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α-Isocupreine, an Enantiocomplementary Catalyst of β-Isocupreidine

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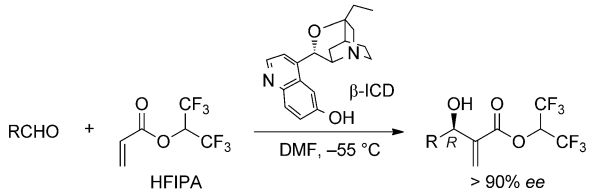
The Morita–Baylis–Hillman (MBH) reaction including the aza-version is an atom-economic, efficient carbon–carbon bond-forming reaction. Due to the utility of highly functionalized products in synthesis, there has been much interest in the asymmetric version of the MBH reaction.[1] In 1999, we developed a highly enantioselective asymmetric MBH reaction of aldehydes[2] by use of β-isocupreidine (β-ICD)[3] as a chiral Lewis base catalyst and 1,1,1,3,3,3-hexafluoroisopropyl acrylate (HFIPA) as an activated alkene (Scheme 1). In addition, we have demonstrated the synthetic



Scheme 1. β-ICD-HFIPA method.

utility of this reaction by the syntheses of biologically intriguing natural products.[4] This β-ICD-HFIPA method has remarkable advantages due to the high enantionselectivity, broad applicability, and availability of both β-ICD and HFIPA.[2c,5] However, one serious drawback is that this method cannot be applied to the synthesis of the products with opposite absolute configuration because the required enantiomer of β-ICD is not easily available.[6] As one solution to this problem, we successfully synthesized two effective enantiocomplementary catalysts of β-ICD from quinine.[7] Nevertheless, since their syntheses required the lengthy transformations, we still need to develop another catalyst that is easily available and shows high and opposite enantioselectivity to that of β-ICD.

In 2002, Jacquesy et al. disclosed a novel rearrangement of quinine in superacid.[8] They found that exposure of quinine hydrochloride to HF-SbF_5 at −30 °C caused a unique skeletal rearrangement to give α-isoquinine (α-IQN) (**1**) in 89% yield. Thereafter, Olah et al. reported that CF_3SO_3H also effectively promoted this rearrangement at 50 °C to produce **1** in 70% yield.[9] The NOESY spectrum and X-ray crystallography demonstrated that compound **1** vastly favors an *anti* conformation with the 6′-methoxyquinoline moiety in a horizontal position.[8,9] Given this structural feature, the demethylated compound **2** is expected to serve as a pseudoenantiomer of β-ICD. We report herein the preparation of α-isocupreine (α-ICPN) (**2**), a new enantiocomplementary catalyst of β-ICD, and its catalytic ability.

α-ICPN **2** was first prepared from quinine in 50% yield by CF_3SO_3H-promoted rearrangement following Olah's procedure[9] and demethylation[10] of the rearranged product **1** by using sodium dodecane-1-thiolate at 130 °C in DMF (Scheme 1). During this examination, we found that the first CF_3SO_3H treatment directly produced **2** in 19% yield together with **1** (59%) although the production of **2** had not been reported in the literature[9] (Table 1, entry 1 and Scheme 2). This finding allowed us to investigate the one-step synthesis of **2** from quinine by using CF_3SO_3H under various conditions. Surprisingly, the rearrangement was found to take place even at room temperature to give **1** in moderate yield although the reaction did not complete within 1 day (entry 2). However, when the reaction was conducted at 50 °C for a longer reaction time, **2** became the major product (entry 3). Among the conditions examined, those listed in entry 4 turned out to be optimum for the preparation of **2**. Thus, when quinine was heated in 28 equivalents of CF_3SO_3H at 50 °C for 24 h and then at 80 °C for 15 h, the rearrangement accompanied by demethylation took place cleanly to give **2** in 90% yield. It is important to note that under conditions in which quinine was

Table 1. One-step preparation of α-isocupreine from quinine.

