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β-Isocupreidine-Catalyzed Baylis–Hillman Reaction of Chiral *N*-Boc-α-Amino Aldehydes

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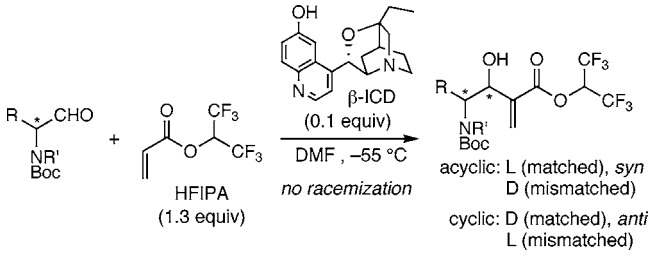
ABSTRACT



***β*-Isocupreidine (*β*-ICD)-catalyzed Baylis–Hillman reaction of chiral *N*-Boc-α-amino aldehydes and 1,1,1,3,3,3-hexafluoroisopropyl acrylate (HFIPA) takes place without racemization and exhibits the match–mismatch relationship between the substrate and the catalyst. In the case of acyclic amino aldehydes, L-substrates show excellent syn selectivity and high reactivity in contrast to D-substrates. On the other hand, in the case of cyclic amino aldehydes, D-substrates rather than L-substrates show excellent anti selectivity and high reactivity.**

The Baylis−Hillman reaction[1] of chiral α-amino aldehydes has attracted considerable interest due to the synthetic utility of the products having a multifunctional α-methylene-*β*-hydroxy-*γ*-amino acid structure. However, the major problems associated with this reaction are the racemization of the substrate and the difficulty in securing high diastereoselectivity.[2] Recently, Coelho et al. successfully developed the racemization-free DABCO-mediated reaction of chiral *N*-Boc-α-amino aldehydes with methyl acrylate under the influence of ultrasound; however, the diastereoselectivity was moderate.[3]

During the course of our synthesis of epopromycin B,[4] we demonstrated that *β*-isocupreidine (*β*-ICD)-catalyzed Baylis−Hillman reaction[5] of *N*-Fmoc-L-leucinal with 1,1,1,3,3,3-hexafluoroisopropyl acrylate (HFIPA) took place without racemization in DMF at −55 °C to produce the corresponding adduct in excellent syn selectivity and in good yield. Interestingly, *N*-Fmoc-D-leucinal was found to exhibit poor reactivity and low diastereoselectivity, suggesting the match−mismatch relationship between the substrate and the catalyst. However, one serious drawback of this reaction is that 1 equiv of *β*-ICD is required to promote the reaction at a reasonable rate. Recently, we found that the azeotropically

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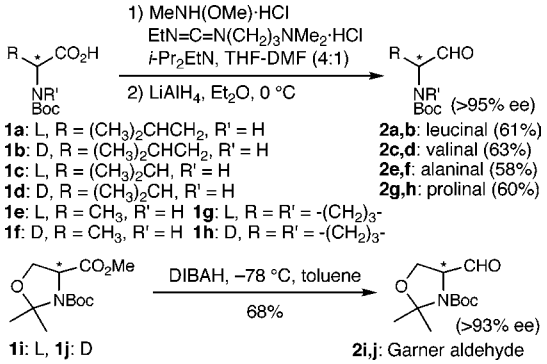
dried β-ICD displayed remarkable catalytic ability in asymmetric Baylis−Hillman reaction of aldehydes with HFIPA.[5d] This finding prompted us to examine this procedure for the reaction of various chiral α-amino aldehydes to solve the above-mentioned drawback. Furthermore, it is thought to be of great significance to probe the influence of the chirality of the substrate in diastereoselectivity from the mechanistic point of view.

