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Tetrahedron Letters 47 (2006) 1933–1935
Tetrahedron Letters

D-Phg-L-Pro Dipeptide-derived prolinol ligands for highly enantioselective Reformatsky reactions

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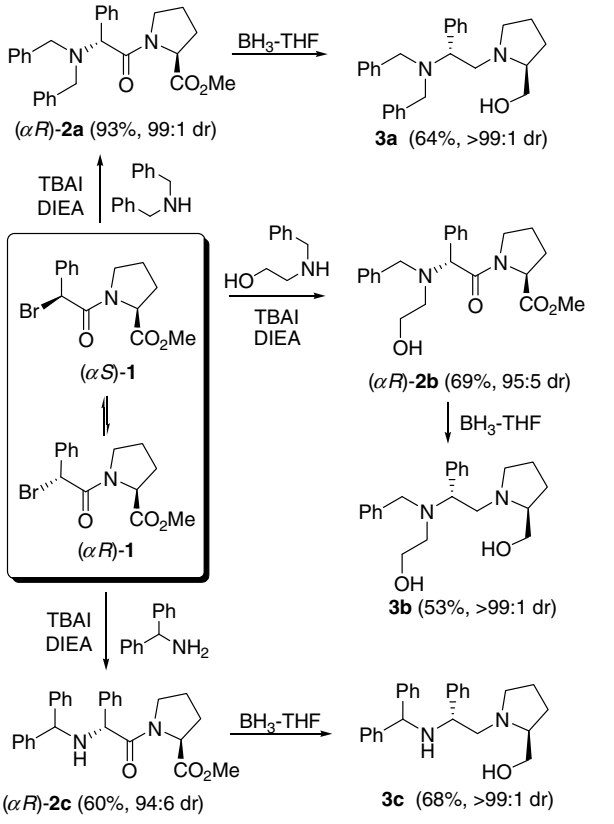
Received 16 December 2005; revised 12 January 2006; accepted 16 January 2006
Available online 3 February 2006

Abstract—Optically pure *N*-aminoethyl prolinol derivatives **3a–c** have been prepared from the dynamic kinetic resolution of *N*-(α-bromo-α-phenylacetyl) proline ester **1** in asymmetric nucleophilic substitution and subsequent reduction. The peptide-derived prolinols are tested as chiral ligands in the asymmetric addition of Reformatsky reagent to aromatic aldehydes. Chiral ligand **3c** has been shown to be effective to produce enantioenriched β-hydroxy esters **5a–j** with up to 98% ee.

The enantioselective addition of Reformatsky reagents to carbonyl compounds is one of the most synthetically useful methods for the asymmetric preparation of β-hydroxy esters.[1,2] Although many existing chiral ligands can induce useful level of selectivity, it is still desirable to develop new chiral ligands for highly enantioselective Reformatsky reaction. Peptides have recently received much attention as sources of chiral ligands, however, to the best of our knowledge there is no successful example of a peptide-derived chiral ligand for asymmetric Reformatsky reaction. Herein, as part of our research on the development of peptide-derived chiral ligands, we describe an efficient asymmetric synthetic method for a new class of chiral ligands based on a D-Phg-L-Pro dipeptide scaffold and their application to highly enantioselective Reformatsky reactions with aromatic aldehydes.

Since a variety of β-amino alcohols derived from proline have been reported to be effective in the enantioselective addition of organozinc reagent,[2i,3] we initially selected phenylglycinyl proline-derived prolinol ligand as a preferred motif. The additional amino group and aromatic groups could participate in the formation of reactive intermediate complex and provide attractive and/or repulsive interaction with aromatic substrates. Recently, we have reported the dynamic kinetic resolution of α-halo acetamides in nucleophilic substitution for asymmetric syntheses of di-, tri- and tetrapeptide analogues.[4]

The methodology was used for asymmetric preparation of chiral ligands **3a–c** as shown in Scheme 1. The



Scheme 1. Preparation of chiral ligands **3a–c**.

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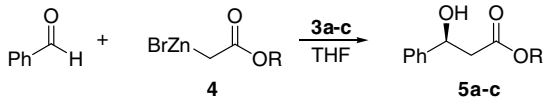
doi:10.1016/j.tetlet.2006.01.070

