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A halide-initiated aza-Baylis–Hillman reaction: generation of unnatural amino acids

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ABSTRACT

A series of allenic ketones react with a glyoxylate-derived imine in the presence of $MgBr_2$ through an aza-Morita–Baylis–Hillman (MBH) reaction. The isolation of a variety of unnatural amino acids with unique allene-containing functional groups provides a conceptually new application of the aza-MBH. The reaction scope and preliminary mechanistic investigations are discussed.

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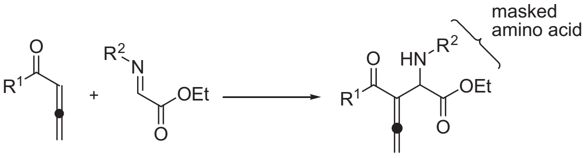
The aza-Morita–Baylis–Hillman (MBH) reaction is a carbon–carbon bond-forming reaction that provides access to highly functionalized molecules from inexpensive starting materials.[1–4] Of specific interest is the application of the aza-MBH reaction in the synthesis of unnatural amino acids, which are valuable substrates for natural product synthesis[5] and biochemical investigations.[6] Currently, the synthesis of unnatural amino acids through a Baylis–Hillman reaction is limited to those that produce β-amino esters,[1,7] β-homoserine, and aspartic acid derivitives.[8] The aza-MBH has not been shown to be a general method to synthesize α-amino acids. We had envisioned developing a method by which an allenic ketone and a glyoxylate-derived imine would react through an aza-MBH reaction to yield masked unnatural amino acids (Scheme 1).

To date there are only a few reports[9] of an aza-MBH reaction between allenoates and imines and these reactions lead primarily to cycloaddition products. Specifically, the aza-MBH reaction between an N-tosylated imine and 2,3-butadienoates have produced pyrrolidine, azetidine, and dihydropyridine derivatives when catalyzed by phosphine, 1,4-diazabicyclo[2.2.2]octane (DABCO) or *N*,*N*-4-dimethylaminopyridine (DMAP), respectively.[10,11] Recently, a Letter by Guan et al. showed that a DABCO-catalyzed aza-MBH reaction between an allenoate and *N*-Boc imines produced 'normal' aza-MBH products.[12] In addition to nitrogen- and phosphorus-based catalysts, halide-containing catalysts (TMSI,[13] $MgBr_2$,[14] and AlI_3[15]) have been used in Morita–Baylis–Hillman-like reactions between aldehydes and propargyl esters.[16]

Despite their utility, there are no reports of aza-MBH reactions between glyoxylate-derived imines and allenic ketones. In addition, aza-MBH reaction between allenoates and imines has been limited to those only using Lewis bases as catalysts. Herein, we present a halide-initiated aza-MBH reaction that results in an atom-economical synthesis of a variety of unnatural amino acids with unique allene-containing functional groups. During an initial screening with acetylallene (**1**) and sulfonylimino acetate (**2**) in the presence of $MgBr_2$, alkylation at either the γ- or the α-position of the allene was observed to yield both the halogenated α,β-unsaturated ketone **4** and the 1,1-disubstituted allene **5**, respectively (Table 1). Formally product **5** is the result of an aza-Baylis–Hillman reaction and product **4**, while not formally an aza-Baylis–Hillman product, may arise from an intermediate generated in the first step of the Baylis–Hillman pathway. Both products contain a masked amino acid moiety and can undergo additional manipulations to generate highly useful substrates. Notably, the product **4** contains a vinyl bromide that can be easily manipulated by using cross-coupling reactions to yield advanced compounds for synthesis.[17–20]



Scheme 1.

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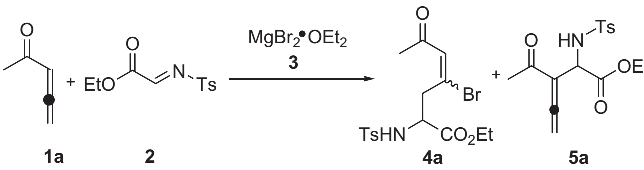
Table 1
Optimization of concentration and substrate ratio[a]



Entry	Ratio (**1a**:**2**:**3**)	**1a** (M)	**4a**[b,d] (%)	**5a**[b] (%)	Mol ratio[c] (**4a**:**5a**)
1	1:1:1	0.5	7	31	1:4.6
2	1:1:0.5	0.5	14	44	1:3.2
3	1:1:0.25	0.5	10	21	1:2
4	1:1:0.5	1	8	49	1:6.2
5	1:1:0.5	0.25	7	23	1:3.1
6	1:2:0.5	0.5	18	73	1:4.2
7	2:1:0.5	1	9	30	1:3.1
8	1:2:0.5	1	10	49	1:4.8

[a] All reactions were run at 0 °C for 30 min in a CH_2Cl_2/THF (1:1) solvent mixture.
[b] Yield of isolated product. Yield based on allene **1**.
[c] Ratios determined by ^1H NMR analysis of the crude reaction mixture.
[d] Based on ^1H NMR analysis of compound **4a**, it was determined there was an overall yield of 2% of an α-alkylated product containing a terminal vinyl bromide which was later identified as **6a** (see below). Ts = *p*-toluenesulfonyl.

