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Organocatalytic Enantioselective Amination of Morita–Baylis–Hillman Carbonates with Masked Ammonia: A Facile Method for the Synthesis of Unprotected α-Methylene-β-Amino Esters

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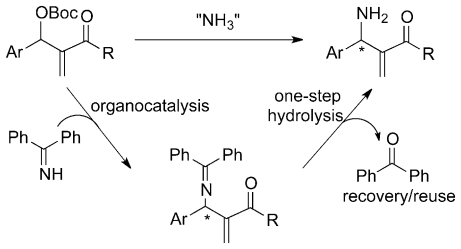
Optically active α-alkylidene-β-amino carbonyl compounds and their derivatives are highly valuable building blocks, which are widely applied in the synthesis of medicinally relevant compounds as well as complex natural products.[1] Therefore, the development of efficient methods for the synthesis of these multifunctional compounds is currently of particular significance. Giving access to valuable compounds and structural complexity, the aza-Morita–Baylis–Hillman (aza-MBH) reaction provides one of the most direct and versatile methods to these compounds.[2] However, the aza-MBH reaction remains to be restricted in enantiocontrol and substrate scope; the nucleophilic catalysts typically utilized in aza-MBH reactions may induce product racemization.[3] Furthermore, the tosyl groups commonly used as activating groups for the poorly reactive azomethine in the aza-MBH adducts were hard to remove,[4] which limited the application of amino adducts in organic synthesis.

Compared with the aza-MBH reaction, the substitution of MBH carbonates with nitrogen nucleophiles is another straightforward strategy to the synthesis of α-methylene-β-amino carbonyl compounds through a direct C–N bond formation reaction.[5] Recently, the asymmetric substitution of MBH carbonates has been established as an effective protocol in C–C bond,[6] C–O bond,[7] C–P bond[8] formation reactions and cycloaddition reactions[9] with high enantioselectivities for a broad range of substrates; however, the asymmetric amination progress was not fruitful. Cyclic imide such as phthalimide was usually employed as the nitrogen nucleophile in this procedure; however, the enantioselectivities of most reported reactions were low to moderate. Searching more suitable nitrogen nucleophiles to achieve higher enantioselectivities and unprotected α-methylene-β-amino esters through a simple operation is still a highly desirable goal.

The smallest nitrogen nucleophile, ammonia, is theoretically the optimal nitrogen nucleophile, concerning atom economy,[10] but its volatile nature, high reactivity and toxicity makes it difficult to work with in catalytic systems. Benzophenone imine, which is industrially produced by condensation of benzophenone and ammonia,[11] has previously been shown to be an appropriate ammonia equivalent in the asymmetric aza-Michael addition reaction of nitroalkenes reported by Jørgensen.[12] The unprotected β-amino nitro compounds were obtained in good yields and enantioselectivities, and the ammonia carrier benzophenone could be recovered and reused in the preparation of the starting benzophenone imine. Inspired by this elegant progress, and continuing our interest in chiral C–X (X = N, O, S, Se) bond formation reactions,[13] herein we report the organocatalytic asymmetric allylic amination reaction of MBH carbonates with benzophenone imine. High enantioselectivities (up to 99% enantiomeric excess (*ee*)) were achieved for a wide range of MBH carbonates; the optically pure unprotected α-methylene-β-amino esters were easily obtained by a one-step acidic hydrolysis protocol (Scheme 1).



Scheme 1. Organocatalytic asymmetric allylic amination of MBH carbonates with masked ammonia (benzophenone imine). Boc = *tert*-butoxycarbonyl.

Initial examination was carried out by using the MBH carbonate **2a** (1.5 equiv) and benzophenone imine **3** (1.0 equiv) as the substrates in the presence of 1,4-diazabicyclo-[2.2.2]octane (DABCO) with $MgSO_4$ (30 mg) in 1,2-dichloroethene (DCE, 0.5 mL) at room temperature.The corresponding *N*-allylic amination product **4a** was isolated in

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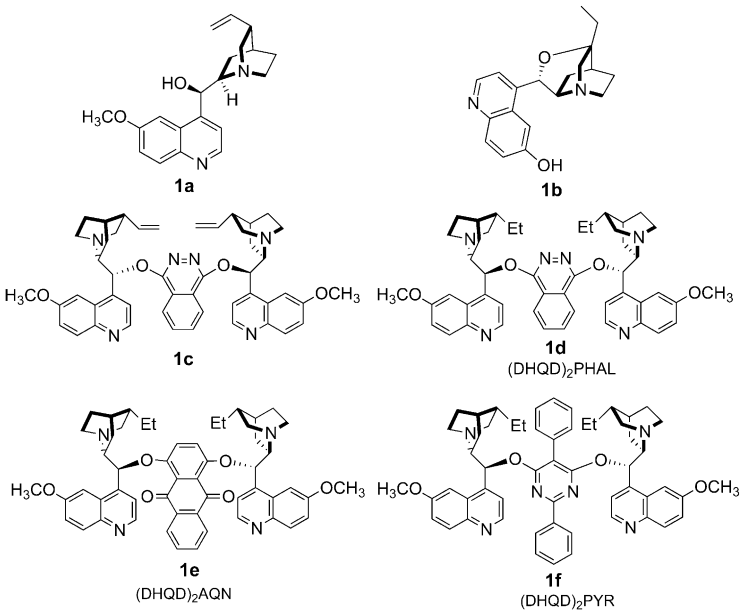
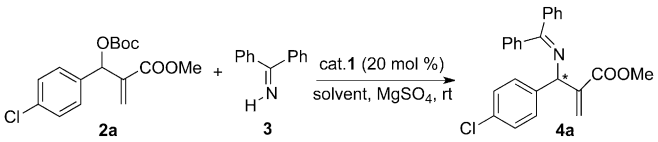


