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Bifunctional Catalysis

A General Asymmetric Formal Synthesis of Aza-Baylis–Hillman Type Products under Bifunctional Catalysis

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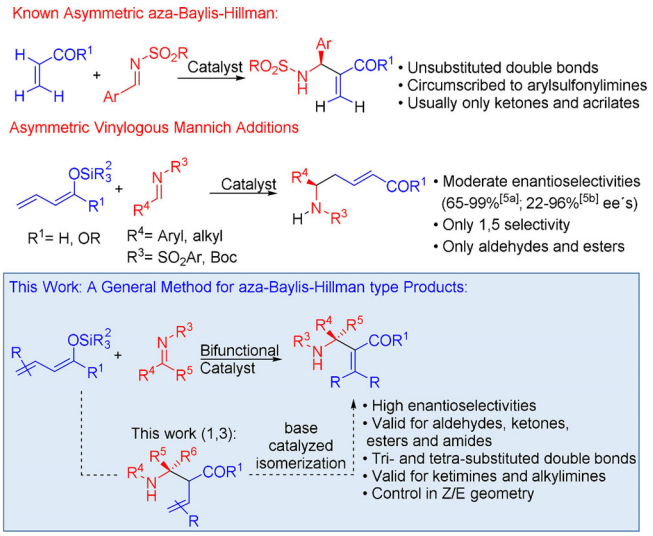
Abstract: A new organocatalytic strategy for the synthesis of enantioenriched aza-Baylis–Hillman type products via a frustrated vinylogous reaction is presented. This process proceeds under mild conditions with good yields, completed *Z/E* selectivity and excellent enantioselectivities. Moreover, easy derivatizations of the final products led to important building blocks of organic synthesis such as 1,3-aminoalcohols and Lewis base catalysts.

Carbon–carbon bond formation is one of the most important reactions in organic chemistry, especially the Csp^2–Csp^3 bonds. In this area, the asymmetric aza-Baylis–Hillman reaction (aza-BHR),[1] represents the most straightforward methodology for the synthesis of chiral allylic amines, which have been used as starting materials or as building blocks for the synthesis of different pharmaceuticals and natural products.[2] Even though this is a well-known reaction, only a few examples in the asymmetric field have been reported and most of these are related to the use of non-substituted double bonds and ketones and esters as EWGs. Since the pioneering asymmetric aza-Baylis–Hillman reaction published by Shi and co-workers using tosylimines,[3] excellent and brilliant asymmetric organocatalyzed examples have been shown by Masson and Zhu,[4a–c] Hatakeyama,[4d] Sasai,[4e,f] and Jacobsen,[4g,h] as well as asymmetric metal catalysis reported in the works of Shibata[4i] and Shibasaki,[4j] amongst others.[4k,l] All these examples have shown that the reaction can only take place with non-substituted double bonds and mostly with ketone and esters (e.g. acrylates or vinylmethyl ketones; top, Scheme 1). The lack of reactivity of the mono-β-substituted and β,β-disubstituted double bonds makes the synthesis of these enantioenriched tri- and tetra-substituted double bonds with different electron-withdrawing groups in the Baylis–Hillman reaction difficult. In addition, most of these examples have employed aryl-tosylimines as the starting material, in which alkyl imines or ketimines were unreactive, or led to moderate enantioselectivities.[4]



Scheme 1. Known aza-BHR and the present work.

