β -Isocupreidine-Catalyzed Asymmetric Baylis–Hillman Reaction of Imines

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Received June 16, 2003

ABSTRACT

 β -Isocupreidine (β -ICD)-catalyzed asymmetric Baylis–Hillman reactions of aromatic imines with 1,1,1,3,3,3-hexafluoroisopropyl acrylate (HFIPA) give (S)-enriched N-protected- α -methylene- β -amino acid esters. In contrast to the corresponding aldehydes, imines show the opposite enantioselectivity. A mechanistic proposal governed by hydrogen bonding is presented.

The Baylis-Hillman reaction has attracted considerable interest due to the fascinating tandem Michael-aldol sequence catalyzed by a Lewis base (such as a tertiary amine) and the promising utility of the multifunctional products. Recent literature continues to record impressive progress in rate acceleration as well as asymmetric induction based on imaginative ideas.¹

We previously reported a highly enantioselective asymmetric Baylis—Hillman reaction of aldehydes giving (*R*)-products by the combination of β -isocupreidine (β -ICD)² as a chiral amine catalyst and 1,1,1,3,3,3-hexafluoroisopropyl acrylate (HFIPA) as an activated alkene (Scheme 1).³ In addition, we have successfully demonstrated the synthetic



10.1021/ol035102j CCC: \$25.00 © 2003 American Chemical Society Published on Web 08/02/2003

utility of this reaction via syntheses of biologically intriguing natural products.⁴

In our ongoing work to exploit the synthetic potential of the β -ICD-catalyzed Baylis—Hillman reaction, we became interested in examining the reaction of imine-type substrates,⁵ which allows us to construct valuable α -methylene- β -amino acid derivatives in optically active form. Recently, Shi et al.⁶ and Adolfsson et al.⁷ reported that the β -ICD-catalyzed

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reaction of *N*-tosyl imines and methyl acrylate produced (R)enriched adducts. However, we report herein that this type of aza-Baylis—Hillman reaction gives (S)-enriched adducts.

We first surveyed the reaction of a series of imines⁸ derived from benzaldehyde with HFIPA using 0.1 equiv of β -ICD in DMF at -55 °C, which revealed that appropriate activation of the imine by the electron-withdrawing group is essential for promotion of the reaction (Table 1). Thus,

Table 1. Reaction of N-Protected Imines of Benzaldehyde ^a						
N´ ^R ∥		HFIPA			R NH O ፤ ∥	CF₃
Ph	~н -	catalyst (β-l		or 3)	Ph	O CF ₃
1		DMF, -55 °C			2	2
entry	imine	e R	catalyst	time (h)	yield (%) ^b	config ^c (% ee ^d)
1	1a	Ph	β -ICD	48	0	
2	1b	HO	β-ICD	72	0	
3	1c	O S S R or S	β -ICD	192	0	
4	1d	Bz	β-ICD	36	73	<i>S</i> (13)
5	1e	Ms	β-ICD	3	100	S (66)
6	1e	Ms	QN	168	44	S (9)
7	1e	Ms	3	72	29	S (33)
8	1f	Ts	β -ICD	72	74	S (46)
9	1g	P(O)Ph ₂	β -ICD	120	90	S (67)

^{*a*} Reactions were carried out at -55 °C in DMF (1.0 M) using imine **1** (1.0 equiv), HFIPA (1.3 equiv), and catalyst (β -ICD, QN, or **3**) (0.1 equiv). ^{*b*} Isolated yield. ^{*c*} Determined by the comparison with the degradation product as shown in Scheme 2. ^{*d*} Determined by HPLC analysis using a chiral column of the corresponding methyl ester obtained by methanolysis.



reactions of 1a-c did not give any Baylis—Hillman products and, instead, gradually afforded di(1,1,1,3,3,3-hexafluoroisopropyl) 2-methyleneglutarate via self-dimerization of HFIPA (entries 1–3). In contrast, imines 1d-g activated by benzoyl, sulfonyl, and diphenylphosphinoyl groups gave the desired products 2d-g in good chemical yields (entries 4–9). Among them, *N*-methanesulfonyl imine 1e and *N*-diphenylphosphinoyl imine 1g turned out to exhibit better enantioselectivity (entries 5 and 9). The observed poor chemical and optical yields of the reaction employing quinidine or

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 β -ICD methyl ether **3** as a catalyst suggest the key role of the phenolic OH of β -ICD on the rate acceleration as well as the enantiocontrolling event (entries 6 and 7). The absolute configurations of **2d**-**g** were unambiguously determined to be (*S*)-enriched by transforming the products to the corresponding phenylglycine derivatives **4**⁹ and comparing them to authetic samples¹⁰ prepared from (*R*)-(-)-phenylglycine as shown in Scheme 2.¹¹



We next focused on the reaction of diphenylphosphinoyl imines due to ease of removal¹² of the activating group (Table 2). Fortunately, the products were crystalline and the optical



^{*a*} Reactions were carried out at -55 °C in DMF (1.0 M) using imine **1** (1.0 equiv), HFIPA (1.3 equiv), and β -ICD (0.1 equiv). ^{*b*} Isolated yield. ^{*c*} Determined by HPLC analysis using a chiral column. ^{*d*} Not determined.

purity was easily enriched by simple recrystallization. It is interesting to note that the electron-donating p-methoxy group as well as the bulkier 1-naphthyl group increased the enantioselectivity (entries 2 and 4), whereas the electronwithdrawing p-nitro group markedly decreased the enantioselectivity (entry 3). The reaction of 2-naphthyl substrate was very sluggish because of its poor solubility in the reaction media (entry 5). Concerning aliphatic imines, satisfactory results were not obtained because of their extremely labile nature.

Scheme 3 exemplifies the synthetic utility of the abovementioned methodology. Upon acid hydrolysis of **2g** in



boiling hydrochloric acid, the diphenylphosphinoyl group was cleaved cleanly to give β -amino acid hydrochloride **5**. Treatment of **5** with BOPCl in the presence of triethylamine gave β -lactam **6**. It is important to note that no racemization occurred during this transformation.

We rationalize the observed enantioselectivity via a reaction mechanism governed by hydrogen-bonding. Michael addition of β -ICD to HFIPA forms enolate **A**, which in turn undergoes Mannich reaction with the imine to furnish an equilibrium mixture of several diastereomers. Among them, there would be two betaine intermediates **B** and **C** that are stabilized through hydrogen-bonding between the amidate ion and the phenolic OH. On taking the anti-periplanar arrangement¹³ of the ammonium portion and the α -hydrogen of the ester group in the subsequent E2 or E1cb reaction (see Newman projection **D**), intermediate C suffers from

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more severe steric interaction than intermediate B as depicted in Scheme 4. Thus, the difference in the reaction rate of the elimination step of B and C would result in (S)-enriched enantioselectivity through equilibration.



In conclusion, we have shown for the first time that the β -ICD-catalyzed Baylis—Hillman reaction of aromatic imines with HFIPA proceeds with (*S*)-selectivity, in contrast to reactions of aldehydes, which afford (*R*)-selectivity. The present work provides an effective method for the preparation of aryl-substituted α -methylene β -amino acid derivatives in >93% ee by the reaction of diphenylphosphinoyl imines followed by recrystallization.

Acknowledgment. This research was supported by a Grant-in-Aid for Scientific Research on Priority Areas (A) "Exploitation of Multi-Element Cyclic Molecules" from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

Supporting Information Available: Experimental details and characterization data for all new compounds and ¹H and ¹³C NMR spectra of **2d**–**k** and **6**. This material is available free of charge via the Internet at http://pubs.acs.org.

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