Enantioselective Synthesis of γ-Functionalized α-Dehydroamino Esters

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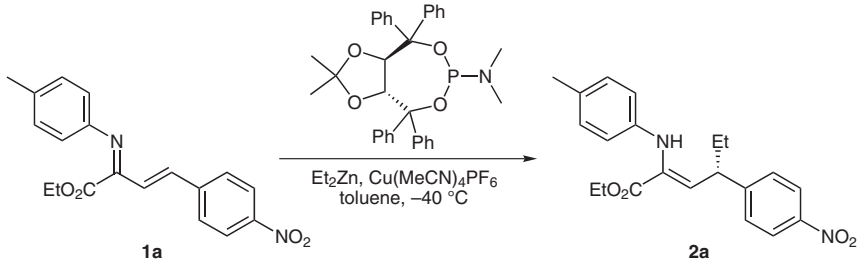
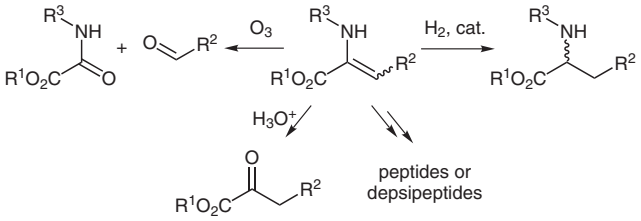
Abstract: Copper-catalyzed asymmetric 1,4-addition of diethylzinc to β,γ-unsaturated α-imino esters **1** using a copper-phosphoramidite complex affords enantiomerically enriched γ-functionalized α-dehydroamino esters **2**.

Key words: amino acids, asymmetric catalysis, imines, Michael addition, organometallics



Scheme 1 Copper-catalyzed asymmetric conjugate addition of Et_2Zn to α,β-unsaturated imine **1a** derived from α-amino acids

α-Dehydroamino acids represent an important family of compounds in organic synthesis, since they are ordinary synthons of natural and unnatural α-amino acids, most commonly through their enantioselective catalytic hydrogenation.[1] They can also be precursors of oxalamic acid derivatives if the C=C bond is ozonolyzed[2] and have been often used as precursors of α-keto acids through the hydrolysis of the imine functional group[3] (Scheme 2).



Scheme 2 Synthetic applications of α-dehydroamino acids

As well as being interesting synthetic intermediates, α-dehydroamino acids also show intriguing biological activities[4] and have been used to modify the conformational properties of peptides.[5] The most common procedure for the preparation of α-dehydroamino acids is the β-elimination of α-amino acid derived alcohols or halides,[6] although other efficient synthesis of α-dehydroamino acids have also been reported; for example, ring opening of imidazolidines[7] or aziridines,[8] nucleophilic addition to alkynoates,[9] or Horner–Emmons condensation of phosphorylglycine esters and aldehydes.[10]

As part of our research in the field of the chemistry of azadienes,[11] we have recently developed an efficient synthetic methodology for the synthesis of α,β-unsaturated imines derived from α-amino acids through aza-Wittig reaction of β,γ-unsaturated α-keto esters and *P*-trimethylphosphazenes.[11b] The easy synthetic availability of such 1-azadienes prompted us to examine their reactivity towards nucleophile species. Specifically we thought that regioselective nucleophilic conjugate addition takes place with simultaneous formation of a new stereogenic center, and therefore we conceived the idea of developing a synthetic methodology for the catalytic enantioselective 1,4 addition of organozinc reagents to α,β-unsaturated imines derived from α-amino acids which would afford chiral α-dehydroamino acid derivatives[12] (Scheme 1).

In a typical procedure, Et_2Zn was added over two hours at –40 °C to a toluene solution of 1-azadiene **1** and the copper catalyst, which was previously prepared 'in situ' from $Cu(MeCN)_4PF_6$ and TADDOL derived phosphoramidite. This method was successfully applied to the synthesis of several (*S*)-α-dehydroamino esters **2**, observing very good enantioselectivities in all the cases (Scheme 3, Table 1).[13]

Although an increase in enantioselectivity can be achieved if the temperature is lowered, a rise in the rates of the double and 1,2 addition products is also observed at –50 °C or –80 °C, whereas lower enantioselectivity and no significant decrease in the rates of the double and 1,2-

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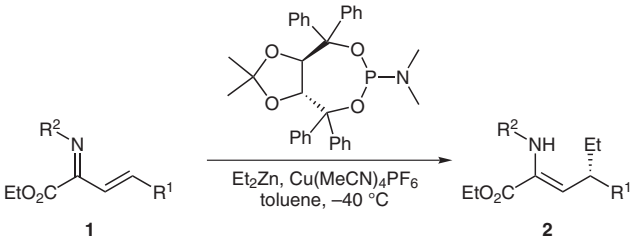

1 2

Scheme 3 Copper-catalyzed asymmetric conjugate addition of Et_2Zn to several α,β-unsaturated imines **1** derived from α-amino acids

Table 1 Enantiomeric Ratio for the Conjugate Addition of Et_2Zn to Several β,γ-Unsaturated α-Imino Esters

Product	R^1	R^2	Yield (%)[a]	er (%)
2a	4-MeC_6H_4	4-$NO_2C_6H_4$	89	94:6
2b	4-$MeOC_6H_4$	4-$NO_2C_6H_4$	87	89:11
2c[b]	4-MeC_6H_4	4-MeC_6H_4	85	88:12
2d[b]	4-$NO_2C_6H_4$	4-MeC_6H_4	83	91:9

[a] After chromatography.
[b] Methyl ester instead of ethyl ester.

addition products are observed when the temperature is raised to –30 °C, 0 °C or 25 °C. A dramatic drop in the enantioselectivity as well as increased rates of 1,2- or/and double addition is also obtained when other noncoordinating solvents (CH_2Cl_2, $CHCl_3$), weakly coordinating solvents (Et_2O, *t*-BuOMe), or stronger coordinating solvents (THF) are used. Both Cu(I) and Cu(II) salts can be used with success as catalysts for enantioselective Michael addition of organozinc to β,β-unsaturated α-imino esters **1**, but slightly better enantioselectivities are obtained if $Cu(MeCN)_4PF_6$ is used.

