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Organocatalyzed Asymmetric Vinylogous Allylic–Allylic Alkylation of Morita–Baylis–Hillman Carbonates with Olefinic Azlactones: Facile Access to Chiral Multifunctional α-Amino Acid Derivatives

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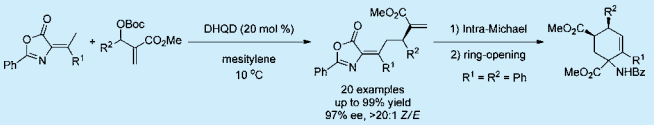
Supporting Information

ABSTRACT: Vinylogous reactivity of olefinic azlactones was realized through the development of a chiral amine-catalyzed highly stereoselective allylic–allylic alkylation with Morita–Baylis–Hillman carbonates. The Lewis base activation of electrophile and Brønsted base activation of nucleophile were efficiently combined, giving access to multifunctional acyclic α-amino acid derivatives in a highly stereocontrolled manner. The synthetic utility of these versatile synthons was further demonstrated by the facile synthesis of protected cyclic quaternary α-amino acids.



The vinylogous reaction is arguably one of the most efficient protocols to build multifunctional allylic compounds, which are widely used in organic synthesis.[1] With the rapid advance of catalytic science in the past few decades, substantial progress has been made in this area with new reactivity of compounds accomplished and more complex products produced.[2] While various nucleophiles have been investigated in catalytic asymmetric vinylogous reactions, the vinylogous reactivity of azlactones, a kind of important α-amino acid precursors,[3] was not revealed until Jørgensen et al. first reported an amino-catalytic vinylogous Michael addition to enals and 2, 4-dienals in 2013.[4a] Recently, our group developed a hydrogen-bond-directed hetero-Diels–Alder reaction of olefinic azlactones with isatins to furnish spirooxindole dihydropyranones.[4b] Considering the huge potential of this privileged scaffold in the synthesis of complex heterocycles and unnatural amino acids, the development of new transformations utilizing the vinylogous reactivity of azlactones, especially in a catalytic asymmetric manner, is still highly desirable.

On the other hand, asymmetric allylic substitution represents another powerful strategy to incorporate allyl functionality selectively into valuable chiral targets. While transition-metal complex catalyzed asymmetric allylic substitution employing various nucleophilic or electrophilic allylic precursors has been intensively investigated,[5] a complementary strategy with the use of Morita–Baylis–Hillman (MBH) adducts as electronic allylic precursors under the catalysis of nucleophilic amine or phosphine has also been highly explored in the past decades.[6] This strategy efficiently combined Lewis base activation of electrophilic allylic precursors and Brønsted base activation of nucleophiles, thus giving rise to a broad array of synthetically useful allyl-substituted scaffolds. We hypothesized that direct coupling of vinylogous nucleophiles with MBH carbonates under the catalysis of proper nucleophilic catalysts would lead to asymmetric assembly of structurally interesting multifunctional 1,5-diene motif, which could serve as important building blocks for further elaboration. With our continuing study on practical organocatalytic methodologies toward valuable molecules,[7] herein we present the first asymmetric vinylogous allylic–allylic alkylation reaction of MBH carbonates with methyl-substituted olefinic azlactones.[8] An array of azlactone-incorporated multifunctional acyclic α-amino acid derivatives were readily synthesized in high yields with excellent diastereo- and enantioselectivities.[9] Moreover, these products were successfully transformed into densely functionalized protected cyclic quaternary α-amino acids.

We initiated the study by investigating the vinylogous allylic–allylic alkylation reaction of **2a** and **3a** in 0.5 mL toluene at 10 °C. A series of nucleophilic catalysts[10] were examined under the conditions (Figure 1), and the results are outlined in Table 1. It

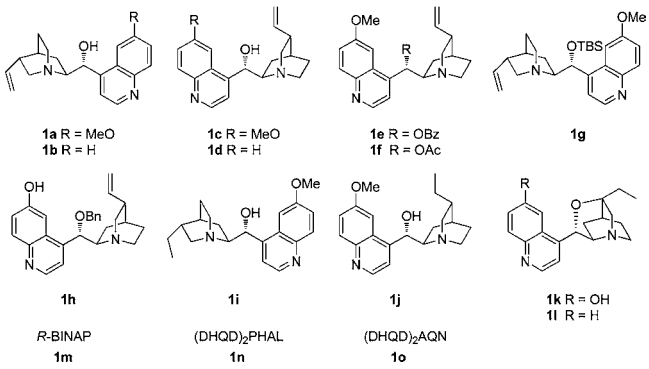


Figure 1. Nucleophilic catalysts screened.