Entry	CF_3SO_3H [equiv]	Conditions	Yield [%][a]	
			1	**2**
1[b]	275	50 °C, 6 h	59	19
2[c]	75	RT, 24 h	64	0
3	28	50 °C, 72 h	13	72
4	28	50 °C, 24 h; 80 °C, 15 h	0	90
5	28	80 °C, 24 h	0	65
6	11	50 °C, 24 h; 80 °C, 15 h	12	53

[a] Isolated yield. [b] Conditions reported by Olah et al. [c] Quinine was recovered in 30% yield.

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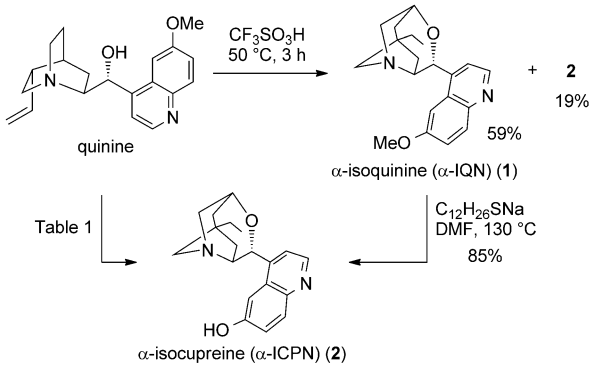


Scheme 2. Preparation of α-isocupreine.

heated at 80 °C from the beginning, the yield markedly diminished due to significant amounts of decomposition (entry 5). It was also found that the decrease of the amount of CF_3SO_3H to 11 equivalents retarded the demethylation of **1** (entry 6). The NOESY spectrum and X-ray crystallography[11] of **2** indicate that it also takes an *anti* conformation in which the nucleophilic nitrogen atom faces toward the phenolic hydroxy group (Figure 1).

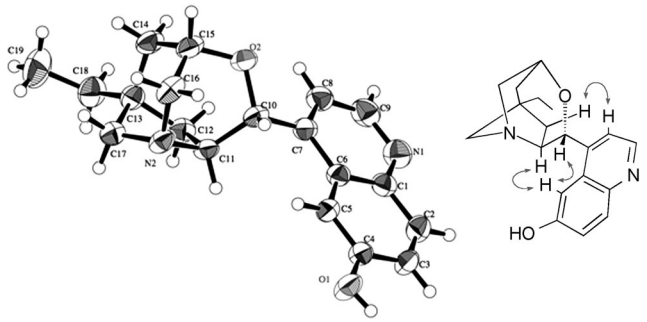
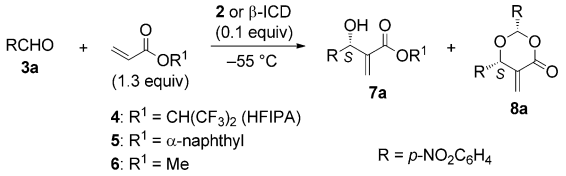


Figure 1. ORTEP drawing and significant NOEs (in $[D_7]$DMF) of **2**.

After having established an effective method for the preparation of **2**, we then explored its catalytic ability to promote the MBH reaction. Initially, we examined the reactions of *p*-nitrobenzaldehyde (**3a**) with three esters **4**, **5**, and **6** under various conditions (Table 2). As shown in entry 2, when **3a** was reacted with 1.3 equivalents of HFIPA by using 0.1 equivalents of **2** in DMF at −55 °C following the procedure we have established for β-ICD-catalyzed reactions,[5a] ester **7a** with a *S* configuration was obtained in moderate yield and high enantioselectivity (59%, 88% *ee*; *ee* = enantiomeric excess) together with *S*-enriched dioxanone **8a** (14%, 40% *ee*). As expected, the enantioselectivity was opposite to that observed for the β-ICD-catalyzed reaction (Table 2, entry 1).[5a] When 0.2 equivalents of **2** were used, aldehyde **3a** was consumed almost completely within 17 h to give **7a** with 90% *ee* in 66% yield. In this case, *S*-enriched **8a** was obtained in moderate enantioselectivity (45% *ee*) and low yield (17%) (entry 3). THF, CH_2Cl_2, and MeCN/DMF turned out to be inferior to DMF as the solvent (entries 4, 5, and 6). Regarding an acrylate, HFIPA was again found to exhibit better results than α-naphtyl acrylate (**5**)[12] and methyl acrylate (**6**) as observed for β-ICD-catalyzed reactions (entries 7 and 8).