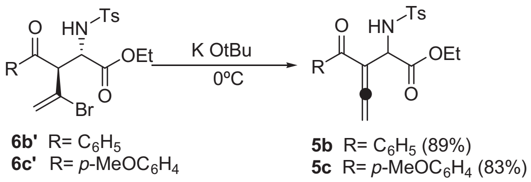
Optimization of the yield of each product, through the variation of several reaction parameters, is shown in Table 1.

The reaction proceeds best when $MgBr_2\cdot OEt_2$ is used in substoichiometric amounts (compare entries 2 and 3 to entry 1 in Table 1): half of an equivalent of $MgBr_2\cdot OEt_2$ leads to a moderate yield of products. Running the reaction at a higher concentration (1.0 M) generates the product **5** in moderate yield; notably, the **4**:**5** ratio is 1:6.2 (Table 1, entry 4). When the concentration was decreased to 0.25 M, lower product yields were obtained and the ratio of **4**:**5** approached 1:1 (Table 1, entry 5). Lastly, the number of equivalents of allene and imine were varied, and a significant increase in yield, especially for **5**, was observed when the number of equivalents of the imine were doubled (Table 1, entry 6). In contrast, an excess of allene did not enhance the yield of the reaction (Table 1, entry 7). Increasing the concentration and simultaneously doubling the number of imine equivalents did not give the anticipated increase in yield (Table 1, entry 8).

By using the optimized reaction conditions identified above (2 equiv imine, 0.5 equiv $MgBr_2\cdot OEt_2$, 0.5 M, and 0 °C for 30 min), reaction parameters, such as reaction time and temperature were varied to additionally optimize the reaction conditions. The reaction proceeded at lower temperatures (−78 °C); however the yields (~40% for **5**) were still low relative to the reaction at 0 °C, even after extending the reaction time to 4 h. Warming the reaction mixture to −45 °C did not seem to greatly affect the product yields of the reaction, even with stirring the reaction mixture for an additional 30 min. Furthermore, allowing the reaction to proceed for a longer time at 0 °C did not increase the product yields significantly and heating the reaction to room temperature resulted in a decrease in both the yield and product ratio, presumably because of product degradation (see Supplementary data).

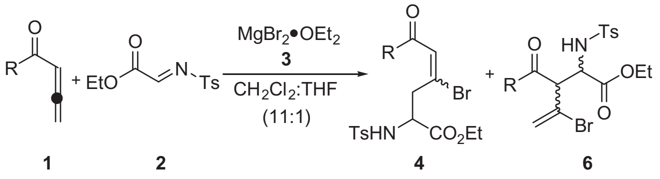
Next, the scope of the reaction was evaluated with respect to the allene substrates. Ketoallenes bearing different groups (R) were subjected to the optimized reaction conditions (Table 2). Interestingly, the γ-substituted product **4** was isolated along with a by-product that was identified as the α-substituted product **6a**′. Compound **6a**′ was presumed to be a precursor to the anticipated α-substituted product **5**, thereby suggesting that either steric or electronic effects were precluding the elimination of Br in **6a**′ to form **5**. This observation was consistent for all the allenic ketone substrates tested (Table 2).

We found that the phenyl ketoallene (**1b**) underwent the reaction to yield **4b** and a diastereomeric mixture of **6b** and **6b**′. This reaction required a longer reaction time to give similar results to those found with the methyl ketoallene (**1a**; Table 2, entries 1 and 2). The original optimization reactions with **1a** did not produce **6a**′ (see Table 1), however, for the larger-scale reaction here, product **6a**′ was isolated. When an electron-donating group (OCH_3) was



Scheme 2.

Table 2
Scope of the reaction



Entry	**1** (R)	Ratio (allene:**2**:**3**)	*T* (°C)	*t* (h)	Yield **4**[a] (%)	Yield **6**[a] (%)	dr of **6** [e]
1[b,c]	**1a** (Me)	1:1:0.5	0	1	14 (**4a**)	44 (**6a**, **6a**′)	1:3.2
2[d]	**1b** (Ph)	1:2:1	0	4	7 (**4b**)	63 (**6b**, **6b**′)	1:2.5[f]
3	**1c** (*p*-$MeOC_6H_4$)	1:1:0.5	0	4	5 (**4c**)	45 (**6c**, **6c**′)	1:2.75
4	**1d** (*p*-BrC_6H_4)	1:2:1	0	2	5 (**4d**)	53 (**6d**, **6d**′)	1:2.12
5	**1e** (cyclohexyl)	1:2:1	0	4	15 (**4e**)	19 (**6e**, **6e**′)	1:2.17
6	**1f** (OEt)	1:1:0.5	25	2.5	—	—	

[a] Yield of isolated product.
[b] 17% of allene **5a** isolated.
[c] Reaction run on a 250 mg scale.
[d] H_2O work-up was used.
[e] Compound **6** was isolated as a mixture of stereoisomers. As denoted **6** is the (*R*/*R*, *S*/*S*) mixture and **6**′ is the (*R*/*S*, *S*/*R*) mixture. See Supplementary data.
[f] The diastereomers were resubmitted to reaction conditions at room temperature overnight and no change in the ratio was observed.

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