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Original article

Enantioselective trapping of oxonium ylide intermediates by *N*-benzhydryl-α-imino ester: Synthesis of β-tetrasubstituted α-amino acids

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ABSTRACT

A synergistic rhodium(II)/phosphoric acid catalyzed three component reaction of 3-diazooxindoles, alcohols and *N*-benzhydryl-α-imino ester is developed for the efficient construction of chiral β-alkoxy C^{β}-tetrasubstituted α-amino acid derivatives in good yields and with excellent diastereoselectivities and high enantioselectivities. The synthetic application of the resulting products was illustrated by reducing with Pd/C under H_2 atmosphere followed reacting with $CSCl_2$ at room temperature to rapid afford 3-spirocyclic oxindole in a good yield with a chirality retainment. The three-component reaction is proposed to proceed through an electrophilic trapping of the oxonium ylides by *N*-benzhydryl-α-imino ester.

1. Introduction

β-Oxa-quaternary α-amino acid derivatives are common and serviceable structural motifs in biologically active natural products and pharmaceuticals [1]. For instance, the ustiloxin and phomopsin families of natural products are potent microtubule depolymerizers [1a]. Furthermore some quaternary β-substituted α-amino acids are incorporated into peptides to modulate secondary and tertiary structural conformations [2]. An array of elegant methods has been developed for the preparation of β-oxa-quaternary α-amino acid derivatives [3–5]. For example, Joullié and co-workers reported a method through ring opening of aziridines to synthesize these compounds [3]. Nevertheless, there has still been an increasing demand for the development of straightforward and convenient methods for the construction of chiral C^{β}-tetrasubstituted α-amino acids and their derivatives.

Multi-component reactions (MCRs) are highly intriguing owing to significant advantages over traditional chemical synthesis on atom- and step-economy [6]. In recent years, our group has developed several novel multi-component reactions by trapping *in situ* generated active intermediates including oxonium ylides [7], ammonium ylides [8] and zwitterionic intermediates [9] with various electrophiles for the highly efficient construction of complex molecules.

As an active electrophile, α-imino esters have been widely used in direct [10], Lewis acid [11] or Brønsted acids [12] catalyzed Mannich-type additions to produce chiral amino acid derivatives. We also employed α-imino esters with Brønsted acids as catalysts to trap ammonium ylides to develop Mannich-type three-component reaction for the construction of β-amino C^{β}-tetrasubstituted α-amino acid derivatives with an excellent diastereoselectivity and enantioselectivity (Scheme 1, Eq. (1)) [12c]. Very recently, we successfully established a four-component reaction using *in situ* generated α-imino esters to trap zwitterionic intermediates, in which α-amino acid derivatives bearing β-all carbon quaternary carbon center were efficiently provided in a rapid fashion (Scheme 1, Eq. (2)) [12e]. However, there is a significant drawback of the above mentioned methods, as only *N*-aryl imino esters have been employed in all the cases. It has been extremely difficult to find compatible reaction conditions to remove the *N*-aryl protecting group from the three-component products maintaining the C^{β}-tetrasubstituted functionalities unchanged, which thus limited the synthetic utility of these efficient methods. As a consequence, we turned our attention to *N*-benzhydryl α-imino ester which could be deprotected effortlessly under mild conditions. The challenges now

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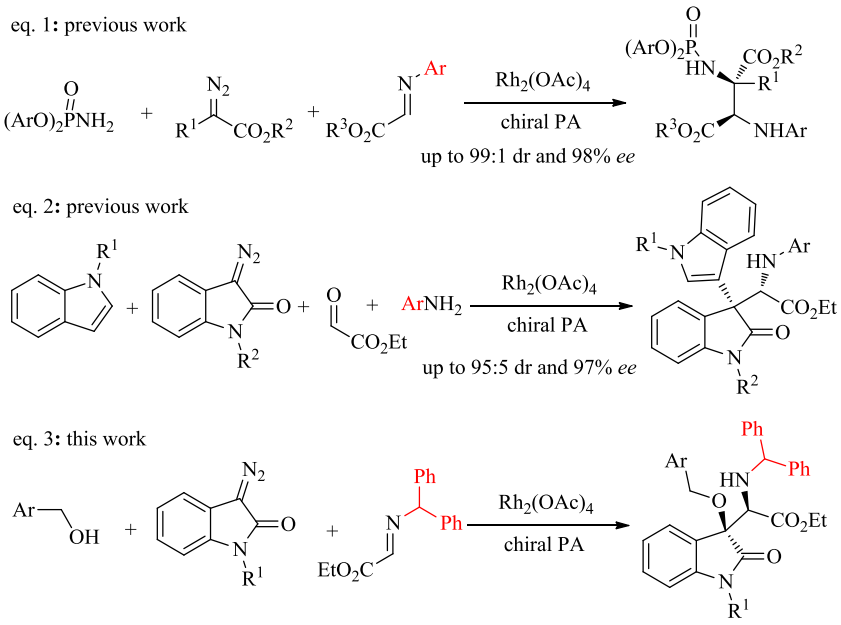


Scheme 1. Electrophilic trapping of active intermediates by α-imino esters.

are to address the reactivity compability of the relatively unreactive *N*-alkyl substituted α-imino ester and the active intermediates, and to achieve a diastereo- and enantioselective control of the reaction. Here, we report the first example of employing *N*-benzhydryl α-imino ester as an effective electrophile to trap oxonium ylide intermediate *in situ* generated from 3-diazooxindoles and alcohols under the co-catalytic system of rhodium(II)/chiral phosphoric acids. β-Alkoxy C^{β}-tetrasubstituted α-amino acid derivatives were obtained in high yields and with an excellent diastereoselectivity and high enantioselectivity (Scheme 1, Eq. (3)).