To start our study, *N*-Boc-α-amino aldehydes **2a**−**h** were prepared in high enantiomeric purity (>95% ee)[6] by $LiAlH_4$ reduction of the Weinreb amides derived from *N*-Boc-α-amino acids **1a**−**h** according to the procedure developed by Taylor et al.[7] (Scheme 1). *N*-Boc-L- and -D-Garner aldehydes

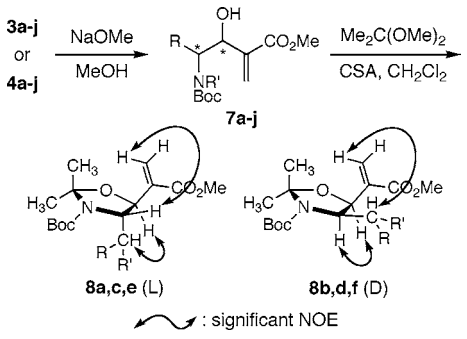
Scheme 1. Preparation of Chiral *N*-Boc-α-Amino Aldehydes



2i,**j** were obtained in >93% ee[6] by DIBAH reduction of the methyl esters of **1i**,**j**.[8]

The Baylis−Hillman reactions of 10 *N*-Boc-α-amino aldehydes **2a**−**j** were then examined using 1.3 equiv of HFIPA and 0.1 equiv of β-ICD in DMF at −55 °C. The syn/anti ratio and optical purity of esters **3a**−**j** and dioxanones **4a**−**j** were determined by HPLC analysis using a chiral column of the corresponding methyl esters **7a**−**j** (Scheme 2). The stereochemistry of **7a**−**j** was confirmed by

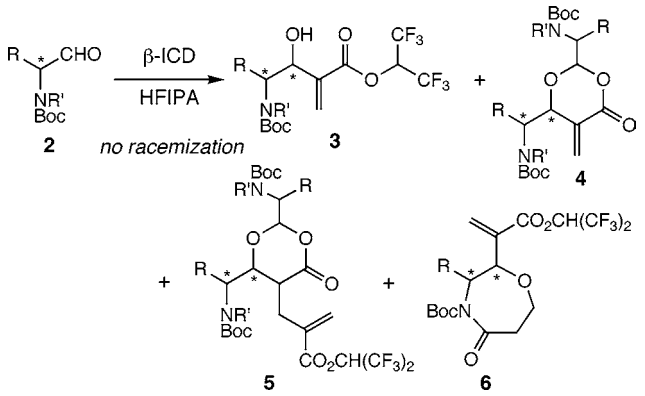
Scheme 2. Preparation of **7a**−**j** and **8a**−**f**



the NOESY spectra of oxazolidines **8a**−**f** and the comparison of the spectral data with those reported for **7a**,**b**,**e**−**j**.[9]

The results are summarized in Table 1, which reveals the marked match−mismatch situation. Thus, *N*-Boc-L-leucinal

Table 1. β-ICD-Catalyzed Reaction of **2a**−**j** with HFIPA[a]



entry	2	time (h)	yield (%)[b] (syn/anti)[c] [ee %][c,d,e] 3	4	5[f]	6[g]	net selectivity (de %)[h]
1	**a** (L)	46	77 (100:0) [>98, −]	4 (75:25) [>98, >98]	−	−	syn (97)
2	**c** (L)	46	83 (100:0) [>98, −]	3 (100:0) [>98, −]	−	−	syn (100)
3	**e** (L)	17	63 (100:0) [>98, −]	18 (21:79) [>98, nd]	−	−	syn (66)
4	**g** (L)	96	10 (100:0) [>98, −]	20 (0:100) [−, >98]	20	−	anti (60)
5	**i** (L)	96	11 (94:6) [>98, −]	1 (13:87) [>98, 95]	30	−	anti (32)
6	**b** (D)	96	45 (0:100) [−, >98]	19 (69:31) [>98, >98]	−	2	anti (60)
7	**d** (D)	96	10 (5:95) [−, nd]	18 (76:24) [>98, nd]	−	−	syn (2)
8	**f** (D)	96	37 (0:100) [−, nd]	15 (50:50) [96, nd]	−	8	anti (75)
9	**h** (D)	96	73 (0:100) [−, >98]	8 (0:100) [−, >98]	−	−	anti (100)
10	**j** (D)	73	67 (0:100) [−, >98]	9 (0:100) [−, >98]	−	−	anti (100)

