^+$]: 729.2342, calcd for $(C_{46}H_{37}N_2O_3PS)^+$: 729.2341; $[\alpha]_D^{21}$+2.4 (*c* 1.0; $CHCl_3$).

4.7. General procedure for the Morita/Baylis/Hillman reaction

Scale-up aza-MBH reactions for **3a** *and* **3d**: *N*-Tosylimine (1.0 mmol), phosphine (2 mol%, 0.02 mmol for **3a** or 5 mol%, 0.05 mmol for **3d**) benzoic acid (1 equiv to phosphine), and MS 3 Å (200 mg) were combined under N_2. DCM (3.5 mL) was added followed by distilled methyl vinyl ketone (MVK) (3.0 mmol) dropwise. The reaction mixture was stirred until completion. The solvent was evaporated and the crude mixture was purified by silica gel flash chromatography (petroleum ether/ethyl acetate) and subjected to chiral HPLC for the ee analysis.

*Smaller scale aza-MBH reactions***3b**, **3c**, **3e**, *and* **3f**: *N*-Tosylimine (0.2 mmol), phosphine (5 mol%, 0.01 mmol or 2 mol%, 0.004 mmol) benzoic acid (1 equiv to phosphine), and MS 3 Å (40 mg) were combined under N_2. DCM (0.7 mL) was added followed by distilled methyl vinyl ketone (MVK) (0.6 mmol) dropwise. The reaction mixture was stirred until completion. The solvent was evaporated and the crude mixture was purified by silica gel flash chromatography (petroleum ether/ethyl acetate) and subjected to chiral HPLC for the ee analysis.

*4.7.1. 3-((4-Nitrophenyl)(tosylamino)methyl)but-3-en-2-one (**3a**)*[5]. Yield: 344 mg, 92%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.14 (s, 3H), 2.39 (s, 3H), 5.34 (d, J=9.3 Hz, 1H), 6.05 (d, J=9.4 Hz, 1H), 6.08 (s, 1H), 6.12 (s, 1H), 7.22 (d, J=8.0 Hz, 2H), 7.32 (d, J=8.6 Hz, 2H), 7.63 (d, J=8.1 Hz, 2H), 8.02 (d, J=8.7 Hz, 2H); ESI [M+Na$^+$]: 397, calcd for $(C_{18}H_{18}N_2O_5SNa)^+$: 397; HPLC: Chiralpak AD column; λ=254 nm; eluent: hexane/isopropanol=80:20. Flow rate: 1.0 mL/min; t_{minor}=22.3 min, t_{major}=28.5 min; ee%=86%.

*4.7.2. 3-((4-Bromophenyl)(tosylamino)methyl)but-3-en-2-one (**3b**)*[5]. Yield: 75 mg, 92%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.15 (s, 3H), 2.41 (s, 3H), 5.21 (d, J=9.0 Hz, 1H), 5.73 (d, J=9.0 Hz, 1H), 6.05 (s, 2H), 6.09 (s, 1H), 6.98 (d, J=8.5 Hz, 2H), 7.23 (d, J=8.2 Hz, 2H), 7.31 (d, J=8.5 Hz, 2H), 7.62 (d, J=8.5 Hz, 2H); ESI [M+Na$^+$]: 430, calcd for $(C_{18}H_{18}BrNO_3SNa)^+$: 430; HPLC: Chiralpak AD column; λ=254 nm; eluent: hexane/isopropanol=80:20. Flow rate: 0.7 mL/min; t_{minor}=16.7 min, t_{major}=18.8 min; ee%=81%.

