One-Pot Preparation of Chiral β-Amino Esters by Rhodium-Catalyzed Three-Components Coupling Reaction

Toshio HONDA,* Hitoshi WAKABAYASHI, and Kazuo KANAI

Faculty of Pharmaceutical Sciences, Hoshi University, 2–4–41 Ebara, Shinagawa-ku, Tokyo 142–8501, Japan.
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Chiral β-amino esters are synthesized in one-pot from three components, amines, aldehydes, and ethyl bromoacetate, under the rhodium-catalyzed Reformatsky-type reaction condition, where complete diastereoselection is achieved in the nucleophilic addition step of ethyl bromoacetate to the imines prepared *in situ*.

Key words chiral β-amino ester; Reformatsky reaction; rhodium-catalyzed coupling reaction; Wilkinson's catalyst; diethylzinc

β-Amino acids or β-amino esters are recognized to be pharmacologically important compounds,[1] since those compounds play key roles in medicinal chemistry, such as precursors of medicinally important β-lactam antibiotics, and as constituents of biologically active unnatural peptides.[2] Moreover, some cyclic β-amino acids are reported to exhibit remarkable antifungal activities.[3] Therefore, development of a new and operationally simple methodology for the preparation of β-amino acids or their ester derivatives in optically pure forms, is highly desirable in this field of chemistry. Based on these considerations, numerous methods for the synthesis of β-amino acids (esters) have been investigated to date.[4] Among the various methodologies developed, a straightforward manner for obtaining β-amino acids (esters) seems to be the addition of the Reformatsky reagents[5] to aldimines.

We recently disclosed a novel rhodium-catalyzed Reformatsky-type reaction in which β-hydroxy esters are produced under very mild reaction conditions.[6]

To extend the usefulness of this type of reaction in the synthesis of biologically active compounds, we investigated the further application of this methodology to the preparation of optically active β-amino esters, and herein we report our successful results.

Although the difficulties were initially encountered for obtaining the desired products by addition of ethyl bromoacetate to imines under the various reaction conditions attempted, probably due to the instabilities of the imines, we found fortunately that ethyl bromoacetate could be introduced to the imines, prepared *in situ*, in the presence of Wilkinson's catalyst and diethylzinc giving β-amino esters by one-pot procedure in reasonable yields. As shown in Table 1, the desired β-amino esters were obtained from both aromatic and aliphatic aldehydes and amines by one-pot preparation[4d] in moderate yields, probably depending on the stability of the imines formed *in situ*. The representative procedure for this addition reaction is as follows: The suspension of an aldehyde (1 mmol), an amine (1.03 mmol), and activated molecular sieves 3A (0.4g) in tetrahydrofuran (THF, 2 ml) are stirred at 0 °C for 4 h under argon. To this mixture at 0 °C was added a solution of Wilkinson's catalyst (0.05 mmol) in THF (3 ml), ethyl bromoacetate (1.1 mmol), and a 1.0 M hexane solution of diethylzinc (4 mmol). After stirring for 10 min at 0 °C, the reaction was quenched by the addition of aqueous saturated $NaHCO_3$.

It is noteworthy that the addition reactions without the presence of Wilkinson's catalyst gave the desired products in the range of 10—20% yields with much longer reaction time (more than 2 h). These results obviously suggested that Wilkinson's catalyst accelerate the reactions in terms of the yield and reaction time. Having developed a method for the preparation of racemic β-amino esters, in one-pot, from three components, aldehydes, amines and ethyl bromoacetate, under rhodium-catalyzed reaction conditions, we next focused our attention on the synthesis of optically pure β-amino esters. Among the various chiral auxiliaries reported in the literatures, we chose readily available (*R*)-phenylglycinol.[4b,5,7]

Following the procedure developed above, we carried out the reaction with (*R*)-phenylglycinol as an amine component, however, none of the desired product was produced. We assumed that the free hydroxyl of (*R*)-phenylglycinol interfered the nucleophilic attack of the intermediate rhodium enolate.[6] Thus, we attempted this reaction with the benzyl ether[8] of (*R*)-phenylglycinol, and were delighted to find that desired β-amino esters were obtained as a single isomer. Table 2 presents the results of the one-pot preparation of chiral β-amino esters. With both aromatic and aliphatic aldehydes, desired β-amino esters were obtained in moderate to good yields without giving any diastereoisomers. The absolute configurations of the coupling products were unambiguously determined by comparison of the specific optical rotations of the corresponding amines (**A**) or debenzylated compound (**B**) as shown in Table 3, with those reported.[9] Figure 1 with its transition state appears to best depict our experimental observations, where the zinc enolates[6] attack from the sterically

