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Organocatalytic Sequential α-Amination–Horner–Wadsworth–Emmons Olefination of Aldehydes: Enantioselective Synthesis of γ-Amino-α,β-Unsaturated Esters

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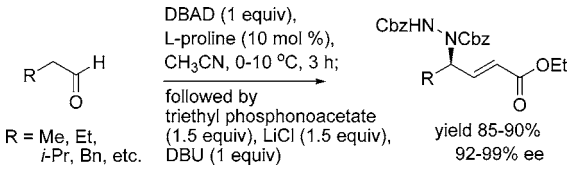
ABSTRACT



A novel and highly enantioselective method for the synthesis of γ-amino-α,β-unsaturated esters via tandem α-amination–Horner–Wadsworth–Emmons (HWE) olefination of aldehydes is described. The one-pot assembly has been demonstrated for the construction of functionalized chiral 2-pyrrolidones, subunits present in several alkaloids.

Chiral allylic amines, particularly γ-amino-α,β-unsaturated esters **3**, are the key structural elements present in a variety of important naturally occurring molecules[1] and are among the most versatile synthetic intermediates for peptide derivatives,[2] iminosugars,[3] glutamate receptors,[4] amino acids,[5] alkaloids,[6] carbohydrate derivatives,[7] etc., possessing various biological activities such as enzyme inhibitors.[1a,7] Moreover, they are readily functionalized to aminodiols,[8]amino epoxy esters,[9] etc. Few general methods of synthesis are described in the literature to obtain enantiomerically pure γ-amino-α,β-unsaturated esters,[10,11] and most of them employ Wittig olefination of α-amino aldehydes that are usually prepared from naturally occurring α-amino acids. However, these methods are limited by the possibility that racemization may

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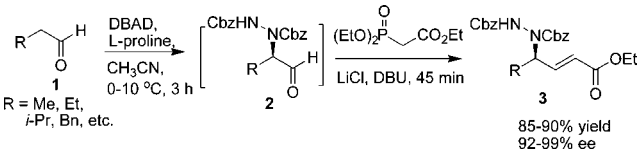
occur during the Wittig reaction.[12] For these reasons, a general synthetic process which employs readily available starting materials and overcomes the above difficulties is still desirable for obtaining chiral γ-amino-α,β-unsaturated esters, **3**.

Organocatalysis is a rapidly growing research field in organic synthesis and has the advantage of being highly selective and reducing synthetic manipulations.[13] It is often associated with mild and simple reaction conditions that are appealing because of the easy handling, cost, and safety issues. In recent years, proline has been employed in a variety of asymmetric reactions including aldol,[14] Diels−Alder,[15] Michael addition,[16] and α-functionalization[17] among many others.[13b,18] Particularly, proline-catalyzed direct α-amination of aldehydes has emerged as a reliable method for the enantioselective synthesis of α-amino acid derivatives.[19]

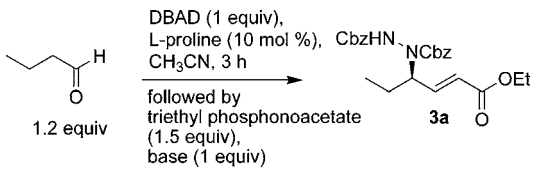
In proline-catalyzed direct α-amination of aldehydes, the reactive intermediate **2**, generated in situ, was transformed into several functionalized organic derivatives: for instance, it was reduced to 1,2-aminoalcohol,[19a] cyclized by intramolecular Wittig olefination to 3,6-dihydropyridazines,[20a] or condensed under aldol conditions to form functionalized β-amino alcohols.[20b] As part of our research program directed toward asymmetric synthesis of biologically active molecules using organocatalysts,[21] we designed experiments in trapping the intermediate **2** with triethyl phosphonoacetate to obtain the corresponding chiral γ-amino-α,β-unsaturated esters **3** (Scheme 1). In this communication, we describe a one-pot procedure for obtaining highly enantioselective synthesis of γ-amino-α,β-unsaturated esters **3** using tandem α-amination−Horner−Wadsworth−Emmons (HWE) olefination of aldehydes **1** (Scheme 1).

Scheme 1. In Situ Trapping of α-Amino Aldehydes with Triethyl Phosphonoacetate



In the preliminary study, α-amination of *n*-butyraldehyde was conducted following List's protocol[19a] to obtain α-amino aldehyde **2** in situ. Because these α-amino aldehydes are prone to racemization,[12] we performed several experiments to identify the most effective and suitable base for HWE olefination. First, the in situ olefination of **2** was carried out by the addition of triethyl phosphonoacetate (1.5 equiv) and Cs_2CO_3[22] (1 equiv) that produced **3a** in 80% yield with low enantioselectivity (22% ee), probably due to racemization caused by the base. However, improvements in ee's (88%) were achieved by screening of other bases, particularly DBU (Masamune−Roush protocol)[23] (Table 1, entries 2 and 3).