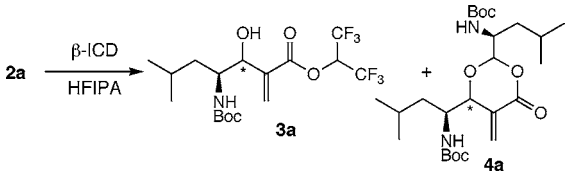
[a] Reactions were carried out at −55 °C in DMF (0.2 M) using **2** (1 equiv), HFIPA (1.3 equiv), and β-ICD (0.1 equiv). [b] Isolated yield. [c] Determined by HPLC analysis of the corresponding methyl ester **7** using a chiral column. [d] The enantiomeric purity of the syn and anti isomers. [e] nd: not determined due to poor separation of the enantiomers by HPLC. [f] The syn/anti ratio was regarded to be the same as that of **4**. [g] The syn/anti ratio was regarded to be the same as that of **3**. [h] Calculated on the basis of the yields and the syn/anti ratio of **3**−**6**.

and *N*-Boc-L-valinal matched with the enantio preference (*R*-selectivity) of β-ICD affording the excellent syn selectivity and high chemical yields (entries 1 and 2), whereas the corresponding D-amino aldehydes mismatched with β-ICD showing moderate anti selectivity or the lack of diastereoselectivity and poor reactivity (entries 6 and 7). *N*-Boc-L-alaninal also exhibited much higher reactivity than *N*-Boc-D-alaninal, although moderate diastereoselectivity was observed in both cases (entries 3 and 8). Interestingly, the cyclic substrates showed the opposite match−mismatch relationship to that observed for the acyclic substrates (entries 4, 5, 9, and 10). Namely, D-substrates rather than L-substrates matched well with β-ICD leading to the excellent anti selectivity and good yields. It was also observed that in the

mismatched cases HFIPA reacted further with ester **3** or dioxanone **4** to give **5** or **6** because of the longer reaction time (entries 4−6 and 8). It is evident from the ee values given that no racemization occurred during the reaction.

Table 2 shows that the appreciable racemization took place above 0 °C but did not below −30 °C. It is also observed that

Table 2. β-ICD-Catalyzed Reaction of **2a** with HFIPA at Various Temperatures[a]