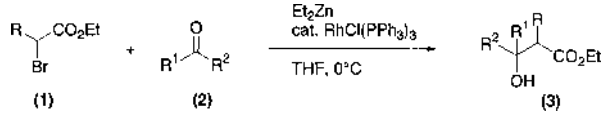
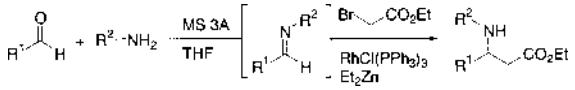
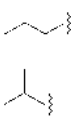
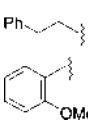


Chart 1. Rhodium-Catalyzed Reformatsky Reaction with Carbonyl Compounds

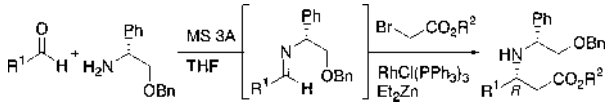
Table 1. One-Pot Preparation of Racemic β-Amino Esters



Entry	R^1	R^2	Product	Yield (%)
1		Ph	**4**	56
2		Ph	**5**	56
3	Ph		**6**	45
4	Ph		**7**	51
5			**8**	54
6			**9**	57

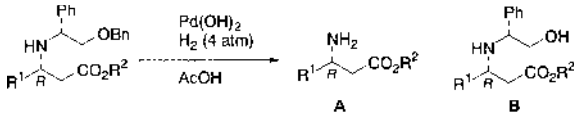
* To whom correspondence should be addressed. e-mail: honda@hoshi.ac.jp

Table 2. One-Pot Preparation of Chiral β-Amino Esters



Entry	R^1	R^2	Product ($[\alpha]_D$ in $CHCl_3$)	Yield (%)
1	Ph	Et	**10** (−3.4)	78
2	Isopropyl	Et	**11** (−50.7)	70
3	Propyl	Et	**12** (−48.3)	85
4	Propyl	Me	**13** (−52.8)	76
5	Cyclohexyl	Et	**14** (−34.6)	62

Table 3. Removal of the Chiral Auxiliary



Entry	Substrate	R^1	R^2	Product ($[\alpha]_D$ in $CHCl_3$)	Yield (%)
1	**10**	Ph	Et	**15A** (+12.9)	58
2	**11**	isopropyl	Et	**16A** (+21.8)	46
				16B (−24.2)	28
3	**12**	propyl	Et	**17A** (+12.3)	39
				17B (−46.1)	59
4	**13**	propyl	Me	**18A** (+12.7[a])	54
5	**14**	cyclohexyl	Et	**19B** (−31.7)	40

a) This value is for the *N*-Boc derivative, derived from **18A** with $(Boc)_2O$.

less hindered *re* face of the imines. The observed stereoselectivity was similar to those of previously reported.[4b)]

Further cleavage of the chiral auxiliary was best achieved by hydrogenolysis in the presence of Pearlman's catalyst under 4 atms of hydrogen in acetic acid or subsequent lead tetraacetate treatment of the debenzylation products.

Thus, we developed an efficient one-pot preparation of chiral β-amino esters *via* three components coupling by applying the rhodium-catalyzed Reformatsky-type reaction. Since both enantiomeric forms of the chiral auxiliaries employed here are readily accessible, both enantiomers of the β-amino esters can be obtained with a same operation. Support was provided by a Grant-in-Aid from the Ministry of Education, Culture, Sports, Science and Technology of Japan.

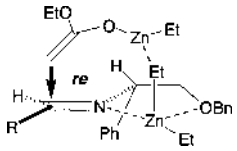


Fig. 1. Plausible Transition State

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8) The reductive cleavage of the methyl ether of (*R*)-phenylglycinol, after the coupling reaction, did not give satisfactory result.
9) The reported specific optical rotations of **15A** are $[\alpha]_D$ +21.1 ($CHCl_3$),[10)] and +4.5 (EtOH).[11)] Also **19B** and the *N*-Boc derivative **17A** exhibited $[\alpha]_D$ −37.2 ($CHCl_3$),[12)] and $[\alpha]_D$ +20.9 ($CHCl_3$),[12)] respectively. Although **16** and **18** are unknown compound, its stereochemistry can tentatively be assigned to be the same as other products based on the reaction mechanism. We assumed that the coupling products seem to be optically pure, since the chiral auxiliary obtained by hydrolysis of the imines prior to the coupling reaction was optically pure, and its removal by catalytic hydrogenolysis, after coupling reaction, usually did not take place any racemization.
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