More recently, List and Carretero's groups have shown elegant organocatalytic and metal-catalyzed methods, respectively, to functionalize the 1,5-positions of silyldienolate derivatives through a vinylogous Mukaiyama–Mannich reaction (Scheme 1, middle).[5] These remarkable examples showed that final aldehydes and esters can be selectivity funcionalized at the 1,5-positions from moderate to good enantioselectivies. The orbital coefficients and electrophilic susceptibility are mainly responsible for this reactivity[6] provoking the observed 1,5-nucleophilic attack. Very recently our group has shown that 1,5- can be easily switched to 1,3-funcionalization using bifunctional catalysis.[7] This provokes a dramatic change in the regioselectivity, from the 1,5 to the 1,3-functionalization. This variation enables the 1,3-addition of silyl-dienol ethers to nitroalkenes for the synthesis of tri- and tetra-substituted double bonds in Rauhut–Currier type products. It would be highly desirable if a catalyst could change to the 1,3-selectivity, and the double bond of the intermediate obtained could be isomerized, leading to Baylis–Hillman type products, which are excellent building blocks for the synthesis of complex molecules (bottom, Scheme 1). In this work, for the first time the addition of silyl-dienol ethers to imines, catalyzed by bifunctional catalysts to obtain any kind of aza-Baylis–Hillman products with high *ee* values is achieved. In addition, a rational mechanistic pathway based on mechanistic experiments is presented.

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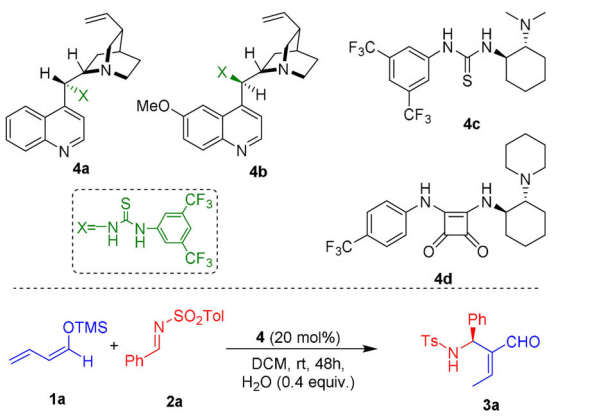
Firstly, we studied the reaction of the silyl-dienol ether **1a** with tosylimine **2a**, and different thiourea and squaramide bifunctional catalysts **4a–d** (Table 1). All the catalysts **4a–d** showed full conversion in the presence of 0.4 equivalents of water. However, Takemoto's catalysts **4c** showed the best enantioselectivity (entry 3). Then, different solvents were studied (entries 5–8), decreasing the reactivity and the enantioselectivity compared to dichloromethane using catalyst **4c**.

Table 1. Optimization of reaction conditions and catalyst for the aza-BHR.[a]

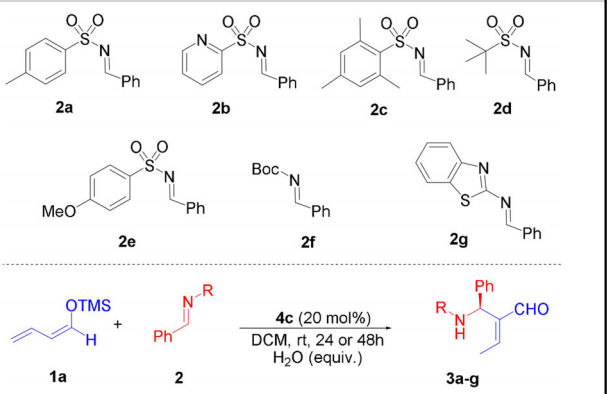


Entry	Catalyst (20 mol%)	Solvent	*ee* [%][b]	Conversion [%][c]
1	**4a**	DCM	20	100
2	**4b**	DCM	46	100
3	**4c**	DCM	50	100
4	**4d**	DCM	28	100
5	**4c**	HFB	42	46
6	**4c**	DCE	44	70
7	**4c**	MeCN	30	55
8	**4c**	THF	49	86

[a] All the reactions were performed in 0.1 mmol scale in 1.0 mL solvent. [b] Determined by SFC chromatography. [c] Determined by ^{1}H NMR analysis of the crude mixture after 48 hours. HFB = hexafluorobenzene, DCE = 1,2-dichloroethane.