Table 1. Optimization of the reaction conditions.[a]



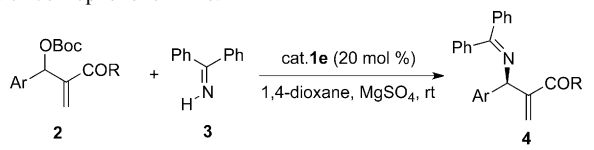
Entry	Cat.	Solvent	*t* [h]	Yield [%][b]	*ee* [%][c]
1	DABCO	DCE	48	78	–
2	**1a**	DCE	60	62	69
3	**1b**	DCE	60	76	−47[d]
4	**1c**	DCE	60	42	−35[d]
5	**1d**	DCE	60	58	84
6	**1e**	DCE	60	70	98
7	**1f**	DCE	60	74	81
8	**1e**	hexane	60	13	98
9	**1e**	CH_2Cl_2	84	44	98
10	**1e**	toluene	84	58	98
11	**1e**	xylene	84	50	98
12	**1e**	THF	60	75	98
13	**1e**	$PhCF_3$	72	52	99
14	**1e**	1,4-dioxane	60	84	99
15	**1e**	1,4-dioxane	60	65	97[e]
16	**1e**	1,4-dioxane	84	68	96[f]
17	**1e**	1,4-dioxane	96	57	94[g]

[a] The reaction was carried out with **2a** (0.15 mmol), **3** (0.10 mmol), catalyst **1** (20 mol%, 0.02 mmol) and $MgSO_4$ (30 mg) in solvent (0.5 mL) at room temperature. [b] Yield of isolated product. [c] *ee* values were determined by chiral HPLC analysis. [d] The opposite configuration. [e] The absence of $MgSO_4$. [f] 10 mol% of catalyst **1e** was used. [g] 5 mol% of catalyst **1e** was used.

78% yield (Table 1, entry 1). Encouraged by this preliminary result, we then examined the enantioselective variant in the presence of chiral tertiary amine catalysts. When catalyst **1a** was tested, the product **4a** was obtained in 62% yield with 69% *ee* (Table 1, entry 2). Then we tested other tertiary amine catalysts derived from cinchona alkaloids[14] and found that **1e** served as the best catalyst, which gave the product **4a** with 98% *ee* (Table 1, entry 6). The examination of solvent effects with catalyst **1e** revealed that 1,4-dioxane was the best reaction media for this reaction, which can significantly facilitate the reaction to produce the corresponding product in 84% yield with 99% *ee* (Table 1, entry 14). The reaction was found to be sluggish in the absence of $MgSO_4$ (Table 1, entry 15). Decreasing the catalyst loading to 10 mol% and 5 mol% had a negative impact on both the yields and the enantioselectivities (Table 1, entries 16 and 17).

Having established the optimal reaction conditions, we then examined a spectrum of MBH carbonates **2** to explore the generality of this asymmetric transformation. The reactions were conducted in 1,4-dioxane (0.5 mL) with catalyst **1e** (20 mol%) at room temperature. The results are summarized in Table 2. The position and electronic properties of the substituent on the aromatic ring had little or no effect on the enantioselectivity and all these MBH carbonates participated in this process in high efficiency (Table 2, entries 1–10). When 2-thienyl-

Table 2. Catalytic enantioselective allylic amination of MBH carbonates **2** with benzophenone imine.[a]



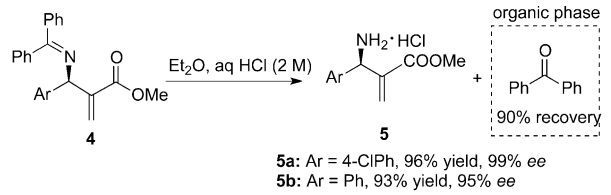
Entry	Ar	R	*t* [h]	Product	Yield [%][b]	*ee* [%][c]
1	4-ClPh	OMe	60	**4a**	84	99
2	Ph	OMe	72	**4b**	80	95
3	4-FPh	OMe	84	**4c**	78	98
4	4-BrPh	OMe	84	**4d**	75	99
5	4-NO_2Ph	OMe	72	**4e**	71	99
6	4-CF_3Ph	OMe	72	**4f**	68	97
7	4-OMePh	OMe	96	**4g**	86	98
8	4-MePh	OMe	96	**4h**	81	99
9	2-ClPh	OMe	84	**4i**	63	99
10	2-$C_{10}H_7$	OMe	84	**4j**	70	96
11	2-thienyl	OMe	96	**4k**	65	90
12	4-ClPh	OEt	84	**4l**	81	93
13	4-ClPh	OPh	84	**4m**	61	90
14	4-ClPh	OBn	84	**4n**	74	95
15	Ph	Me	144	**4o**	53	91