Table 1. Proline-Catalyzed α-Amination/HWE Olefination of *n*-Butyraldehyde



entry	base[a]	temp (°C)	time (min)	yield[b] (%)	ee[c] (%)
1	Cs_2CO_3	25	120	80	22
2	$Ba(OH)_2$	25	120	78	67
3	DBU	25	120	87	88
4	DBU	5	45	84	99

[a] LiCl (1.5 equiv) was used in the case of DBU. [b] Yield of isolated product after column chromatography. [c] Enantiomeric excess was determined by chiral HPLC analysis (Chiracel OD−H, hexane/2-propanol = 96:4).

Because of the epimerizable nature of α-amino aldehydes, we believed that a shorter reaction time and lower temperature should prevent racemization without compromising on the yields. Expectedly, by performing the reaction at 5 °C for 45 min, **3a** was indeed obtained in 84% yield with excellent enantioselectivity (99% ee) (Table 1).

We examined the scope of several aldehydes bearing different functionalities under the optimized reaction conditions.[24] In all cases studied, the desired γ-amino-α,β-unsaturated esters **3a**−**f** were obtained in excellent yields (80−88%) and enantioselectivities (92−99%) (Table 2). However, use of other solvents such as THF and CH_2Cl_2 for the tandem protocol resulted in a sluggish reaction with poor yields (<50%).

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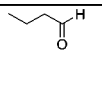
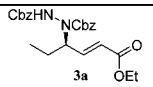
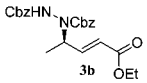
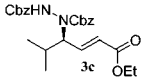
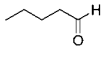
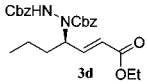
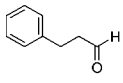
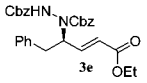
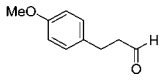
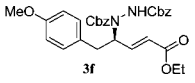
Table 2. Proline-Catalyzed Asymmetric Tandem α-Amination/HWE Olefination[a]

entry	substrates 1(a-f)	products (3 a-f)	yield[b] (%)	ee[c] (%)
1		 3a	84	99
2		 3b	83	92
3		 3c	80	92
4		 3d	85	95
5		 3e	88	99
6		 3f	88	99

[a] Reaction conditions: aldehyde (1.2 equiv), DBAD (1 equiv), L-proline (10 mol %), triethyl phosphonoacetate (1.5 equiv), LiCl (1.5 equiv), DBU (1 equiv), and CH_3CN were used. [b] Yields of isolated product after column chromatography. [c] Enantiomeric excess was determined by chiral HPLC analysis (Chiracel OD−H).

The absolute configuration of the newly generated amine center was assigned on the basis of the previously established configuration of α-amino aldehyde,[19a] which was also confirmed by matching the sign of the optical rotation of pyrrolidone **8**[25] as well as by X-ray crystallographic analysis of triacetate **6** (Figure 1).

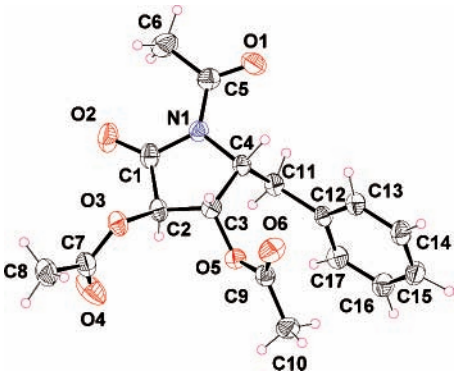
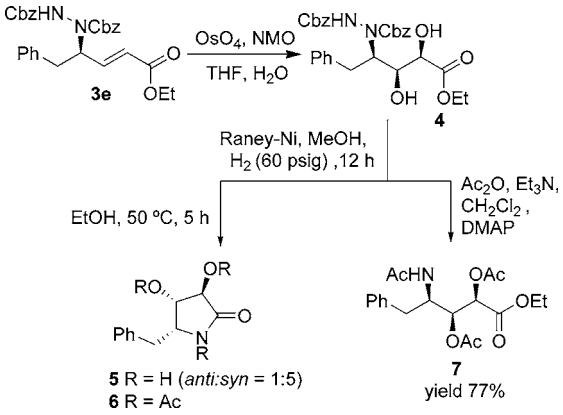


Figure 1. ORTEP diagram of triacetate **6**.