When the conventional procedure for the addition of organozinc to conjugated systems is followed,[14] double addition product and the starting 1-azadiene **1** are mostly recovered. This is probably due to the concomitance of the resulting enamine with an excess of the very reactive organometallic species, which can undergo a second catalyzed or non-catalyzed nucleophilic 1,2-addition. Several attempts to extend this methodology to the regioselective asymmetric addition of dimethylzinc were unsuccessful, due to the massive presence of 1,2- and double addition products.

In conclusion, the synthesis of chiral γ-functionalized α-dehydroamino acid derivatives is achieved through asymmetric conjugate addition of diethylzinc to β,γ-unsaturated α-imino esters.

Solvents for extraction and chromatography were of technical grade. All solvents used in reactions were freshly distilled from appropriate drying agents before use. All other reagents were recrystallized or distilled as necessary. All reactions were performed under an atmosphere of dry N_2. ^1H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded on a Varian VXR 300 MHz spectrometer using $CDCl_3$ solutions with TMS as an internal reference (δ = 0.00). Low-resolution mass spectra (MS) were obtained at 50–70 eV by electron impact (EIMS) on a Hewlett Packard 5973 spectrometer and by chemical ionization (CI, N_2) on a Hewlett Packard 1100MSD. IR spectra were taken on a Nicolet IRFT Magna 550 spectrometer, and were obtained in KBr for solids or neat for oils. Elemental analyses were performed in a LECO CHNS-932 apparatus. Determination of the enantiomeric ratios was carried out by HPLC analysis (Chiracel OD-H, hexane–EtOH, 99:1, 0.5 mL/min). TADDOL derived phoshoramidite ligand is commercially available and α,β-unsaturated imines **1** derived from α-amino acids were prepared following a literature procedure.[11b]

Asymmetric Conjugate Addition of Et_2Zn to α,β-Unsaturated Imine 1a Derived from α-Amino Acids; Chiral α-Dehydroamino Ester 2a; Typical Procedure

A solution of $Cu(MeCN)_4PF_6$ (1.86 mg, 5 μmol) and TADDOL derived phosphoramidite ligand (5.40 mg, 10 μmol) in toluene (500 μL) was stirred at r.t. for 1 h. The resulting copper-phosphoramidite complex solution was cooled to –40 °C and α,β-unsaturated imine **1a** (100 μmol) was then added. The resulting solution was stirred at –40 °C for 15 min and a 1.5 M solution of Et_2Zn in toluene (100 μL, 150 μmol) was then added over a period of 2 h. The resulting dark solution was quenched with sat. aq NH_4Cl (1 mL) and stirred vigorously until a clear mixture was obtained. The resulting mixture was warmed to r.t and extracted with Et_2O (3 mL), which was dried ($MgSO_4$), and concentrated under vacuum. The crude residue was purified by chromatography (SiO_2, Et_2O–pentane, 1:3) to afford 33.6 mg (89%) of α-dehydroamino ester **2a** as a pale yellow oil; er = 94:6.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.81 (t, $^3J_{H,H}$ = 7.7 Hz, 3 H, CH_3), 1.27 (t, $^3J_{H,H}$ = 7.2 Hz, 3 H, CH_3), 1.74 (m, 2 H, CH_2), 2.26 (s, 3 H, CH_3), 3.53 (m, 1 H, CH), 4.22 (q, $^3J_{H,H}$ = 7.2 Hz, 2 H, CH_2O), 5.34 (s, 1 H, NH), 6.46 (d, $^3J_{H,H}$ = 9.9 Hz, 1 H, CH=), 6.53 (d, $^3J_{H,H}$ = 7.2 Hz, 2 H_{arom}), 6.94 (d, $^3J_{H,H}$ = 7.5 Hz, 2 H_{arom}), 7.20 (d, $^3J_{H,H}$ = 7.5 Hz, 2 H_{arom}), 8.10 (d, $^3J_{H,H}$ = 7.5 Hz, 2 H_{arom}).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.8 (CH_3), 14.1 (CH_3), 20.5 (CH_3), 29.8 (CH_2), 45.3 (CH), 61.5 (CH_2O), 116.9 (2 × CH_{arom}), 123.5 (2 × CH_{arom}), 123.8 (C_{quat}), 128.5 (2 × CH_{arom}), 129.4 (2 × CH_{arom}), 129.9 (=CH), 130.8 (C_{quat}), 141.3 (C_{quat}), 146.4 (C_{quat}), 150.9 (C_{quat}), 165.7 (C=O).

MS (CIMS): *m/z* (%) = 369 (100, $[M^+ + 1]$), 295 (76, $[M^+ – CO_2Et]$).

Anal. Calcd for $C_{21}H_{24}N_2O_4$: C, 68.46; H, 6.57; N, 7.60. Found: C, 68.54; H, 6.60; N, 7.57.

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(13) The absolute configuration of the stereogenic center of α-dehydroamino esters **2** was established by comparison of the rotary power of the known carboxylic acid resulting from ozonolysis and subsequent oxidation of the intermediate aldehyde.
(14) The conventional process involves the addition of a solution of 1-azadiene **1** to a toluene solution of diethylzinc together with the copper catalyst.