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Highly Enantioselective Aza-Baylis–Hillman-Type Reaction of α,β-Unsaturated Aldehydes with In Situ Generated *N*-Boc- and *N*-Cbz-Imines

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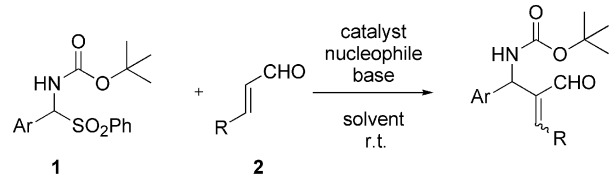
An organocatalytic highly enantioselective aza-Baylis–Hillman reaction of α,β-unsaturated aldehydes with in situ generated *N*-Boc- and *N*-Cbz-imines is presented. This novel process opens the pathway for the synthesis of β-amino carbonyl compounds bearing an α-alkylidene group under mild and simple conditions.

Introduction

The discovery of new reactions that allow complex molecular scaffolds to be built in an efficient way from readily available starting materials remains a challenging goal in organic synthesis. One of the most important tools for converting simple starting materials into densely functionalized products in a catalytic and atom-economic way is the aza-Baylis–Hillman reaction, which was first reported in 1972.[1] This type of reaction can open the way for the synthesis of β-amino carbonyl compounds bearing an α-alkylidene group, which is a versatile chiral building block for biologically important compounds.[2] Thus, the development of efficient synthetic methods for enantioselective aza-Baylis–Hillman reactions is of general interest.

Up to date, many different types of catalysts have been used for the enantioselective aza-Baylis–Hillman reaction: chiral quinidine derivatives,[2a,2b] thiourea derivatives,[3] BINOL-derived catalysts,[2f,4] the combination of proline with bases like imidazole[5] or DABCO,[6] and so on. However, all of the reported approaches have used preformed imines, which are inherently highly reactive and highly sensitive to moisture. The significantly simpler procedure involving the use of stable α-amido sulfones as imine precursors has been applied in phase-transfer-catalyzed aza-Henry-type reactions,[7] and cinchona alkaloid[8] or thiourea-cinchona alkaloid[9] catalyzed Mannich reactions of malonates. Recently, Melchiorre[10] reported an elegant TMS-diphenylprolinol-catalyzed anti-Mannich reaction of aldehydes with in situ generated *N*-Cbz and *N*-Boc imines. However, to the best of our knowledge, there are no enantioselective organocatalytic examples of aza-Baylis–Hillman-type reactions involving the use of α-amido sulfones as an imine surrogate. With respect to the above mentioned, and our previous experience,[6] we envisioned the possibility of developing an easy and direct route to aza-Baylis–Hillman adducts by the reaction of α,β-unsaturated aldehydes **2** and α-amido sulfones **1** (Scheme 1).



Scheme 1. Direct Aza-Baylis–Hillman reaction of α,β-unsaturated aldehydes with α-amido sulfones.

Results and Discussion

In initial experiments, we screened different solvents, catalysts, and base systems to achieve high enantioselectivities, diastereoselectivities, and yields. For the exploratory studies, the reaction of (*E*)-2-pentenal (**2a**) with stable α-amido sulfone **1a** catalyzed by (*S*)-proline was selected (Table 1).

To our delight, when polar aprotic solvents such as DMF, CH_3CN, or THF were used, the reaction proceeded in moderate yields (32–58%) and good enantioselectivities (up to 98%), but with low diastereoselectivity (*E*/*Z*, 1:1 to 2:1). When toluene (Table 1, Entry 4) was used as the solvent, a poor yield and moderate enantioselectivity (87%) and diastereoselectivity (1:2) were observed. Surprisingly when $CHCl_3$ was used as a solvent, we achieved very high enantioselectivity (99%), good yield (63%), and enhanced diastereoselectivity (*E*/*Z*, 4:1; Table 1, Entry 5). From other