In view of these moderate results, we investigated different imines **2a–g** (Table 2). When pyridylsulfonylimine **2b**[8] was used, a moderate enantioselectivity was found (entry 2), whereas the other bulkier imines such as **2c** and **2d** gave a lower conversion and worse enantioselectivities (entries 3 and 4). The use of a sulfonyl group with a electron-donanting group such as **2e** did not improve the results (entry 5) and Boc-imine **2f** did not afford the desired product (entry 6). All these imines (**2a–2e**) have a moderate capability of forming a hydrogen bond with Takemoto's catalyst **4c** because the sulfonyl group weakens the availability of the lone pair on the nitrogen (C=N:). Therefore, we hypothesized that a more hydrogen coordinated imine such as **2g**[9] would increase the enantiomeric excess. Pleasantly, the reaction of imine **2g** led to the final product **3g** with the highest enantiomeric excess (>99% *ee*, entry 7) with a moderate conversion of 67% due to the lower reactivity of this imine compared with the sulfonylimines. In order to increase the conversion, we studied the influence of different quantities of water (entries 8–10). We determined that 4.5 equivalents of water were needed to obtain a full conversion after 24 hours. When a water free reaction was carried out only 7% conversion was obtained (entry 12) and the use of 1.5 and 3 equivalents did not afford full conversions after 24 h (entries 8 and 9). The amount of catalyst was reduced to 10 mol% with the same result but with a slightly longer reaction time of 48 h (entry 11).

Table 2. Different imines for the aza-BHR.[a]

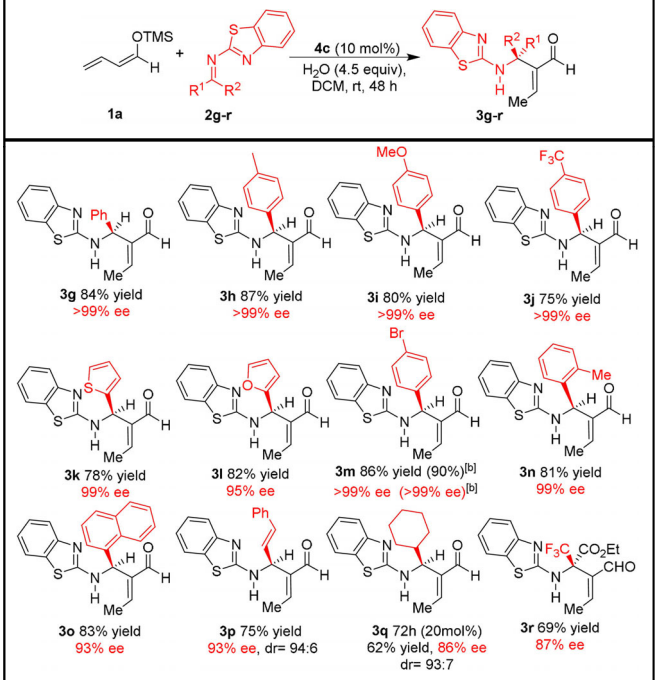


Entry	Imine	Water [equiv]	*ee* [%][b]	Time [h]	Conversion [%][c]
1	**2a**	0.4	50	48	100
2	**2b**	0.4	53	48	100
3	**2c**	0.4	n.d.	48	22
4	**2d**	0.4	12	48	61
5	**2e**	0.4	48	48	46
6	**2f**	0.4	–	48	n.r.
7	**2g**	0.4	>99	48	67
8	**2g**	1.5	>99	24 (48)	22 (51)[d]
9	**2g**	3	>99	24 (48)	58 (100)[d]
10	**2g**	4.5	>99	24	100
11[e]	**2g**	**4.5**	**>99**	**48**	**100**
12	**2g**	–	n.d.	48	7