[a] The reaction was carried out with **2** (0.15 mmol), **3** (0.10 mmol), catalyst **1e** (20 mol%, 0.02 mmol) and $MgSO_4$ (30 mg) in 1,4-dioxane (0.5 mL) at room temperature. [b] Yield of isolated product. [c] *ee* values were determined by chiral HPLC analysis.

substituted MBH carbonate was used as the substrate, the asymmetric amination reaction could be completed with 90% *ee* (Table 2, entry 11). Further exploration of the substrate scope focused on the ester group. Different esters yielded the desired products in good yields with high enantioselectivities (Table 2, entries 12–14). MBH carbonates derived from methyl vinyl ketone (MVK) could also be transformed with a good *ee* value under the same reaction condition (Table 2, entry 15). Unfortunately, when β-alkyl-substi-

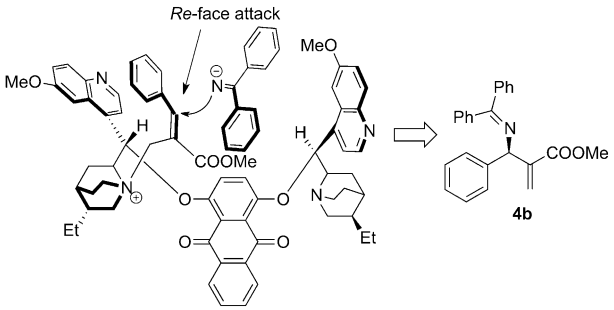
tuted MBH carbonates were tested under the optimal protocol the results were not as positive as presented above and they failed to afford the desired allylic amination products.[15]

As shown in Scheme 2, the unprotected α-methylene-β-amino esters could be easily obtained by one-step acidic hydrolysis protocol. Upon completion of the substitution step, products **4** were quickly isolated by flash column chromatography, then 2 M HCl (aq) and Et_2O were added. Isolating the aqueous phase, and subsequent removal of water as azeotrope with toluene, the hydrochloride salt of the primary β-amino esters **5** were obtained as a white solid with retained enantiopurity; the benzophenone could be recovered in 90% yield from the organic phase. The absolute configurations of product **4a** and **4b** were assigned to be *R* by chemical correlation with the corresponding described *N*-Boc-protected amines.[16] The remaining configurations of adducts **4** and salts **5a** and **5b** were assumed by analogy.



Scheme 2. One-step acidic hydrolysis protocol for the synthesis of unprotected α-methylene-β-amino esters.

On the basis of the experimental results, a plausible activation model for the *R*-selective formation of **4b** catalyzed by **1e** is outlined in Scheme 3. The MBH carbonate presumably first undergoes the Michael-type addition at the nitrogen atom of the quinuclidine to afford a cationic intermediates, the resulting complex would be preferentially formed as the *E* isomer[17] and stabilized through the π–π stacking between the quinoline moiety and phenyl ring.[18] The *Si* face of the complex is effectively blocked by the left half of the quinoline moiety, which is bonded to the MBH moiety through the N−C covalent bond. Thus the benzophenone imine anion is much more accessible to attack from the *Re* face, affording the corresponding β-amination product **4b** in the *R* configuration.



Scheme 3. Proposed transition state for the formation of β-amination product **4b**.

In summary, we have provided a highly efficient asymmetric allylic amination of MBH carbonates with masked ammonia (benzophenone imine) under the catalysis of modified cinchona alkaloids. The reaction proceeded in good yields with excellent enantioselectivities (up to 99% *ee*) for a wide range of MBH carbonates. Furthermore, the unprotected α-methylene-β-amino esters were easily obtained with retentive enantioselectivities through a one-step acidic hydrolysis protocol, and the recovered benzophenone could be reused in the preparation of the starting benzophenone imine. We believe that this methodology presented herein may potentially expand the synthetic utility of α-methylene-β-amino esters in organic chemistry and medicinal chemistry. Further synthetic application of this transformation and mechanistic studies are underway in our laboratory.

Experimental Section

General procedure for the organocatalytic asymmetric allylic amination of Morita–Baylis–Hillman carbonates with benzophenone imine: A mixture of catalyst **1e** (17.2 mg, 0.02 mmol), MBH carbonate **2a** (48.9 mg, 0.15 mmol) and $MgSO_4$ (30 mg) in 1,4-dioxane (0.5 mL) was stirred for 30 min at room temperature before the benzophenone imine **3** (18.1 mg, 0.10 mmol) was added, then the resulting mixture was stirred for another 60 h. The crude reaction mixture was diluted with ethyl acetate and then directly purified by flash chromatography on silica gel (petroleum ether/ethyl acetate PE/EA) to afford the corresponding product **4a**.

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Keywords: allylic compounds · amination · ammonia · benzophenone imine · organocatalysis · Morita–Baylis–Hillman carbonates

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