Table 2. α-Isocupreine-catalyzed reactions of *p*-nitrobenzaldehyde with acrylates.

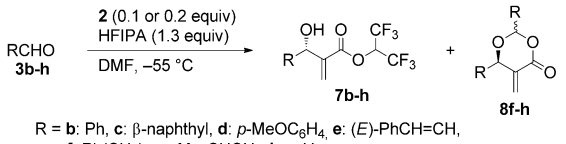


Entry	Cat.	Ester	Solvent	*t* [h]	Yield [%],[a] (% *ee*)[b]	
					7a	**8a**
1	β-ICD	4	DMF	2	57 (−95)	17 (−49)
2	2	4	DMF	24	59 (88)	14 (40)
3[c]	2	4	DMF	17	64 (90)	17 (45)
4	2	4	THF	60	57 (82)	9 (37)
5	2	4	CH_2Cl_2	48	37 (66)	0
6	2	4	MeCN/DMF[d]	24	53 (80)	0
7	2	5	DMF	24	32 (53)	0
8	2	6	DMF	24	0	0

[a] Isolated yield. [b] Determined by HPLC analysis of the corresponding methyl esters on a chiral stationary phase. [c] 0.2 equiv of **2** was used. [d] A 1:1 mixture was used because **2** was not completely dissolved in MeCN.

We next examined the reactions of various aldehydes with HFIPA (Table 3). In the case of aromatic aldehydes **3b–e**, esters **7b–e** were obtained with high *S* selectivity in the range of 82–93% *ee* in moderate to good yields although 0.2 equivalents of **2** were required for the reaction to proceed at a reasonable rate. Interestingly, the corresponding dioxanones **8b–e** were not produced unlike the reaction of reactive *p*-nitrobezaldehyde (**3a**). On the other hand, the reactions of aliphatic aldehydes **3f–h** yielded *S*-enriched esters

Table 3. α-Isocupreine-catalyzed reactions of aldehydes with HFIPA.



R = **b**: Ph, **c**: β-naphthyl, **d**: *p*-$MeOC_6H_4$, **e**: (*E*)-PhCH=CH, **f**: $Ph(CH_2)_2$, **g**: Me_2CHCH_2, **h**: *c*-Hex

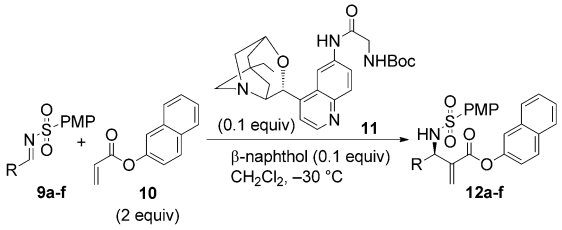
Entry	**3**	**2** [equiv]	*t* [h]	Yield [%],[a] Config. (% *ee*)[b]	
				7	**8**
1	**b**	0.2	24	91, *S* (88)	0
2	**c**	0.2	48	73 [84],[c] *S* (93)	0
3	**d**	0.2	72	24 [93],[c] *S* (82)	0
4	**e**	0.2	48	64 [76],[c] *S* (88)	0
5	**f**	0.1	15	45, *S* (87)	20, *R* (37)[d]
6	**g**	0.1	24	72, *S* (83)	10, *R* (46)[e]
7	**h**	0.1	13	59, *S* (93)	17, *R* (14)[f]

[a] Isolated yield. [b] Determined by HPLC analysis of the corresponding methyl esters on a chiral stationary phase. [c] The yield in the square bracket was calculated based on the recovered aldehyde. [d] 67:33 *cis*/*trans* mixture. [e] 75:25 *cis*/*trans* mixture. [f] 91:9 *cis*/*trans* mixture.