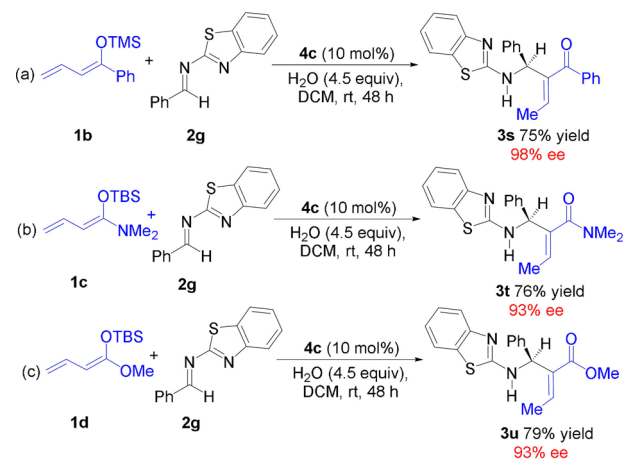
[a] All the reactions were performed in 0.1 mmol scale in 1.0 mL solvent. [b] Determined by SFC chromatography. [c] Determined by ^{1}H NMR analysis of the crude mixture after 24 or 48 hours. [d] Conversion after 48 h in brackets. [e] 10 mol% of catalyst **4c**.

Under these optimized conditions the scope of the reaction using different imines **2** (Table 3) and silyl reagents **1** (Schemes 2 and 3) was carried out. Different electron-donating groups (*p*-Me, *p*-MeO **2h**, **2i**) or electron-withdrawing groups (*p*-CF_3, **2j**) worked with excellent enantioselectivies (all examples; >99% *ee*). Heteroaromatic groups such as thienyl or furyl moieties also afforded aza-BHR products with good to excellent enantioselectivities (95–99% *ee*, **2k**,**l**). Bromo (**2m**), and the bulkier substituents such as **2n** and **2o** were also tolerated under these conditions, providing **3m**, **3n** and **3o** with good *ee* values. The reaction was scale up (1.2 mmol) with the bromo derivative **3m** with a similar yield and enantioselectivity (result between brackets). A double bond such as imine **2p** or an alkyl imine such as **2q** also led to the corresponding adducts (**3p** and **3q**) under these catalytic conditions, which are difficult to obtain with the standard aza-BHR, with a slightly lower *Z*/*E* selectivity (dr = 94:6 and 93:7). In addition, the more challenging ketimine **2r** was also studied and afforded the

Table 3. Scope of the aza-BHR with different imines **2g–r**.[a]



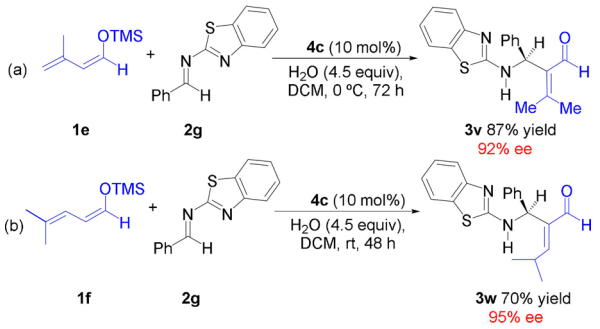
[a] Conditions: **1** (0.3 mmol), **2** (0.1 mmol), **4c** (10 mol%) and H_2O (4.5 equiv) in DCM (0.3 mL) at RT after 48 h. [b] Reaction carried out at 1.2 mmol scale.



Scheme 2. Synthesis of ester, ketone and amide aza-BH type products.

optically enriched quaternary center product **3r** in a good yield and enantioselectivity.

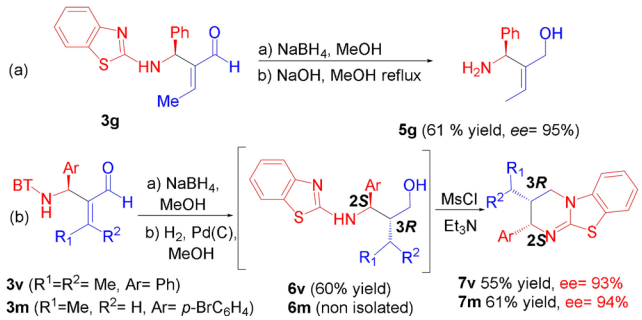
The reaction also tolerated different groups at the α-position to the TMSO group at the silyl-dienol ether **1b–d** (Scheme 2). Therefore, the phenyl group led to the ketone **3s** with an excellent enantioselectivity (equation a), whereas the use of enolate **1c** afforded the amide **3t** in an excellent yield and enantioselectivity (equation b) which cannot be activated under the standard aza-Baylis–Hillman reaction conditions due to the low electrophilic character of the double bond. In a similar manner, the silyl reagent **1d** reacted with the imine **2g** to give the ester **3u** with excellent *ee* and yield (equation c).



