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

Sakie Kawahara, Ayako Nakano, Tomoyuki Esumi, Yoshiharu Iwabuchi, and Susumi Hatakeyama*

Graduate School of Biomedical Sciences, Nagasaki University, Nagasaki 852-8521, Japan

susumi@net.nagasaki-u.ac.jp

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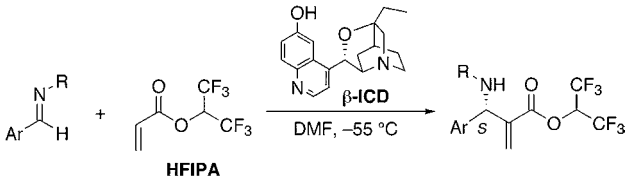
ABSTRACT

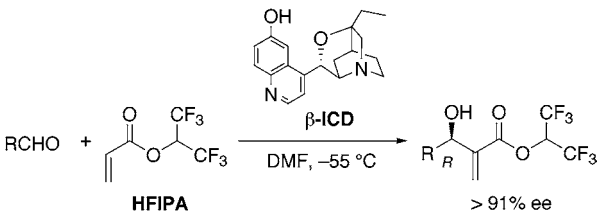


β-Isocupreidine (β-ICD)-catalyzed asymmetric Baylis–Hillman reactions of aromatic imines with 1,1,1,3,3,3-hexafluoroisopropyl acrylate (HFIPA) give (*S*)-enriched N-protected-α-methylene-β-amino acid esters. In contrast to the corresponding aldehydes, imines show the opposite enantioselectivity. A mechanistic 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 utility of this reaction via syntheses of biologically intriguing natural products.[4]

Scheme 1. β-ICD-Catalyzed Baylis−Hillman Reaction of Aldehydes



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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(2) We recently found that this compound was named β-isocupreidine in the early study of *cinchona* alkaloids: Suszko, J. *Rocz. Chem.* **1935**, *15*, 209. For structural elucidation: Dega-Szafran, Z. *Bull. Acad. Pol. Sci., Ser. Sci. Chim.* **1966**, *14*, 529.

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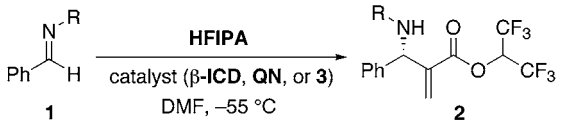
reaction of *N*-tosyl imines and methyl acrylate produced (*R*)-enriched adducts. However, we report herein that this type of aza-Baylis−Hillman reaction gives (*S*)-enriched adducts.

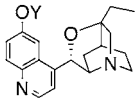
We first surveyed the reaction of a series of imines[8] derived from benzaldehyde with HFIPA using 0.1 equiv of *β*-ICD in DMF at −55 °C, which revealed that appropriate activation of the imine by the electron-withdrawing group is essential for promotion of the reaction (Table 1). Thus,

Table 1. Reaction of N-Protected Imines of Benzaldehyde[a]

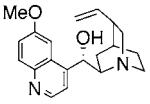


entry	imine	R	catalyst	time (h)	yield (%)[b]	config[c] (% ee[d])
1	**1a**	Ph	β-**ICD**	48	0	
2	**1b**		β-**ICD**	72	0	
3	**1c**		β-**ICD**	192	0	
4	**1d**	Bz	β-**ICD**	36	73	*S* (13)
5	**1e**	Ms	β-**ICD**	3	100	*S* (66)
6	**1e**	Ms	**QN**	168	44	*S* (9)
7	**1e**	Ms	**3**	72	29	*S* (33)
8	**1f**	Ts	β-**ICD**	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.



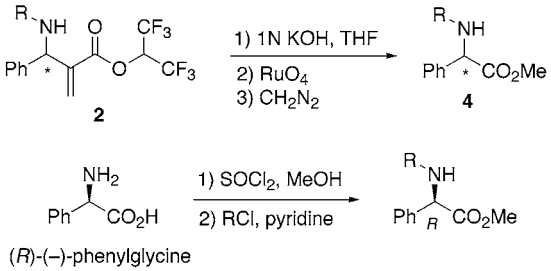
β-**ICD**: Y = H
3: Y = Me



quinidine (**QN**)

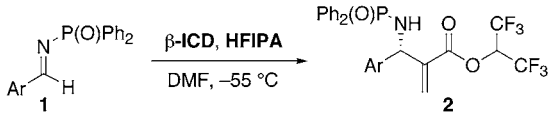
reactions of **1a**−**c** did not give any Baylis−Hillman products and, instead, gradually afforded di(1,1,1,3,3,3-hexafluoroisopropyl) 2-methyleneglutarate via self-dimerization of HFIPA (entries 1−3). In contrast, imines **1d**−**g** activated by benzoyl, sulfonyl, and diphenylphosphinoyl groups gave 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 *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 samples[10] prepared from (*R*)-(−)-phenylglycine as shown in Scheme 2.[11]