2. Experimental

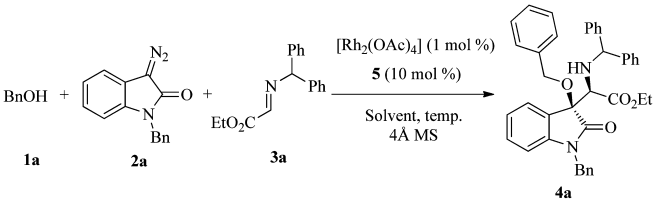
^{1}H NMR and ^{13}C NMR spectra were recorded on Brucker Asend 400 MHz spectrometers. ESI-HRMS spectra were recorded on a Waters Micromass Q-TOF micro Synapt High Definition Mass Spectrometer. Enantiomeric ratio (er) was determined by HPLC analysis on Chiralpak IA columns. The spectral data and spectra of all the compounds are presented in the Supporting information. Commercial grade solvents were dried and redistilled before use. All other reagents were purchased from commercial sources and used without further purification.

General procedure for the preparation of racemic products: A mixture of $Rh_2(OAc)_4$ (0.002 mmol), substituted alcohols **1** (0.3 mmol), imine **3** (0.2 mmol), **5** (10 mol%), and 4 Å MS (100 mg) in 2 mL of CH_2Cl_2 under an argon atmosphere was cooled to 0 °C. Diazo compound **2** (0.3 mmol) in 1 mL of CH_2Cl_2 was then added over 1 h *via* a syringe pump. After completion of the addition, the reaction mixture was stirred for another 0.5 h, then filtrated and evaporated *in vacuo* to give the crude product. The crude products was purified by flash chromatography on silica gel (EtOAc/light petroleum ether = 1:25 ~ 1:10) to give the pure product.

3. Results and discussion

3,3-Disubstituted oxindoles are privileged structural motifs in many biologically active molecules [13]. We decided to perform our three-component reaction of 3-diazooxindole, benzyl alcohol and *N*-benzhydryl α-imino ester, aiming to synthesize the C^{β}-tetrasubstituted α-amino acid derivatives bearing an oxindole framework. A previously established synergistic catalytic system of the $Rh_2(OAc)_4$ and phosphoric acid (PPA) was employed to catalyze the reaction. To our delight, the desired three-component product **4a** was obtained in 61% yield and with >95:5 diastereoselectivity (Table 1, entry 1) at 0 °C. According to our previous experience on activing imines using chiral BINOL-derived phosphoric acid, we evaluated a series of chiral BINOL-derived PPA catalysts **5a**–**g** (Fig. 1) to develop the enantioselective version of this reaction. Among them, (*R*)-3,3′-bis(2,4,6-triisopropylphenyl)-binol phosphoric acid **5e** gave the best result, yielding **4a** in 72% yield and with >95:5 dr and 93:7 er. (Table 1, entries 2–7). With 1 mol% $Rh_2(OAc)_4$ and 10 mol% **5e**, the effects of solvent and temperature were further investigated and CH_2Cl_2 (DCM) was

Table 1
Optimization of the reaction conditions.[a]



Entry	Catalyst **5**	Solvent	T (°C)	Yield (%)[b]	dr (syn:anti)[c]	er [d]
1	*rac*-**5a**	DCM	0	61	>20:1	–
2	**5b**	DCM	0	75	>20:1	57:43
3	**5c**	DCM	0	72	>20:1	67:33
4	**5d**	DCM	0	30	>20:1	54:46
5	**5e**	DCM	0	72	>20:1	93:7
6	**5f**	DCM	0	45	>20:1	87:13
7	**5g**	DCM	0	68	>20:1	67:33
8	**5e**	PhMe	0	87	>20:1	80:20
9	**5e**	DCE	0	67	>20:1	89:11
10	**5e**	$CHCl_3$	0	61	>20:1	93:7
11	**5e**	DCM	25	66	>20:1	88:12
12	**5e**	DCM	−10	70	>20:1	92:8

[a] Reactions were conducted in 0.10 mmol scale of **3a. 1a**:**2a**:**3a**:**5** = 1.5:1.5:1.0:0.1.
[b] Isolated yield after column chromatography.
[c] Determined by ^{1}H NMR analysis of crude reaction mixture.
[d] Determined by chiral HPLC of major diastereomer.

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