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Cinchona 알칼로이드를 키랄 리간드로 이용한 비대칭 Reformatsky 반응

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Enantioselective Reformatsky Reaction Using Cinchona Alkaloids as Chiral Ligands

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요 약. Cinchona 알칼로이드(1-4)들을 비대칭 Reformatsky 반응에 키랄 리간드로 사용하였다. 알데히드, 리간드, Reformatsky 시약의 적가 순서에 따라 반응의 수율이 달라지며, Reformatsky 시약과 알데히드, 리간드와의 비율도 수율에 크게 영향을 주었다.

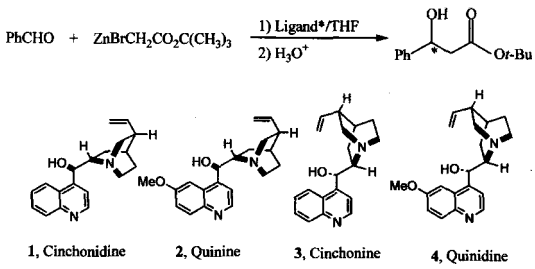
주제어: Cinchona 알칼로이드, 비대칭 Reformatsky 반응

ABSTRACT. Cinchona alkaloids (**1-4**) were used as chiral ligands for the enantioselective Reformatsky reactions. The order of addition of the Reformatsky reagent to ligands was the important factors for the chiral induction. The ratio of Reformatsky reagent to ligand and aldehyde was also effected on the reaction yields.

Keywords: CInchona Alkaloid, Enantioselective Reformatsky Reaction

INTRODUCTION

Enantioselective Reformatsky reactions is one of the most generally applicable procedures for the preparation of optically active β-hydroxy esters.[1] Although the diastereoselective Reformatsky reactions using a covalently bonded chiral auxiliary were reported, the stereocontrolled Reformatsky reactions utilizing external chiral ligands have been received very little attention,[2] which is on contrast to the case of rapidly developing enantioselective addition of dialkylzinc to carbonyl compounds.[3] In 1991 Soai first reported that chiral amino alcohols have been shown to be a good chiral ligand for the enantioselective Reformatsky reactions.[4a] Since then, a few amino alcohols were used to promote the enantioselective addition of the Reformatsky reactions and it has been found that the use of amino alcohols with bulky substituents on nitrogen atom and free hydroxyl group is necessary to achieve good enantioselectivity.[4b,c] Based on these observations, it could be imagined that the cinchona alkaloids may become one of the promising chiral ligands for the enantioselective Reformatsky reactions. However, some years ago, it was reported that zinc-induced Reformatsky reactions using cinchona alkaloids as a chiral ligand gave no trace of β-hydroxy esters in which stoichiometric amount of Reformatsky reagent was used.[5] Because of the hydroxy group in amino alcohol, excess amounts of Reformatsky



Scheme 1.

reagent may be required to achieve enantioselectivity. Thus, we reexamined the chiral induction effects of the cinchona alkaloids as a chiral ligand for the enantioselective Reformatsky reactions by using excess amounts of Reformatsky reagent.

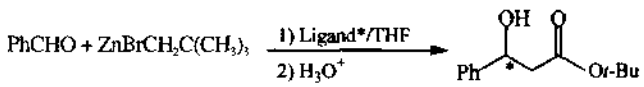
RESULTS AND DISCUSSION

In the first time, the reactions were carried out according to the reported procedure[4a] except the amount of the employed Reformatsky reagent. Thus, three equivalent amounts of the Reformatsky reagent, prepared from *tert*-buty bromoacetate and Zn-Cu couple,[7] was added to a 1:1 molar mixture of benzaldehyde and ligand in THF at room temperature.

The reaction was quenched by addition of 1N aqueous HCl solution, and usual chromatographic separation afforded the expected β-hydroxy ester in excellent chemical yields (91-98%), which is in contrast to the reported observation.[5] All reactions were completed within 2 hrs but the optical yields were largely dependent on the ligand. When cinchonine was used as a chiral ligand, the optical purity was estimated to be 15% by comparison of the reported $[\alpha]_D$ value[4a], and the absolute configuration of the major enantiomer was determined to be (*S*) based on the sign of optical rotation of the isolated β-hydroxy ester (entry 3). However, when the ligand was changed to cinchonidine and quinidine, the optical yields were decreased to 5% and 4%, respectively (entry 1 and 4). The quinine ligand afforded racemic β-hydroxy ester in 91% yield (entry 2).