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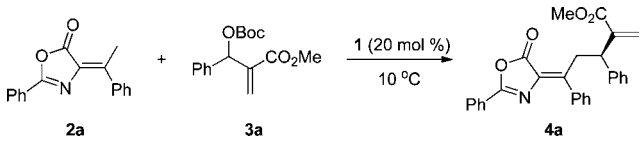
Table 1. Optimization of Reaction Parameters[a]



2a 3a 4a

entry	1	time (h)	yield[b] (%)	ee[c] (%)	Z/E[d]
1	**1a**	30	54	−44	2:1
2	**1b**	120	62	−33	4:1
3	**1c**	48	64	88	6:1
4	**1d**	216	18	87	3:1
5	**1e**	144	12	ND	ND
6	**1f**	144	14	ND	ND
7	**1g**	30	55	−42	3:1
8	**1h**	216	86	−37	4:1
9	**1i**	8	71	−12	3:1
10	**1j**	30	57	90	3:1
11	**1k**	8	93	38	2:1
12	**1l**	8	99	30	3:1
13	**1m**	72	18	−57	11:1
14	**1n**	216	61	59	3:1
15	**1o**	216	73	73	2:1
16[e]	**1j**	30	65	86	>20:1
17[f]	**1j**	30	94	89	18:1
18[g]	**1j**	72	96	93	11:1

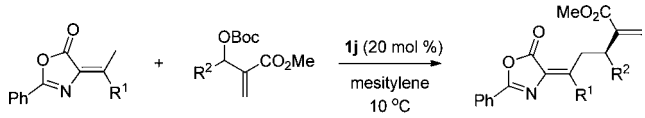
[a]Unless otherwise noted, the reaction was carried out with **2a** (0.1 mmol), **3a** (0.2 mmol), and **1** (20 mol %) in 0.5 mL of toluene at 10 °C. [b]The isolated yield of both *Z*- and *E*-isomers. [c]Determined by HPLC. [d]Determined by ^{1}H NMR. [e]The *E*-isomer of **2a** was used. [f]The reaction was carried out in 1 mL of toluene. [g]The reaction was carried out in 1 mL of mesitylene.

was found that all four cinchona alkaloids **1a−d** were able to catalyze the reaction, and the desired product **4a** was produced with moderate yield and good ee value albeit with a low *Z*/*E* selectivity (Table 1, entries 1−4). Among these cinchona alkaloids, quinidine **1c** gave the best results. However, all the modified cinchona alkaloids **1e−h** failed to give satisfactory results (Table 1, entries 5−8). We then turned to the hydrogenated analogues **1i** and **1j**, and to our delight, we found that **1j** gave a higher ee value even than **1c** albeit with a lower yield (Table 1, entries 10). The *β*-isocupreidine (*β*-ICD) **1k** and its analogue **1l** showed very high catalytic activity but gave sharply decreased ee values (Table 1, entries 11 and 12). Nucleophilic phosphine catalyst **1m** was also tested for the reaction, although it gave disappointing results (Table 1, entries 13). Nucleophilic catalysts **1n** and **1o** only gave moderate enantioselectivities and *Z*/*E* selectivity (Table 1, entries 14 and 15). In conclusion, hydroquinidine **1j** was selected as the best catalyst for the reaction.

The *E*-isomer of **2a** was also tested for the reaction, and the product was obtained with a sharply decreased ee value albeit with a much better *Z*/*E* selectivity (Table 1, entry 16). Considering that the major side reaction was probably caused by the high reactivity of **2a**, we carried out the reaction with **2a** at a lower concentration (0.1 M). To our delight, the desired product was obtained with a higher yield and *Z*/*E* selectivity albeit with a slightly decreased ee value (Table 1, entries 17). Next, different solvents were investigated with **2a** at this concentration (see the Supporting Information), and mesitylene was found to be an optimal one based on comprehensive consideration of reaction time, yield, ee value, and *Z*/*E* selectivity (Table 1, entries 18). As a summary, the optimal reaction conditions are catalyst **1j** (20 mol %), solvent mesitylene (1 mL), and reaction temperature 10 °C.

Under the optimized reaction conditions, the substrate scope of the asymmetric vinylogous allylic−allylic alkylation reaction was investigated, and the results are outlined in Table 2. A variety

Table 2. Substrate Scope of the Asymmetric Vinylogous Allylic Alkylation Reaction[a]