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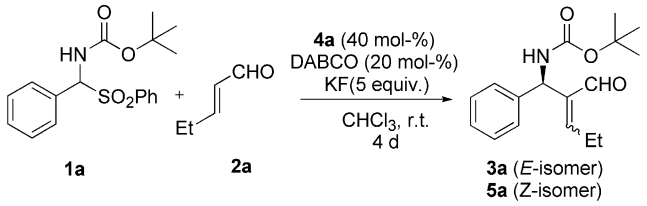
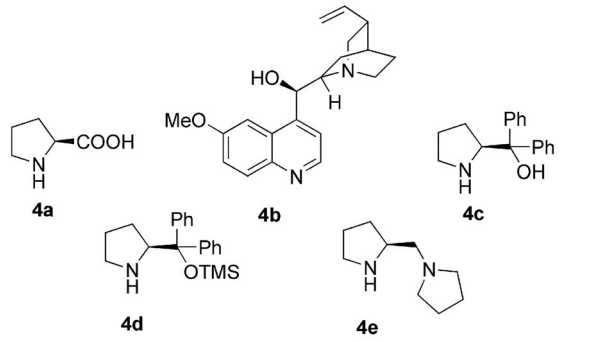
Table 1. Effects of solvents and additives on the asymmetric aza-Baylis–Hillman reaction.[a]



Entry	Solvent	Conv. [%][b]	Yield of **3a** [%][c]	Ratio of **3a**/**5a**	*ee* of **3a** [%][d]
1	DMF	full	32	2:1	86
2	CH_3CN	full	58	1:1	98
3	THF	full	52	2:3	96
4	toluene	full	36	1:2	87
5	$CHCl_3$	full	63	4:1	99
6[e]	$CHCl_3$	full	53	2:1	99
7[f]	$CHCl_3$	full	32	2:1	96

[a] Performed with α-amido sulfone **1a** (0.2 mmol), KF (1 mmol), $CHCl_3$ (1 mL), (*S*)-proline (**4a**; 0.08 mmol, 40 mol-%), DABCO (0.04 mmol), and α,β-unsaturated aldehyde **2** (0.6 mmol, 3 equiv.). [b] Determined by NMR spectroscopic analysis of the crude reaction mixture. [c] Isolated yield. [d] The *ee* values were determined by chiral HPLC analysis. [e] 1.0 equiv. of KF was used. [f] Imidazole (0.2 equiv.) was used instead of DABCO.

Table 2. Organocatalysts screened in the asymmetric aza-Baylis–Hillman reaction.[a]



Entry	Catalyst	Conv. [%][b]	Yield of **3a** [%][c]	Ratio of **3a/5a**	*ee* of **3a** [%][d]
1	**4a**	full	63	4:1	99
2	**4b**	n.r.	n.d.	n.d.	n.d.
3	**4c**	n.r.	n.d.	n.d.	n.d.
4	**4d**	full	36	4:1	50
5	**4e**	full	49	3:4	56

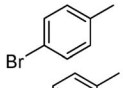
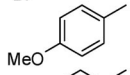
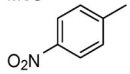
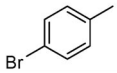
[a] Performed with α-amido sulfone **1a** (0.2 mmol), KF (1 mmol), $CHCl_3$ (1 mL), catalyst **4a**–**e** (0.08 mmol, 40 mol-%), DABCO (0.04 mmol), and α,β-unsaturated aldehyde **2** (0.6 mmol, 3 equiv.). [b] Determined by NMR spectroscopic analysis of the crude reaction mixture. [c] Isolated yield. [d] The *ee* values were determined by chiral HPLC analysis.

experiments it seems that the use of DABCO as nucleophile is more convenient than imidazole (Table 1, Entry 7) and an excess amount of KF in the reaction is crucial for enhancement of the diastereoselectivity of the reaction (Table 1, Entry 6). With other bases (K_3PO_3, Cs_2CO_3, and K_2CO_3) already screened for the generation of imines from α-amido sulfones,[7b,10] low yields (less than 21%) were obtained, but the enantioselectivity was maintained. Surprisingly, from all the reactions we only obtained compound **3a**; *Z*-isomer **5a** was not isolated after column chromatography.