Scheme 3. Different substitution at the silyl-dienol ethers for the synthesis of tri and tetrasubstituted aza-BHR type products.

In addition, the substitution at the 4 and 5-positions of the silyl-enolether (**1e** and **1f**) led to the β,β-disubstituted **3v** and β-monosubstituted **3w** adducts, respectively in good yields and enantioselectivies (Scheme 3, equations a and b). It is remarkable that it is not possible to obtain these enantio-enriched adducts using other methods described in the literature.

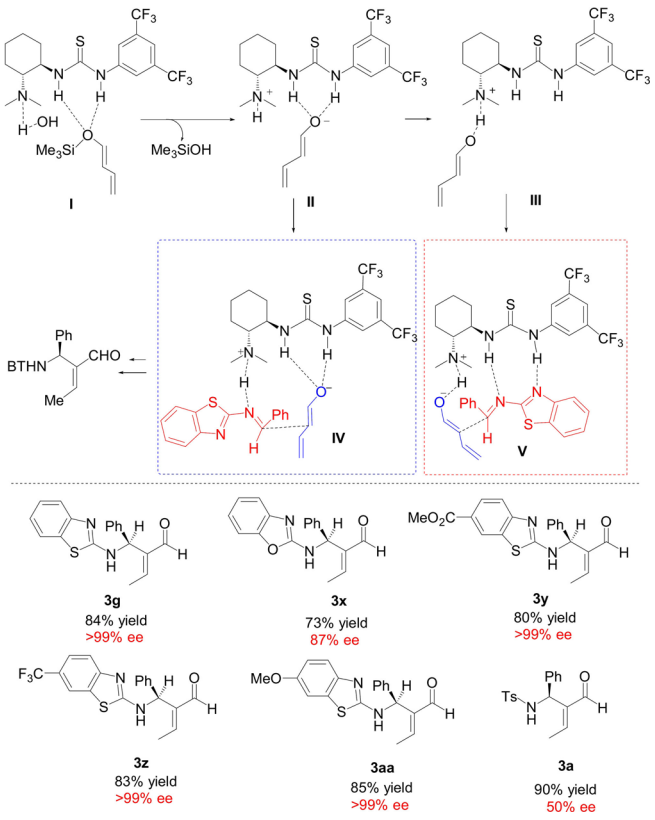
Finally, we carried out different transformations of adducts obtained to synthesize privileged compounds. Thus, the benzothiazole group could be easily removed after reduction of the aldehyde **3g** and subsequent hydrolysis in basic conditions, giving the 1,3-aminoalcohol **5g** (equation a, Scheme 4),



Scheme 4. Derivatization of tri- and tetra-substituted aza-BHR type products (BT = benzothiazole).

which can be used as precursor for a large number of pharmaceutical products.[2] Moreover, our methodology also provided the possibility of synthetize privileged structures such as catalysts **7v** and **7m** that have been previously used as Lewis super-bases (equation b, Scheme 4).[10] The procedure started with the reduction of **3v** and **3m** to give **6v** and **6m**, which after cyclization afforded the catalysts **7v** and **7m**. The absolute configuration of Baylis–Hillman products **3** were assigned by correlation with known compounds in the literature (**6v** and **7v**)[10b] and were determined as 2*S* and 3*R*, whereas the configuration of the double bond was determined as *E* by n.O.e. NMR experiments (see Supporting Information).