Among the potential applications of this methodology, a short asymmetric synthesis of substituted 2-pyrrolidone derivatives **5** and **8**, common subunits present in a variety of alkaloids,[26] seemed attractive to us due to their chemotherapeutic utilities such as anti-HIV and anticancer agents.[27]

For the synthesis of **5**, amino olefinic ester **3e** underwent Os-catalyzed dihydroxylation in a diastereoselective manner[8] to produce the corresponding aminodiol **4** (92% yield), which was hydrogenated over Raney nickel, thus affording either the cyclized dihydroxy pyrrolidone **5** (dr = 1:5, 65% yield) or its triacetate derivative **7**, a building block found in sphingosines,[28] depending upon the reaction conditions (Scheme 2).

Scheme 2. Synthesis of 2-Pyrrolidone **5** and Triacetate **7**



The stereochemistry in **5** is assigned unambiguously on the basis of COSY and NOESY studies[29] and X-ray crystallographic analysis (Figure 1) of its triacetate **6** as well as by the literature precedence.[19a] The single-step transformation of **3c** under hydrogenation conditions (Raney nickel, H_2, 60 psig) to obtain 2-pyrrolidone **8** (70% yield, 91% ee) constitutes another application of this methodology (Scheme 3).

In summary, we have reported, for the first time, a novel, one-pot procedure of sequential α-amination−HWE olefi-

(24) **General experimental procedure:** To a cooled solution of dibenzyl azodicarboxylate (DBAD) (328 mg, 1 mmol) and L-proline (11.5 mg, 10 mol %) in dry CH_3CN (10 mL) at 0 °C was added *n*-butyraldehyde (87 mg, 1.2 mmol), and the mixture was stirred for 2 h at 0 °C and further at 10 °C for 1 h. This was followed by addition of lithium bromide (130 mg, 1.5 mmol), triethyl phosphonoacetate (336 mg, 1.5 mmol), and DBU (152 mg, 1 mmol) in that sequence, and the whole mixture was stirred at 5 °C for 45 min. It was then quenched by the addition of aqueous ammonium chloride solution and extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give the crude product **3a**, which was then purified by flash column chromatography (packed with silica gel 60−120 mesh) using petroleum ether and ethyl acetate as eluents to afford the pure product **3a**. Viscous liquid: yield, 84%; HPLC, Chiracel OD−H column (2-propanol/*n*-hexane = 4:96, flow rate 1.0 mL/min, λ = 260 nm). Retention time (min): 40.15 (major) and 54.95 (minor). The racemic standard was prepared in the same way with DL-proline as catalyst [99% ee, $[\alpha]^{25}_D$ +10 (*c* 1.0, $CHCl_3$)]. IR ($CHCl_3$) ν 3389, 3020, 2926, 2852, 1758, 1715, 1289, 1215, 1041, 757 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 0.94 (m, 3H), 1.25 (t, J = 7 Hz, 3H), 1.62 (m, 2H), 4.13 (q, J = 7.3 Hz, 2H), 4.64 (m, 1H), 5.11 (m, 4H), 5.85 (d, J = 15.6 Hz, 1H), 6.86 (m, 2H), 7.28 (m, 10H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 10.42, 13.90, 23.88, 60.32, 64.70, 67.45, 68.01, 122.25, 127.48, 127.87, 128.25, 144.77, 155.53, 156.56, 166.09. Anal. calcd $C_{24}H_{28}N_2O_6$: C, 65.44; H, 6.41; N, 6.36. Found: C, 65.25; H, 6.28; N, 6.59%.

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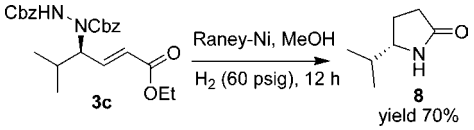
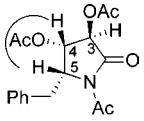
Scheme 3. Synthesis of (*S*)-5-Isopropylpyrrolidin-2-one (**8**)



nation of aldehydes that leads to enantioselective synthesis of γ-amino-α,β-unsaturated esters **3** with excellent yields and high enantioselectivities. The potential of this reaction has been demonstrated by its easy and efficient incorporation in the synthesis of important optically active 2-pyrrolidinone derivatives **5** and **8** in good yields and by the great substrate generality. We hope that this method will find tremendous applications in the synthesis of various biologically active organic molecules due to its salient features such as (1) easy availability of starting materials, (2) simple environmentally friendly procedure, and (3) availability of proline in both enantiomeric forms.

(29) The relative stereochemistry of **5** was confirmed by COSY and NOESY studies. A significant NOESY correlation was observed between H_4 and H_5. There was no observed correlation between H_3-H_4 and H_3-H_5 confirming a syn relationship between H_4 and H_5.



Triacetate **6**

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Supporting Information Available: Spectral data for all the compounds are given. This material is available free of charge via the Internet at http://pubs.acs.org.

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