Once we determined the conditions to perform the reaction, several secondary amines were screened as catalysts for the reaction. As is shown in Table 2, (*S*)-proline (**4a**) gave us the best enantioselectivity and yield (Table 2, Entry 1), whereas the use of catalysts **4d** and **4e** led to lower enantioselectivities and yields. The reaction did not proceed in the presence of cinchonidine (**4b**; Table 2, Entry 2) or (*S*)-α,α-diphenylprolinol (**4c**; Table 2, Entry 3).

Next, we screened different α,β-unsaturated aldehydes **2** and different α-amido sulfones **1** to study the scope of the reaction (Table 3). In all the examples screened, the reaction furnished the desired β-amino carbonyl compounds bearing an α-alkylidene group (**3**) in moderate yields (50–87%), good diastereoselectivity (*dr* up to 19:1), and excellent enantioselectivities (97–99 *ee*). The use of strongly electron-withdrawing substituents in the benzene ring of sulfone **1f** increased the rate of the reaction, maintained the yield of the reaction, and only slightly decreased the enantioselectivity of the reaction (Table 3, Entry 6). In contrast, when sulfone **1g** bearing a five-membered heterocyclic moiety was used, the yield and the diastereoselectivity of the

Table 3. Scope of the asymmetric aza-Baylis–Hillman reaction of α,β-unsaturated aldehydes with α-amido sulfones.[a]

Entry	R^1	R^2	R^3	Ratio of **3**/**5**[a]		Yield of **3** [%][b]	*ee* [%][c]
1	Ph	*t*Bu	Et	4:1	**3a**	63	99
2	Ph	*t*Bu	*n*Bu	3:1	**3b**	55	99
3	Ph	*t*Bu	4-butenyl	2:1	**3c**	60	97
4		*t*Bu	Et	5:1	**3d**	54	99
5		*t*Bu	Et	19:1	**3e**	51	98
6[d]		*t*Bu	Et	9:1	**3f**	50	97
7		*t*Bu	Et	19:1	**3g**	87	99
8	Ph	Bn	Et	4:1	**3h**	69	96
9		Bn	Et	10:1	**3i**	56	95

[a] Determined by NMR spectroscopic analysis of the crude reaction mixture. [b] Isolated yield. [c] The *ee* values were determined by chiral HPLC analysis. [d] Full conversion was observed within 24 h; therefore, the reaction mixture was worked up.

reaction greatly increased (Table 3, Entry 7). Besides the use of *N*-Boc sulfones we tried to explore the effect of a carbamoyl moiety on the reaction. In comparison with the Boc functionality, the reaction of *N*-Cbz sulfones **1h** and **1i** with (*E*)-2-pentenal furnished the corresponding β-amino carbonyl compounds bearing an α-alkylidene group in slightly higher yields but lower enantioselectivities (Table 3, Entries 8 and 9). Although the reaction conditions tolerate various functional groups (halogen, ether, nitro, double-bond moiety), the limitation of this reaction is in the aldehyde substrate. The reaction with aromatic α,β-unsaturated aldehydes (like cinnamic aldehyde) did not proceed.

To elucidate the structures of isolated compounds **3a**–**i**, X-ray diffraction analysis[11] of compound **3e** was performed (Figure 1). The absolute configuration of compound **3a** was ascertained by chemical correlation. Comparison with the literature data revealed that the absolute configuration of compound **3a** is (3*S*) $[a]_D$ = +80.0 (*c* = 0.6, $CHCl_3$) {ref.[6] $[a]_D$ = +68.0 (*c* = 1.0, $CHCl_3$)}.