Scheme 2. Determination of the Absolute Configuration



We next focused on the reaction of diphenylphosphinoyl imines due to ease of removal[12] of the activating group (Table 2). Fortunately, the products were crystalline and the optical

Table 2. Reaction of Diphenylphosphinoyl Imines[a]



						after recrytalization	
entry	imine	Ar	time (h)	yield (%)[b]	ee (%)[c]	net yield[b] (%)	ee (%)[c]
1	**1g**		120	90	67	55	95
2	**1h**		96	42	73	32	96
3	**1i**		2	97	54	57	93
4	**1j**		48	79	72	40	100
5	**1k**		120	16	*d*	not examined	

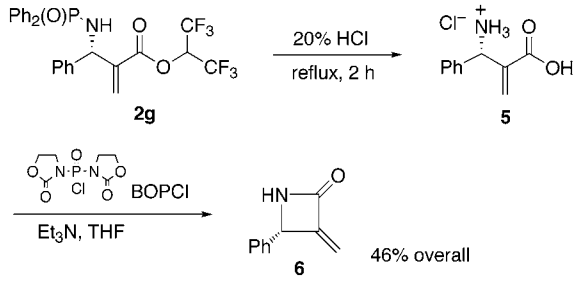
[a] Reactions were carried out at −55 °C in DMF (1.0 M) using imine **1** (1.0 equiv), HFIPA (1.3 equiv), and *β*-ICD (0.1 equiv). [b] Isolated yield. [c] Determined by HPLC analysis using a chiral column. [d] Not determined.

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 electron-withdrawing *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 above-mentioned methodology. Upon acid hydrolysis of **2g** in

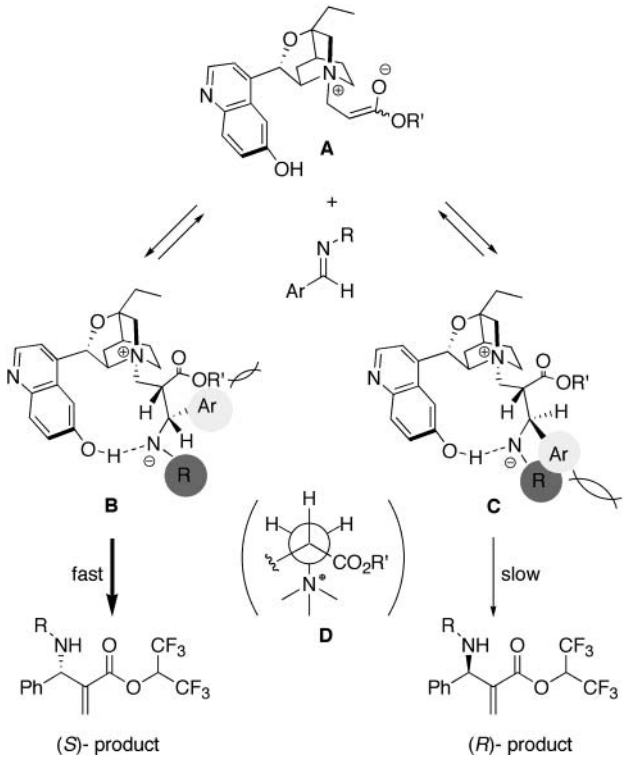
Scheme 3. Conversion of **2g** to β-Lactam **6**



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 arrangement[13] 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 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.

Scheme 4. Proposed Reaction Mechanism



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 ^{1}H and ^{13}C 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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(11) For example, **2f** (46% ee) was converted to methyl (+)-*N*-(*p*-toluenesulfonyl)phenylglycinate, $[\alpha]_D^{17}$ +57.4° (*c* 0.51, $CHCl_3$). Since the (*R*)-enantiomer prepared from (*R*)-(−)-phenylglycine showed $[\alpha]_D^{25}$ −113.6° (*c* 2.33, $CHCl_3$),[11] **2f** was found to be (*S*)-enriched. The corresponding (*S*)-enriched methyl ester obtained by methanolysis of **2f** showed $[\alpha]^{17}_D$ +11.7° (*c* 1.80, $CHCl_3$). These results allowed us to conclude that Shi et al.[6] and Adolfsson et al.[7] incorrectly determined the (+)-ester {+19.5° (83% ee),[6] +16.8° (68% ee)[7]} to be (*R*)-enriched. Shi et al. did not clearly mention how they deduced the absolute configuration. Adolfsson et al. determined it on the basis of the specific rotation reported by Shi et al.

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