Since the formation of complex between organozinc and chiral ligand is important to give enantioselectivities in addition of dialkylzinc to aldehyde using aminoalcohol ligands,[4] the cinchona alkaloid was added to the Reformatsky reagent to make complex first, then benzaldehyde was added. In this reaction condition, the optical yields were increased about 2-4 times (entry 5-7). Interestingly, the (2*S*)-enantiomer was produced as a major (about 10% optical purity) by using quinine (entry 5) which has the same absolute configurations at the stereocenters in cinchonidine. Moreover, the reactions proceeded very slowly and provided low yields of β-hydroxy ester. However, when eight-fold excess of Reformatsky reagent was used, the chemical yield and reaction rate were increased whereas racemate was obtained (entry 8).

Table 1. Enantioselective reformatsky reactions of benzaldehyde catalysed by **1-4**



Entry	Reaction condition[a]	Ligand	Yields[b] (%)	$[\alpha]^{25}_D$[c] (conc.)	Otical purity (%)[d]	Config.[f]
1	A	1	95	+2.0(1.73)	4.7 (4.8)[e]	*R*
2	A	2	91	0(2.11)	0	–
3	A	3	96	–6.5(2.0)	15.1	*S*
4	A	4	98	–1.5(1.72)	3.7	*S*
5	B	2	30	+4.4 (1.77)	10.2	*R*
6	B	3	53	–11.6 (2.03)	26.7	*S*
7	B	4	34	–7.1 (1.17)	16.4	*S*
8[g]	B	2	95	0 (2.07)	0	–

[a]A: ligand was added to benzaldehyde solution first; B: ligand was added to Reformatsky reagent first. [b]Isolated yield. [c]$CHCl_3$ solvent. [d]Calculated from specific rotation (ref 4a). [e]Determined by ^1H NMR analysis using quinine as chiral solvating agent (ref 6). [f]Determined by the sign of specific rotation of the isolated product. [g]Eight-fold excess of the Reformatsky reagent was used.

If an equimolar ratio of aldehyde/Reformatsky reagent/chiral ligand **2** was employed, the reaction was completely inhibited, which was the same results reported by Johar.[5] It has been also found that the stereochemistry of the hydroxy group play an essential role in determining the stereochemical out-come of the products. The ligands **1** and **2** having (*R*)-hydroxy group produced the (2*S*)-enantiomer as a major whereas (2*R*)-enantiomer was obtained with ligands **3** and **4**.

Thus, the following conclusions were drawn from the results: (1) cinchona alkaloids also can be used as chiral ligands for the enantioselective Reformatsky reactions. (2) The order of addition of the Reformatsky reagent to ligand may be one of the important factors for the chiral induction. (3) The ratio of Reformatsky reagent to ligand and aldehyde is also important factor for the reaction yields.

EXPERIMENTAL SECTION

^{1}H NMR and ^{13}C NMR were recorded on a Varian Gemini 300 MHz spectrometer and IR spectra were recorded on a MIDAC 101025 FT-IR. Column chromatography was performed on silicagel 60 (230-400 mesh) and TLC was carried out using glass sheets precoated with silica gel 60F254 purchased from Merck.

Preparation of the Reformatsky reagent (*tert*-butoxycarbonylmethylzinc bromide)

The *tert*-butyl bromoacetate (1.33 mL, 9.0 mmol) was added to a suspension of Zn-Cu (0.59 g, 9.0 mmol) in 30 mL of dry THF under nitrogen atmosphere. After addition of trace amount of iodine, the mixture was refluxed for 2 hrs, and allowed to cool to room temperature which was used without further purification.

Typical Procedure of Enantioselective Reformatsky reaction

Condition A. A solution of benzaldehyde (3.0 mmol) and cinchona alkaloid ligand (3.0 mmol) in THF (10 mL) was stirred for 1 hr at room temperature. To this solution, the Reformatsky reagent prepared as described above was added *via* syringe, and the mixture was stirred at room temperature. After completion of the reaction (by TLC), the reaction was quenched with 1N aqueous HCl solution, and the mixture was extracted with ethyl acetate. The organic layer was dried (Na_2SO_4), and evaporated under reduced pressure. The residue was purified by chromatography on silica gel column to give *tert*-butyl 3-hydroxy-3-phenylpropanoate. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40-7.21 (5H, m), 5.07 (1H, q), 2.90-2.68 (2H, m), 1.20 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.64, 142.62, 128.54, 127.65, 125.80, 70.52, 61.12, 45.20, 16.14; IR (film) 3450, 2970, 1720, 1490, 1450 cm^{-1}

Condition B. The cinchona alkaloid chiral ligand (3 mmol) was added to the Reformatsky reagent. After stirring for 1 hr at room temperature, benzaldehyde (3 mmol) was added to the mixture. After completion of the reaction (by TLC), the reaction was quenched and worked up by the same method described in condition A.

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