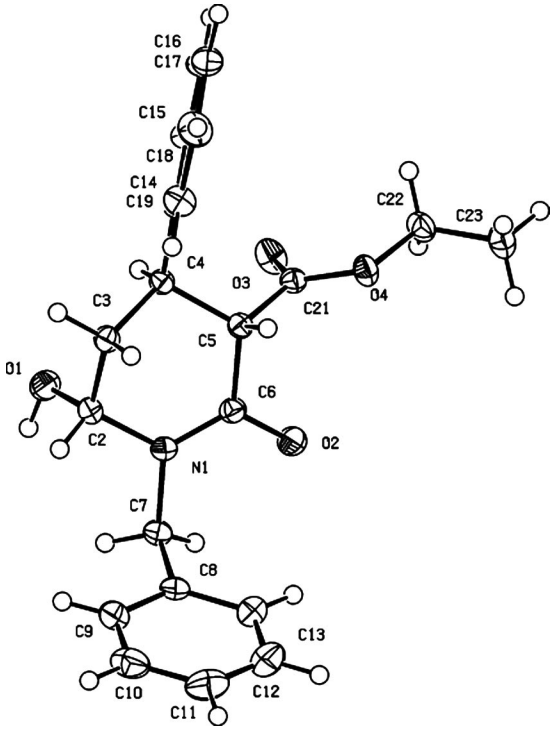
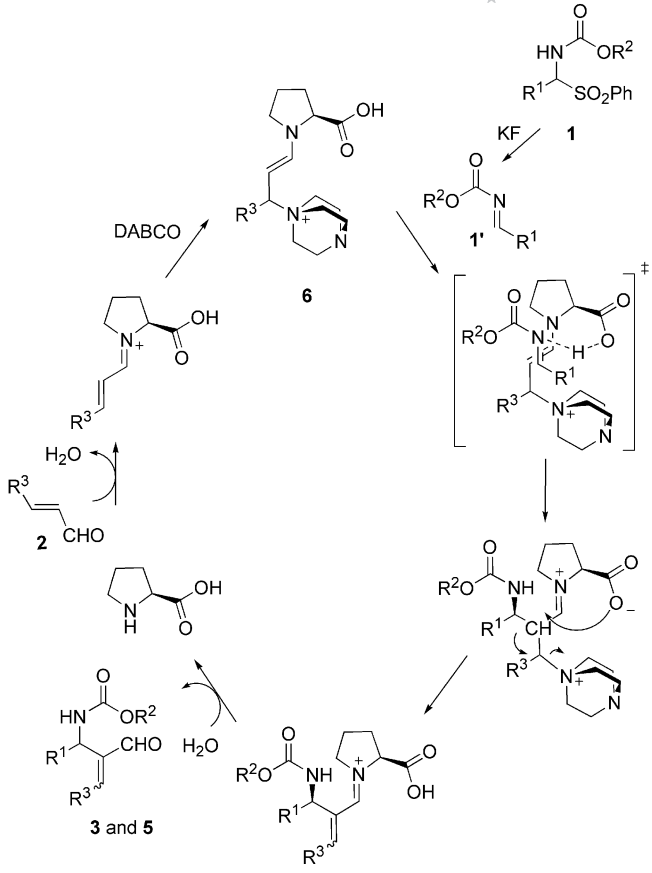


Figure 1. X-ray diffraction analysis of compound **3e**.

On the basis of the absolute configuration, the stereochemical outcome could be rationalized by the mechanistic proposal outlined in Scheme 2. Thus, enamine **6** formed from (*S*)-proline and aldehyde in the presence of a nucleophile is attacked from the *Si*-face by in situ generated imine **1′**, providing the (3*S*)-β-amino carbonyl compound. This is in accordance with the transition states of previously reported proline-catalyzed aza-Baylis–Hillman and Mannich reactions, in which *Si*-facial attack occurs.[12]



Scheme 2. Proposed mechanism of aza-Baylis–Hillman reaction of α,β-unsaturated aldehydes with α-amido sulfones.

Conclusions

In summary we have reported an organocatalytic highly enantioselective aza-Baylis–Hillman reaction of α,β-unsaturated aldehydes with in situ generated *N*-Boc and *N*-Cbz imines from the corresponding sulfones under mild and easy conditions. In contrast to other methods, it avoids working with preformed imines, which are inherently highly reactive and highly sensitive to moisture. Further elaboration of this novel transformation, mechanistic studies, and synthetic applications are ongoing in our laboratory.