2 3 4

entry	R^1/ R^2	time (h)	yield[b] (%)	ee[c] (%)	Z/E[d]
1	Ph/Ph	72	96 (**4a**)	93	11:1
2[e]	Ph/Ph	72	86 (**4a**)	93	>20:1
3	2-furyl/Ph	144	97 (**4b**)	92	>20:1
4	4-$CF_3C_6H_4$/Ph	72	90 (**4c**)	92	18:1
5	2-naphthyl/Ph	96	86 (**4d**)	94	7:1
6	4-BrC_6H_4/2-BrC_6H_4	60	66 (**4e**)	93	7:1
7	Ph/4-$MeOC_6H_4$	96	96 (**4f**)	94	>20:1
8	Ph/4-$NO_2C_6H_4$	30	97 (**4g**)	87	12:1
9	Ph/4-$CF_3C_6H_4$	48	95 (**4h**)	89	>20:1
10	Ph/3-BrC_6H_4	48	95 (**4i**)	93	>20:1
11	Ph/2-MeC_6H_4	72	70 (**4j**)	94	19:1
12	Ph/3-MeC_6H_4	60	98 (**4k**)	96	7:1
13	Ph/4-MeC_6H_4	72	99 (**4l**)	96	17:1
14	Ph/4-FC_6H_4	48	85 (**4m**)	96	7:1
15	Ph/4-ClC_6H_4	30	94 (**4n**)	95	>20:1
16	Ph/1-naphthyl	72	76 (**4o**)	97	>20:1
17	Ph/4-CNC_6H_4	24	95 (**4p**)	93	>20:1
18	Ph/2-thienyl	80	71 (**4q**)	91	12:1
19	Ph/3,5-$(Br)_2C_6H_3$	48	78 (**4r**)	92	6:1
20	Ph/4-BrC_6H_4	72	80 (**4s**)	95	16:1
21	Ph/Me	144	6[d]	ND	3:1

[a]Unless otherwise noted, the reaction was carried out with **2** (0.1 mmol), **3** (0.2 mmol), and **1j** (20 mol %) in 1 mL of mesitylene at 10 °C. [b]The isolated yield of both *Z*- and *E*-isomers. [c]Determined by HPLC. [d]Determined by ^{1}H NMR. [e]The reaction was carried out with **2a** (4 mmol, 1.05g), **3a** (8 mmol, 2.34g), and **1j** (20 mol %, 260 mg) in 40 mL of mesitylene at 10 °C.

of substituted olefinic azlactones and MBH carbonates were well tolerated in this catalytic system, providing the desired products in moderate to high yields (up to 99%) with excellent enantioselectivities (up to 97%) and *Z*/*E* selectivity (up to >20:1).[11] For olefinic azlactone **2**, comparable results were obtained when the exocyclic phenyl ring was replaced with furyl and naphthyl substituents, although longer reaction times were needed (Table 2, entries 3 and 5). Better *Z*/*E* selectivity was observed when CF_3-substituted azlactone was used (Table 2, entries 4). Reaction between bromo-substituted azlactone and bromo-substituted MBH carbonate gave a moderate yield with 93% ee (Table 2, entries 6). When the exocyclic phenyl ring was replaced by a methyl group, double vinylogous allylic−allylic alkylation product with one molecule of **3** on each methyl was mainly obtained in moderate yield with excellent enantioselectivity and *Z*/*E* selectivity (Scheme 1, eq a). With respect to the MBH carbonate **3**, both electron-donating and -withdrawing substituents of the phenyl ring were compatible with this catalytic system. In contrast to the electron-withdrawing substituents,

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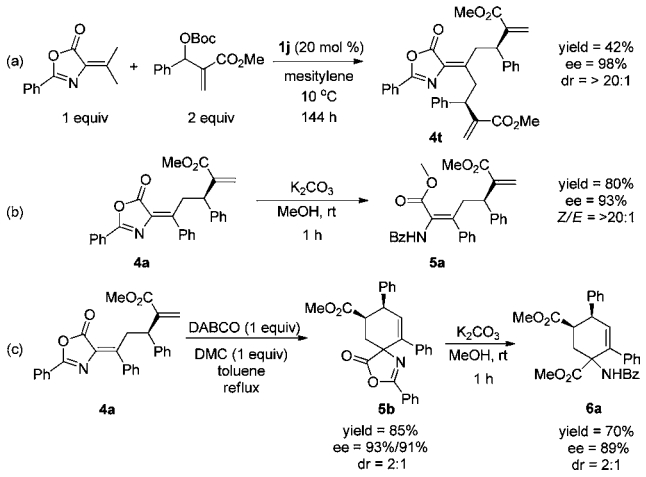
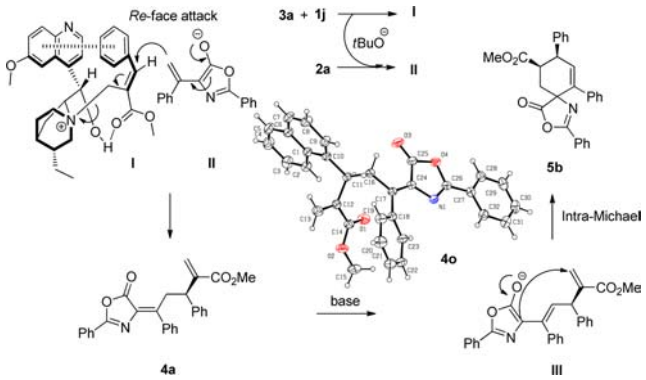
Scheme 1. (a). Double Vinylogous Allylic−Allylic Alkylation Reaction To Produce 4t. (b) Ring-Opening of 4a with MeOH To Produce the Protected α-Amino Acid 5a. (c) Synthesis of Protected Cyclic Quaternary α-Amino Acid 6a