4f–h in high enantioselectivity between 82 and 93% *ee*, although the isolated yields were moderate because of the production of dioxanones **3f–h** (entries 6–8). In these cases, the use of 0.1 equivalents of **2** led to the consumption of most of the aldehydes due to the higher reactivity compared with aromatic aldehydes.

To further demonstrate the utility of **2** we next examined aza-MBH reactions of aromatic imines **9** with β-naphthyl acrylate (**10**) employing catalyst **11**[13] derived from **2** and β-naphthol under dual catalysis conditions developed by Masson and Zhu et al.[14] As summarized in Table 4, the reactions of **9a–f** and **10** produced aza-MBH adducts **12a–f** with high *R* selectivity in the range of 80 to 96% *ee*, which is opposite to that observed in the reactions catalyzed by the corresponding β-ICD-derived catalyst.[14a]

Table 4. aza-MBH reactions of aromatic imines with β-naphthyl acrylate.



Entry	R	*t* [h]	Yield [%][a]	*ee* [%][b]
1	Ph (**9a**)	48	93	83
2	*p*-ClC_6H_4 (**9b**)	48	100	95
3	*m*-BrC_6H_4 (**9c**)	72	96	81
4[c]	*p*-$(NO_2)C_6H_4$ (**9d**)	72	51	96
5	β-naphtyl (**9e**)	72	100	80
6	*p*-$(MeO)C_6H_4$ (**9f**)	72	80	83

[a] Isolated yield. [b] Determined by HPLC analysis on a chiral stationary phase. [c] The reaction became sluggish due to the poor solubility of **9d** in the reaction media.

The *S* selectivity of α-ICPN-catalyzed MBH reactions and the *R* selectivity of aza-MBH reactions catalyzed by α-ICPN-derived catalyst **11** can be explained by assuming zwitter ionic intermediates **13**[5b] and **14**[14a] stabilized by hydrogen bonding, respectively (Figure 2). From these intermediates, a six-membered proton transfer followed by E1cb elimination of the catalyst[15] takes place to give a (*S*)-MBH product or a (*R*)-aza-MBH product.

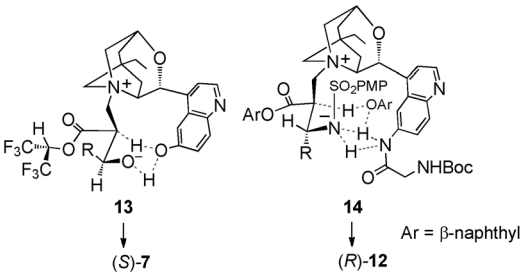


Figure 2. Predominant production of (*S*)-**7** and (*R*)-**12**. Boc = *tert*-butoxycarbonyl; PMP = *p*-methoxyphenyl.

In conclusion, we have developed a new cinchona alkaloid derived catalyst, α-isocupreine (α-ICPN), which is available in excellent yields in one step from quinine. The present work demonstrates that α-ICPN can be utilized as an enantiocomplementary catalyst of β-ICD in various β-ICD-catalyzed asymmetric reactions[16] previously established as well as MBH and aza-MBH reactions.

Experimental Section

α-Isocupreine (2): Quinine (1.02 g, 3.08 mmol) was dissolved in CF_3SO_3H (7.7 mL, 86.6 mmol) at 0 °C and the solution was stirred at room temperature for 10 min. The mixture was heated at 50 °C for 24 h and then at 80 °C for 15 h, cooled to room temperature, diluted with ice water (20 mL) with cooling in an ice bath, and carefully basified by the addition of Na_2CO_3 (5.0 g). The mixture was diluted with water, extracted with $CHCl_3$, washed with brine, dried over K_2CO_3, and concentrated. Purification of the residue with flash column chromatography (SiO_2 200 g, $CHCl_3$/MeOH/Et_3N = 100:2:1) gave **2** (861 mg, 90%) as a yellow solid, which upon recrystallization ($CHCl_3$/hexane = 7:1), afforded colorless crystals.

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Keywords: asymmetric synthesis · cinchona alkaloid · enantioselectivity · Morita–Baylis–Hillman reaction · organocatalysts

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