Experimental Section

General: Chemicals and solvents were either purchased puriss p.A. from commercial suppliers or purified by standard techniques. For thin-layer chromatography (TLC), silica gel plates Merck 60_{F254} were used, and compounds were visualized by irradiation with UV light and/or by treatment with a solution of phosphomolybdic acid (25 g), $Ce(SO_4)2{\cdot}H_2O$ (10 g), followed by heating. Flash chromatography was performed by using silica gel Merck 60 (particle size 0.063–0.200 mm), ^1H and ^{13}C NMR spectra were recorded with a Varian UNITY INOVA-300. Chemical shifts for protons are given in δ relative to tetramethylsilane (TMS) and are referenced to residual protium in the NMR solvent ($CDCl_3$: δ = 7.26 ppm).

Chemical shifts for carbon are given in δ relative to tetramethylsilane (TMS) and are referenced to the carbon resonances in the solvent ($CDCl_3$: δ = 77.0 ppm). Chiral HPLC was carried out by using a LCP 5020 Ignos liquid chromatography pump with LCD 5000 spectrophotometric detector. High-resolution mass spectroscopic data were obtained at the University of Barcelona, Department of Organic Chemistry "A. Mangini" Mass Spectroscopy facility.

General Procedure for the Aza-Baylis–Hillman Reactions: To a sample vial equipped with a magnetic stirring bar was added KF (58 mg, 1 mmol, 5 equiv.), $CHCl_3$ (1 mL), sulfone **2** (0.2 mmol, 1 equiv.), (*S*)-proline (40 mol-%, 0.08 mmol), and DABCO (5 mg, 0.04 mmol, 0.2 equiv.). Subsequently, aldehyde **1** (0.6 mmol, 3 equiv.) was added, and the reaction mixture was stirred at room temperature. After 4 d, the crude mixture was purified by column chromatography (hexane/EtOAc, 7:1) to give final product **3**.

***tert*-Butyl-(*E*)-2-formyl-1-phenylpent-2-enylcarbamate (3a):** Yield: 36 mg (63%), colorless oil. IR (KBr): $\tilde{\nu}$ = 3435, 2976, 2932, 2875, 1713, 1685, 1495, 1366, 1234, 1166, 1047, 698 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 9.37 (d, J = 1.5 Hz, 1 H, C*H*O), 7.18–7.33 (m, 5 H, Ph), 6.65 (t, J = 7.5 Hz, 1 H, =C*H*CH_2CH_3), 6.16 (br. d, J = 9.9 Hz, 1 H, N*H*Boc), 5.89 (br. d, J = 9.9 Hz, 1 H, C*H*Ph), 2.43–2.55 (m, 2 H, =CHCH_2CH_3), 1.44 [s, 9 H, OC-OC(CH_3)$_3$], 1.18 (t, J = 7.5 Hz, 3 H, =CHCH$_2$CH_3) ppm. ^{13}C NMR (300 MHz, $CDCl_3$, 25 °C): δ = 195.5, 159.0, 155.7, 141.6, 140.4, 128.7, 128.6, 127.4, 126.1, 125.8, 79.8, 50.7, 28.6, 22.9, 13.2 ppm. $[\alpha]_D$ = +80.0 (c = 0.63, $CHCl_3$). HRMS (ESI): calcd. for $C_{17}H_{23}NO_3$ $[M + Na]^+$ 312.1570; found 312.1566. The enantiomeric excess (99%) was determined by HPLC with an IC column. (*n*-heptane/*i*PrOH, 90:10; λ = 230 nm; 1.0 mL min^{-1}): t_R = 14.6 (major), 25.4 (minor) min.

Supporting Information (see footnote on the first page of this article): Analytical data for all prepared compounds (**3a**–**i**) with copies of the ^1H and ^{13}C NMR spectra and HPLC chromatographs.

Acknowledgments

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[11] CCDC-734860 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.
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