treatment of two diastereomeric mixtures (ca. 50:50) of *N*-(α-bromo-α-phenylacetyl)-(L)-proline methyl ester **1** with a nucleophile in the presence of tetrabutylammonium iodide (TBAI) and diisopropylethylamine (DIEA) in CH_2Cl_2 at room temperature gave the D-Phg-L-Pro dipeptide analogues **2a**–**c** in 93–60% yields with 99:1–94:6 diastereomeric ratios (dr). The epimerization at the α-position promoted by TBAI and DIEA is sufficiently fast with respect to the rate of substitution and the (α*S*)-**1** is the faster reacting diastereomer than (α*R*)-**1**.[5] In the asymmetric C–N bond formation, the chiral information of L-proline is transferred to the substitution at α-bromo carbon center via dynamic kinetic resolution in the nucleophilic substitution with the nucleophiles. Functional diversity of *N*-alkyl group of the dipeptides can be introduced through the use of various primary or secondary amine nucleophiles.[6] The subsequent reduction of **2a**–**c** using an excess of BH_3–THF (10 equiv) in THF furnished the expected prolinols as a mixture of two isomers. In all cases, the optically pure β-amino alcohols **3a**–**c** were easily isolated in 64%, 53% and 68% yields, respectively, by flash column chromatographic separation.[7] We then explored asymmetric Reformatsky reactions as a preliminary evaluation of the catalytic properties of three chiral ligands **3a**–**c**, which have different *N*-alkyl amino groups.

We initially used the reaction of benzaldehyde with $BrZnCH_2CO_2R$ (**4**) in refluxing THF as a standard condition to test the effects of changing chiral ligands. The mixture of benzaldehyde, bromoacetate and a chiral ligand was added to previously activated zinc metal with trimethylchlorosilane[8,2d] and subsequent stirring for 2 h at reflux provided β-hydroxy esters **5a**–**c**.[9] In this preliminary screen of the chiral ligands **3a**–**c**, the chiral ligand **3c** gave a promising result to give (*R*)-β-hydroxy ester **5a** in 44% yield and 86% ee, while the *N*,*N*-dibenzylated prolinol derivative **3a** and bis-amino alcohol **3b** failed to induce noticeable enantioselectivities (entries 1–4).

In order to obtain the optimized condition for the reaction with chiral ligand **3c**, we have examined some experimental parameters such as solvent, molar ratio of reactants and reaction temperature. Among the solvents examined, THF was found to be the best for chiral ligand **3c**. The results in entries 5–7 suggested that the molar ratio of benzaldehyde: Reformatsky reagent (**4**): chiral ligand (**3c**) was important. When a 1:8:0.5 ratio, rather than a 1:4:0.5 ratio was used, the enantioselectivity was improved (98% ee, entry 5). As shown in entries 6 and 7, the use of 0.1 and 1.0 equiv of chiral ligand resulted in a decrease in the enantioselectivity (86% ee and 92% ee, respectively). Utilization of ethyl bromoacetate and methyl bromoacetate instead of *t*-butyl bromoacetate gave **5b** and **5c** in lower yields with comparable enantioselectivities (entries 8 and 9). Lowering the reaction temperature to 45 °C abated enantioselectivity and the reactions below 30 °C did not produce β-hydroxy esters **5**. It should be noted that in most reactions with chiral ligand **3c** shown in Table 1, the reaction in THF at reflux caused dehydration of **5** to form cinnamates in 10–30% isolated yields. Attempts to improve the yield by increasing reaction time failed because more dehydration of **5** took place. Thus the optimal condition was identified when the reactions were carried out in refluxing THF for 2 h with *t*-butyl bromoacetate.

Table 1. Asymmetric Reformatsky reactions with benzaldehyde



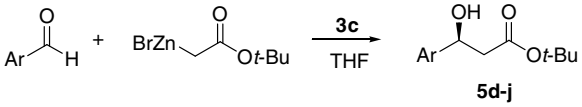
4 5a-c

Entry	R	Ligand (PhCHO:**4**:ligand)[a]	Yield (%)	% ee[b,c]
1	*t*-Bu	**3a** (1:4:0.5)	88 (**5a**)	2
2	Et	**3a** (1:4:0.5)	68 (**5b**)	14
3	*t*-Bu	**3b** (1:4:0.5)	85 (**5a**)	0
4	*t*-Bu	**3c** (1:4:0.5)	44 (**5a**)	86
5	*t*-Bu	**3c** (1:8:0.5)	50 (**5a**)	98
6	*t*-Bu	**3c** (1:8:0.1)	38 (**5a**)	86
7	*t*-Bu	**3c** (1:8:1.0)	37 (**5a**)	92
8	Et	**3c** (1:8:0.5)	24 (**5b**)	95
9	Me	**3c** (1:8:0.5)	25 (**5c**)	97

[a] Molar ratio of benzaldehyde:$BrZnCH_2CO_2R$:ligand **3**.
[b] The % ee is determined by CSP-HPLC (Chiralcel OJ-H).
[c] Absolute configuration of (*R*)-**5** is assigned by the sign of optical rotation of the isolated product.