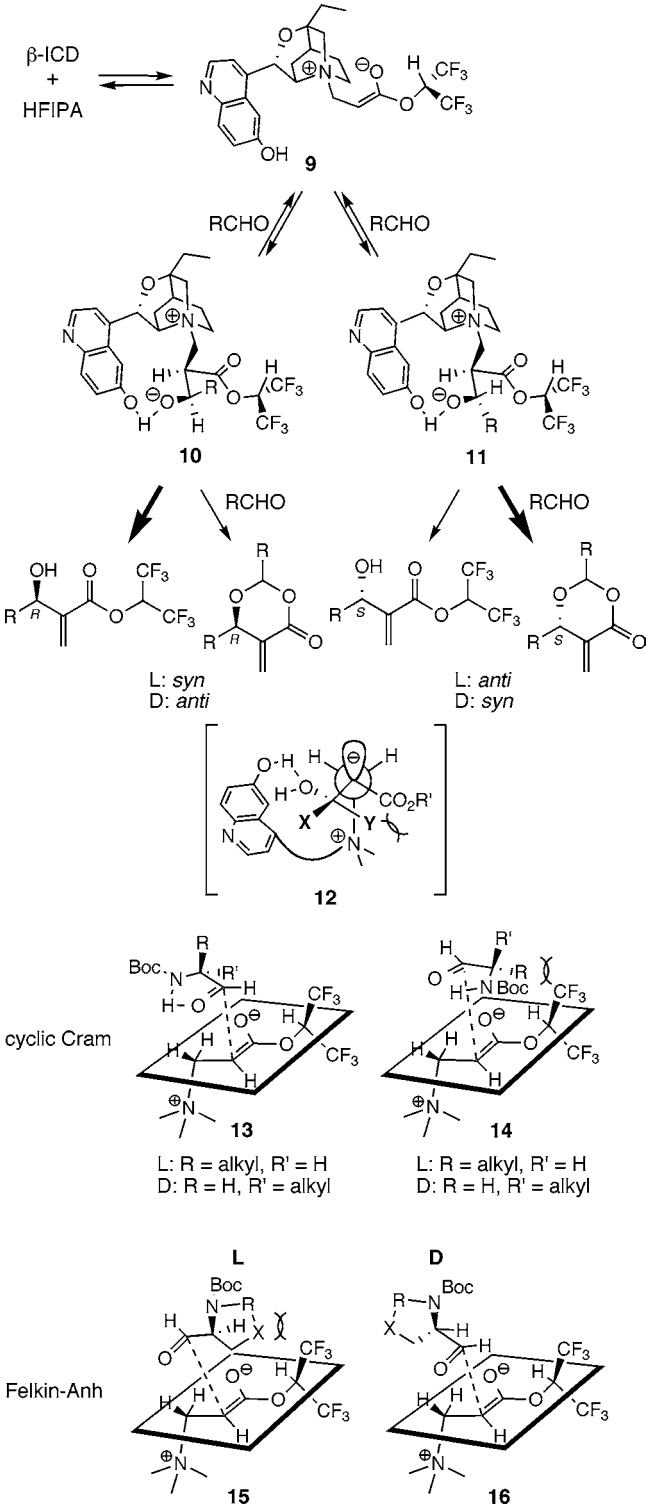
entry	temp (°C)	time (h)	yield (%)[b] (syn/anti)[c] 3a	4a	ee (%)[c] syn	anti	net selectivity (de %)[d]
1	−55	46	77 (100:0)	4 (75:25)	>98	>98	syn (97)
2	−30	46	80 (100:0)	6 (79:21)	>98	95	syn (97)
3	0	96	52 (85:15)	16 (94:6)	97	70	syn (74)
4	rt	96	26 (76:24)	3 (75:25)	86	66	syn (52)

[a] Reactions were carried out at the indicated temperature in DMF (0.2 M) using **2a** (1 equiv), HFIPA (1.3 equiv), and β-ICD (0.1 equiv). [b] Isolated yield. [c] Determined by HPLC analysis of methyl ester **7a** using a chiral column. [d] Calculated on the basis of the yields and the syn/anti ratio of **3a** and **4a**.

the total yield of the Baylis−Hillman products and the diastereoselectivity (net de) markedly decreased above 0 °C. At such temperatures, HFIPA was found to largely dimerize to produce di(1,1,1,3,3,3-hexafluoroisopropyl) 2-methyleneglutarate.

The stereochemical outcomes observed for the acyclic amino aldehydes can be interpreted by assuming the cyclic Cram model of **13** and **14**[2c,d,10] governed by hydrogen bonding. If an aldehyde approaches from the sterically less hindered *si* face of *E*-enolate **9**[11] in anti-periplaner fashion, in the case of L-substrates, **13** is much more favorable than **14**. Consequently, the reaction proceeds predominantly via **13** to produce zwitterionic intermediate **10**, which undergoes the E1cB process[12,13] via **12** (X = R, Y = H) to give the syn adduct. It is assumed that, in the case of *N*-Boc-L-alaninal, the energy difference between **13** and **14** would not be large enough to lead to the high syn selectivity due to the sterically less demanding methyl group. Thus, in addition to the major reaction via **13** giving **10**, the reaction via **14** largely occurs to give zwitterionic intermediate **11**. However, **11** suffers from severe steric interactions between the substituent of the aldehyde and the branched HFIPA ester in the E1cB step (see **12** (X = H, Y = R)) and thus undergoes reaction with a second aldehyde molecule rather than elimination to form the dioxanone. On the contrary, in the case of D-amino aldehydes, approach via either **13** or **14** is disfavored by the steric interactions so that these two reaction courses are under competition leading to the observed mismatched situation. The match−mismatch relationship observed for the cyclic amino aldehydes is consistent with the interpretation based on the Felkin−Anh model of **15** and **16** (Scheme 3).[1c,d,8]