*4.7.3. 3-((2-Chlorophenyl)(tosylamino)methyl)but-3-en-2-one (**3c**)*[5]. Yield: 70 mg, 96%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.19 (s, 3H), 2.36 (s, 3H), 5.70 (d, J=8.7 Hz, 1H), 5.85 (d, J=8.7 Hz, 1H), 6.12 (s, 1H), 6.14 (s, 1H), 7.04–7.13 (m, 2H), 7.16 (d, J=8.2 Hz, 2H), 7.21 (m, 1H), 7.29–7.33 (m, 1H), 7.62 (d, J=8.2 Hz, 2H); ESI [M+Na$^+$]: 386, calcd for $(C_{18}H_{18}ClN_2O_3SNa)^+$: 386; HPLC: Chiralpak AD column; λ=230 nm; eluent: hexane/isopropanol=80:20. Flow rate: 0.7 mL/min; t_{minor}=18.1 min, t_{major}=20.6 min; ee%=54%.

*4.7.4. 3-((4-Methylphenyl)(tosylamino)methyl)but-3-en-2-one (**3d**)*[5]. Yield: 319 mg, 93%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.15 (s, 3H), 2.26 (s, 3H), 2.41 (s, 3H), 5.23 (d, J=8.4 Hz, 1H), 5.57 (d, J=8.4 Hz, 1H), 6.02 (s, 2H), 6.96 (d, J=8.1 Hz, 2H), 7.01 (d, J=8.2 Hz, 2H), 7.23 (d, J=8.1 Hz, 2H), 7.65 (d, J=8.2 Hz, 2H); ESI [M+Na$^+$]: 366, calcd for $(C_{19}H_{21}NO_3SNa)^+$: 366; HPLC: Chiralpak AD column; λ=254 nm; eluent: hexane/isopropanol=80:20. Flow rate: 0.7 mL/min; t_{minor}=16.5 min, t_{major}=18.1 min; ee%=70%.

*4.7.5. 3-((3-Nitrophenyl)(tosylamino)methyl)but-3-en-2-one (**3e**)*[5]. Yield: 75 mg, 97%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.17 (s, 3H), 2.40 (s, 3H), 5.33 (d, J=9.4 Hz, 1H), 5.93 (d, J=9.4 Hz, 1H), 6.11 (s, 1H), 6.16 (s, 1H), 7.23 (d, J=8.2 Hz, 2H), 7.40 (t, J=8.0 Hz, 1H), 7.57 (d, J=8.0 Hz, 2H), 7.64 (d, J=8.2 Hz, 2H), 7.87 (m, 1H), 8.03 (d, J=8.2 Hz, 1H); ESI [M+Na$^+$]: 397, calcd for $(C_{18}H_{18}N_2O_5SNa)^+$: 397; HPLC: Whelk-O1 column; λ=230 nm; eluent: hexane/isopropanol=80:20. Flow rate: 0.7 mL/min; t_{minor}=41.5 min, t_{major}=45.4 min; ee%=86%.

*4.7.6. 3-((2-Methoxyphenyl)(tosylamino)methyl)but-3-en-2-one (**3f**)*[5]. Yield: 65 mg, 91%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.18 (s, 3H), 2.34 (s, 3H), 5.59 (d, J=9.3 Hz, 1H), 5.91 (d, J=9.3 Hz, 1H), 6.09 (s, 1H), 6.13 (s, 1H), 6.67 (d, J=8.4 Hz, 1H), 6.73 (t, J=7.4 Hz, 1H), 7.08 (d, J=7.4 Hz, 2H), 7.12 (d, J=8.4 Hz, 2H), 7.58 (d, J=8.4 Hz, 2H); ESI [M+Na$^+$]: 382, calcd for $(C_{19}H_{21}NO_4SNa)^+$: 382; HPLC: Whelk-O1 column; λ=230 nm; eluent: hexane/isopropanol=80:20. Flow rate: 0.7 mL/min; t_{minor}=64.5 min, t_{major}=72.6 min; ee%=60%.

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Supplementary data

Supplementary data for this article (NMR spectra of aldehydes **7**, **10**, **12**, and **13** and catalysts **1b**–**1e**) can be found. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2010.05.007. This data include MOL files and InChIKeys of the most important compounds described in this article.

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