slightly lower reactivity but higher ee values were observed with the electron-donating ones (Table 2, entries 7 and 11−13). The position of the substituents on the phenyl ring of MBH carbonates was also investigated. The ortho-substituted substrate gave lower yield than the corresponding meta- and para-substituted ones, which was probably due to its steric hindrance (Table 2, entries 11−13). The reactions of **3** with naphthyl and thienyl substituents also proceeded smoothly under the optimal conditions (Table 2, entries 16 and 18). When the MBH carbonate from the acetaldehyde was used, the corresponding product was obtained in a very low yield over a long time (Table 2, entry 21).The stereochemistry of **4o** was determined on the basis of X-ray crystallography (Scheme 2).[12]

Scheme 2. Proposed Mechanism of the Vinylogous Allylic−Allylic Alkylation Reaction and the Intramolecular Michael Reaction



To demonstrate the potential application of this methodology, we also performed a gram-scale synthesis of **4a** (Table 2, entry 2). The reaction proceeded smoothly to afford the corresponding product with excellent results (86% yield, 93% ee, >20:1 *Z*/*E*). The ring-opening reaction of **4a** with MeOH under basic conditions furnished the desired protected amino acid **5a** in high yield with excellent *Z*/*E* selectivity, while the ee value was maintained (Scheme 1, eq b). The methylene of **4a** could be deprotonated by another base and gave intermediate **III** (Scheme 2), which immediately underwent intramolecular Michael addition to produce cyclic quaternary α-amino acid derivative **5b** as a mixture of two diastereomers (Scheme 1, eq c).[13] Different bases were tested for the reaction (see the Supporting Information). The achiral base DABCO gave a higher yield albeit with a lower diastereoselective ratio than chiral cinchona alkaloids and their derivatives. The configuration of the two diastereomers of **5b** was unambiguously assigned by NOE experiments (see the Supporting Information). Under the ring-opening conditions of **4a**, protected cyclic quaternary α-amino acid **6a** could also be produced from **5b**.

Based on the experimental observation and literature reports, a plausible transition state is proposed for the vinylogous allylic−allylic alkylation reaction (Scheme 2).[14] The DHQD−MBH ester adduct **I** would be preferentially formed as the *E*-isomer in accordance with the conformational analysis of quinuclidine−MBH ester adducts by Mayr and co-workers.[14c] An intramolecular hydrogen bond between the hydroxyl group of DHQD and the ester moiety is probably the reason for the high yield and excellent stereocontrol of the reaction (Table1, entry 3 vs 5 and 6). The hydrogen bond not only activates the ester moiety to accelerate the reaction but also plays a vital role in shielding the *Si*-face of the alkene for enantioselective control. The cation intermediate **I** can also be stabilized through the π−π stacking between the quinoline moiety and phenyl ring. In the meantime, the intermediate **II** activated by *t*-BuO$^-$ prefers to attack the intermediate **I** as an s-cis conformation no matter which configuration **2a** is originally in (Table 1, entry 16). As the *Si*-face of intermediate **I** is blocked by the catalyst, the intermediate **II** would presumably approach the *Re*-face in the preferable S_N2'/anti elimination manner to give the final product and release the catalyst.

In conclusion, we have developed the first asymmetric vinylogous allylic−allylic alkylation of MBH carbonates with olefinic azlactones catalyzed by a nucleophilic amine. A series of multifunctional chiral α-amino acid derivatives were obtained in moderate to high yield (up to 99%) with excellent enantioselectivity (up to 97%) and *Z*/*E* selectivity (up to >20:1). Different manipulations of the products have been conducted to prove the synthetic potential of the disclosed methodology. Densely functionalized chiral cyclic quaternary α-amino acid derivatives could be readily obtained from the vinylogous allylic−allylic alkylation products.

■ ASSOCIATED CONTENT

Supporting Information

Additional optimization of reaction parameters, experimental procedure and characterization data for all new compounds; X-ray crystal structure data (CIF) for compound **4o**. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01066.

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Notes

The authors declare no competing financial interest.

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(11) The *Z*/*E* ratios of some products may gradually decrease in the process of column chromatography.

(12) CCDC 1045147 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(13) The product **4a** needs to be isolated before the intramolecular Michael addition. This is probably because the excess MBH carbonate after alkylation may undergo another vinylogous allylic−allylic alkylation with the product **4a** under reflux conditions, which will decrease the yield of **5b**.

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