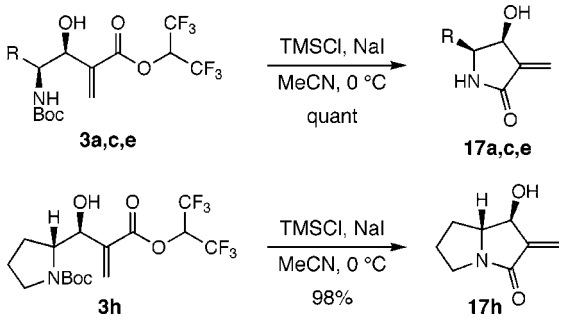
Scheme 3. Plausible Reaction Mechanism



Scheme 4 exemplifies the synthetic utility of the above-mentioned methodology. Treatment of **3a**,**c**,**e**,**h** with iodot-

(6) Determined by HPLC analysis of the corresponding benzoate, prepared by $NaBH_4$ reduction followed by benzoylation.

Scheme 4. Synthesis of Functionalized Pyrrolidinones



rimethylsilane in situ generated from chlorotrimethylsilane and NaI in acetonitrile at 0 °C promoted cleavage of the Boc group and concomitant cyclization of the resulting amine to give the highly functionalized pyrrolidinones **17a**,**c**,**e**,**h** almost quantitatively.

In conclusion, we have developed a highly diastereoselective racemization-free Baylis−Hillman reaction of chiral *N*-Boc-α-amino aldehydes for the first time. The observed matched−mismatched results allow us to propose a mechanism where both the diastereoselectivity of the aldol step and the feasibility of the E1cB process are crucial. The present work provides an effective method for the preparation of highly enantiomerically pure α-methylene-*β*-hydroxy-*γ*-amino acid derivatives.

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Supporting Information Available: Experimental details, characterization data for **3a**−**j**, **4a**−**j**, **5g**,**i**, **6b**,**f**, **7a**−**j**, **8a**−**f**, and **17a**,**c**,**e**,**h**, and ^{1}H and ^{13}C NMR spectra of **7a**−**j** and **17a**,**c**,**e**,**h**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) See reference 2c,d for **7e**,**f**,**i**,**j**. **7a**,**b**,**g**,**h** were determined by comparison with the ^{1}H and ^{13}C NMR data provided by Professor F. Coelho.

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(11) Because molecular mechanics calculations (MMFF, Macro Model 8.5) reveal that the *E*-enolate is energetically more stable than the *Z*-enolate by over 6 kcal mol^{-1}, the *E*-enolate is assumed to preferentially intervene in the aldol reaction. Molecular mechanics calculations also suggest an enolate structure where the CF_3 group sticks out from the enolate plane as depicted in Scheme 3. By such an enolate, it is understood why the branched structure of HFIPA is so influential on enantioselectivity as reported earlier.[5d]

(12) This E1cB process is assumed to involve a six-membered proton transfer from the phenolic OH to the alkoxide of zwitterionic intermediate **10** or **11** with concomitant deprotonation of the α-methine to give an enolate, followed by elimination of *β*-ICD via **12** as proposed by Aggarwal et al. Aggarwal, V. K.; Fulford, S. Y.; Lloyd-Jones, G. C. *Angew. Chem. Int. Ed.* **2005**, *44*, 1706−1708.

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