To investigate the scope of the methodology, Reformatsky reactions with a variety of aromatic aldehydes were carried out under the optimal condition, using the 1:8:0.5 molar ratio of benzaldehyde: Reformatsky reagent **4**: chiral ligand **3c**, and the results are summarized in Table 2. The reactions of *m*-methoxybenzaldehyde, *p*-methoxybenzaldehyde, *p*-phenylbenzaldehyde and 2-naphthylaldehyde provided the corresponding β-hydroxy esters **5d**–**f** and **5j** with high enantioselectivities. However, the reactions of *p*-methylbenzaldehyde, *p*-chlorobenzaldehyde and 1-naphthylaldehyde resulted in slightly decreased enantioselectivities, which indicate that the enantioselectivity depends on the substituent of the aldehyde. At present rational explanation about the variation of enantioselectivity with the aldehydes is not possible due to the uncertainty on the structures of Reformatsky reagent and transition state.

Table 2. Asymmetric Reformatsky reactions with various aldehydes



5d-j

Entry[a]	Ar	Yield (%)	% ee[b]
1	*m*-MeO–Ph	55 (**5d**)	96
2	*p*-MeO–Ph	32 (**5e**)	98
3	*p*-Ph–Ph	45 (**5f**)	98
4	*p*-CH_3–Ph	70 (**5g**)	80
5	*p*-Cl–Ph	32 (**5h**)	81
6	1-Naphthyl	41 (**5i**)	89
7	2-Naphthyl	49 (**5j**)	96

[a] All reactions were carried out in refluxing THF for 2 h with a 1:8:0.5 molar ratio of benzaldehyde:$BrZnCH_2CO_2R$:ligand.
[b] The % ee is determined by CSP-HPLC (Chiralcel OJ-H).

In summary, we have developed dipeptide-derived chiral ligand **3c** which is effective in asymmetric Reformatsky reaction with various aromatic aldehydes.[10] Some of the enantioselectivities are, to the best of our knowledge, higher than the best record which has been attained.[1,2] Importantly, after the reaction was completed, the chiral ligand could be easily separated from the adduct by simple extractive work-up and silicagel chromatography. While the effective chiral ligand was found in this work, the structures of the zinc complex and transition state are still unclear. Further studies to clarify them as well as to use them in other asymmetric catalytic reactions are currently in progress in our laboratory.

Acknowledgements

This paper was supported by a Grant from Molecular & Cellular BioDiscovery Research Program (M1-0311-13-0003) from the Ministry of Science and Technology, Korea and Korea Research Foundation (KRF-2004-F00019).

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6. Reactions of **1** with cyclic secondary amines such as pyrrolidine, piperidine, morpholine and 1,2,3,4-tetrahydroisoquinoline gave the substituted products with low selectivities (74:26–67:33 dr). Unpublished results.
7. Optical purities of **3a**–**c** were evaluated by ^{1}H NMR and confirmed by CSP-HPLC. Absolute configurations of α-position of **3a** and **3c** were assigned to be (*R*) by comparison to the ^{1}H NMR of authentic epimers prepared from reduction of *N*-diphenylmethylene-D-Phg-L-Pro ester and *N*,*N*-dibenzyl D-Phg-L-Pro ester, respectively. That of **3b** was assigned by analogy to the formation of **3a** and **3c**.
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9. *General procedure for asymmetric Reformatsky reactions*: Trimethylchloro-silane (0.1 equiv) was added to a suspension of zinc metal (8.0 equiv) in anhydrous THF (2 ml). After the mixture was refluxed for 30 min, the heating was stopped, and a solution of ligand (0.5 equiv), *t*-butyl bromoacetate (8.0 equiv) and aromatic aldehyde (0.5 mmol, 1.0 equiv) in THF (2 ml) was slowly added. The mixture was stirred at reflux for 2 h and then quenched at 0 °C with 10% HCl solution. The resulting mixture was extracted with methylene chloride (3 × 5 ml) and the combined extracts were washed with saturated aqueous sodium bicarbonate solution and brine. The solvents were removed under reduced pressure and the residue purified by flash column chromatography to give **5** (32–70% yield) and **3c** (50–75% recovery). The enantioselectivities of **5b**–**j** were determined by HPLC using Chiralcel OJ-H column (0.5 ml/min, 2% 2-propanol/hexane). For better chromatographic separation in CSP-HPLC analysis, *t*-butyl ester **5a** was converted to methyl ester **5c**.
10. By employing the L-Phg-L-Pro dipeptide-derived diastereomeric prolinol ligand of **3c**, the product (*R*)-**5a** was formed with 68% ee. Also, reactions of some aliphatic aldehydes in the presence of **3c** gave lower selectivities and yields under the same reaction condition.