Based on our previous calculations[7] and the additional experimental data obtained in this work (see below), a proposed mechanism is outlined in Scheme 5. A water molecule can easily attack the Si center (**I**) and further evolution of this



Scheme 5. Different substitution at the benzothiazole core to test the influence on the enantioselectivity of the reaction (BT = benzothiazole).

system implies firstly a proton transfer from the water molecule to the amine nitrogen, followed by a nucleophilic attack of the resulting hydroxide to the silicon atom. After the hydrolysis step, two intermediates before the coordination to the imine can be postulated (**II** and **III**). The hydrogen bond formation with the imine **2** leads to the intermediates **IV** or **V**. Intermediate **V** is based on Takemoto's model,[11] in which the coordination with the electrophile, in this case the imine **2a**, is taking place through the thiourea moiety. By contrast, the intermediate **IV** is based on the well-known Pápai's model.[12] Such pre-organization is characterized by the coordination of the electrophile through the ammonium salt, whereas the nucleophile can be strongly stabilized by the thiourea group. In order to differentiate between these two models (Takemoto's and Papai)[11,12] different imines **2** with different aromatic residues at the benzothiazole group were synthesized (bottom, Scheme 5).

The use of different benzothiazole imines with EWG and EDGs were not found to have any influence of the enantioselectivity, and in all the cases high enantioselectivities, >99% for products **3y**, **3z** and **3aa** were obtained. Therefore, the coordination of the benzothiazolinic nitrogen to the catalyst is implausible since the influence of these EWG and EDGs has a scarce influence in this *para*-positon. Conversely, the use of imines with a strong electron-withdrawing character such as the tosyl group, provoke a dramatic decrease in the enantioselecitivy (**3a**, *ee* = 50%). In addition, when a sulfur atom is substituted by one with a stronger electronegativity such as oxygen (benzo[*d*]oxazole **3x**), the resultant enantioselectivity is also lower (*ee* = 87%). These last two results indicate that the key coordination hydrogen bond is the lone pair of the iminic nitrogen (C=N:), indicating that the more plausible mechanism is Pápai's model, in which the dienolate is strongly stabilized by the thiourea moiety[13] and the imine is coordinated to the ammonium ion group (see **IV**). In addition, the different size of the tosyl and benzothiazole group could also have an important role. Then, after the addition (C–C bond formation) and isomerization of the double bond gives the final aza-Baylis–Hillman products with high enantioselectivity.

In conclusion, a new organocatalytic strategy for the synthesis of enantioenriched aza-Baylis–Hillman type products via a frustrated vinylogous reaction is presented. This process proceeds under mild conditions with good yields and excellent enantioselectivities. The reaction tolerates a large numer of different imines, and the synthesis of tri- and tetra-substituted aza-Baylis–Hillman type products. Moreover, easy derivatizations of the final products led to important building blocks in organic synthesis such as 1,3-aminoalcohols and Lewis superbase catalysts. A mechanism for this reaction based on the experimental data has been proposed.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: asymmetric synthesis · Baylis–Hillman reaction · bifunctional catalysis · silyl-enol ethers · thiourea

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[13] In our previous studies (Ref. [7]), we calculated both models (Takemoto and Pápai's mechanisms) in the reaction of silyl-dienol ethers with nitroalkenes. However, according to the obtained energy values, we described that both models were plausible and only a difference of nearly 5 kcal mol^{-1} between the energy of these two models were found.

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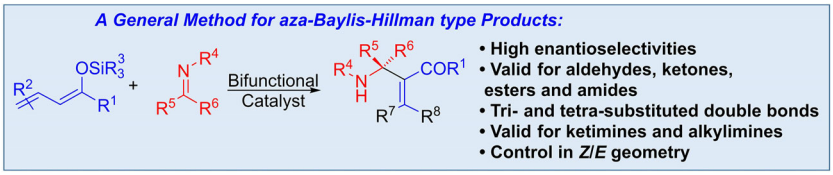

With frustration to success: A new organocatalytic strategy for the synthesis of enantioenriched aza-Baylis–Hillman type products via a frustrated vinylogous reaction is presented.