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Copper-Catalyzed Asymmetric Conjugate Addition of Diethylzinc to α,β-Unsaturated Imines Derived from α-Aminoacids. Enantioselective Synthesis of γ-Substituted α-Dehydroaminoesters

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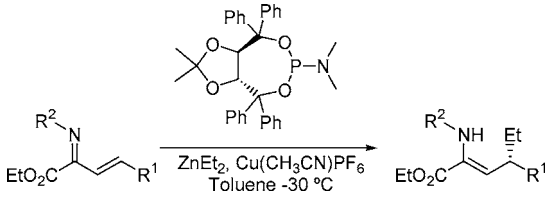
ABSTRACT



A highly enantioselective synthesis of α-dehydroaminoacids with a stereogenic center in the γ position through copper-catalyzed asymmetric conjugate addition of diethylzinc to α,β-unsaturated imines using a TADDOL-derived phosphoramidite complex is reported.

The asymmetric conjugate addition of dialkylzinc to prochiral α,β-unsaturated systems is one of the most powerful synthetic tools in organic chemistry.[1] The first application of a copper-catalyzed addition of $ZnEt_2$ to enones with 32% ee was reported by Alexakis in 1993.[2] Since then, a lot of effort has been made in the development of new ligands for this reaction, culminating in 1997 with the first highly enantioselective conjugate addition of organozinc reagents, using a copper-phosphoramidite ligand derived from BINOL, reported by Feringa.[3] Within this context, although the asymmetric conjugate addition of dialkylzinc to α,β-unsaturated carbonylic compounds is well documented, to the best of our knowledge only two reports of this reaction with the related α,β-unsaturated imines by using imines[4] derived from chalcones have been previously reported. In both cases the presence of a sulfonyl group directly bonded to the imine nitrogen atom seemed to be essential for this reaction to proceed.

We have been involved in the chemistry of 1-[5] and 2-azadienes,[6] and recently we reported an efficient synthesis of α,β-unsaturated imines derived from α-aminoacids.[7] As a continuation of our work on the reactivity of functionalized

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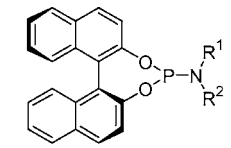
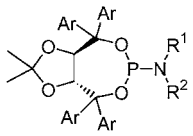
azadienes, we report here the first enantioselective conjugate addition of diethylzinc to conjugated imines derived from α-aminoacids, catalyzed by a copper-phosphoramidite complex, to afford α-dehydroaminoesters with a stereogenic center in the γ position.

In a first approach we tested the ability of copper(II) triflate complexes with a broad branch of ligands (Figure 1) as chiral





L1: $R^1 = R^2 = CH_3$
L2: NR^1R^2 = Pyrrolidine
L3: $R^1 = CH_2Ph$, $R^2 = H$
L4: $R^1 = R^2 = (R)$-1-Ph-Et
L5: $R^1 = R^2 = (S)$-1-Ph-Et
L6: $R^1 = (R)$-1-Ph-Et, $R^2 = H$
L7: $R^1 = R^2 = CH_3$, Ar = Ph
L8: $R^1 = (S)$-1-Ph-Et, $R^2 = H$, Ar = Ph
L9: $R^1 = R^2 = (R)$-1-Ph-Et, Ar = Ph
L10: $R^1 = R^2 = (S)$-1-Ph-Et, Ar = Ph
L11: $R^1 = R^2 = CH_3$, Ar = 2-Naph

Figure 1. Ligands tested in the asymmetric conjugate addition of $ZnEt_2$ to α,β-unsaturated imines **1** derived from α-aminoacids.

inductors. The racemic reaction was carried out using the α,β-unsaturated imine **1a** ($R^1 = p$-NO_2-Ph, $R^2 = p$-Me-Ph) and 1.5 equiv of $ZnEt_2$ in toluene at −30 °C and using $Cu(OTf)_2(PPh_3)_2$ as catalyst (Table 1, entry 2). On the basis of

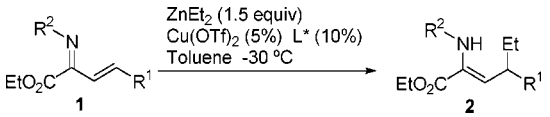
Table 1. Ligand Optimization for Conjugate Addition of $ZnEt_2$ to β,γ-Unsaturated α-Iminoester **1a** ($R^1 = p$-Me-C_6H_6, $R^2 = p$-NO_2-C_6H_6) in Toluene at −30 °C

entry	L	time (h)	convn (%)	1,4:1,2:double	er[a]
1		16	30	99:<1:<1	
2	PPh_3	1.5	>99	98:1:1	
3	**L1**	2	>99	97:2:2	19:81
4	**L2**	2	>99	94:6:<1	23:77
5	**L3**	2	>99	94:<1:6	22:78
6	**L4**	2	>99	90:3:7	45:55
7	**L5**	2	>99	85:5:5	59:41
8	**L6**	2	>99	81:9:10	14:86
9	**L7**	2	>99	92:1:7	89:11
10	**L8**	2	>99	98:1:1	70:30
11	**L9**	2	>99	94:3:3	85:15
12	**L10**	2	>99	92:5:3	61:39
13	**L11**	2	>99	92:5:3	80:20

[a] According to R. E. Gawley we report er instead of the usual ee[8].

^{1}H NMR-NOE experiments, a *Z* configuration of the α-dehydroaminoesters **2** was established. As expected, the background reaction was very slow in the absence of the copper catalyst or in the presence of just $Cu(OTf)_2$ (Table 1, entry 1). Full conversions and good enantioselectivities were obtained when binaphtol phosphoramidites (Figure 1, **L1**−**L6**; Table 1, entries 3−8) were used. It is worth noting the increased rate observed when dimethylamine (**L1**) was changed by (*R*)-2-phenylethylamine (**L6**).

Scheme 1. Copper-Catalyzed Conjugate Addition of $ZnEt_2$ to α,β-Unsaturated Imines **1** Derived from α-Aminoacids



On the other hand, a promising result with good enantioselectivity was observed when the copper-TADDOL phosphoramidite derived from dimethylamine was used (Figure 1, **L7**; Table 1, entry 9), Unfortunately, the use of the new TADDOL-derived phosphoramidite ligand **L8** (Table 1, entry 10) did not show the same improvement in enantioselectivity as was observed with binaphthol ligands. Likewise, neither was any improvement in enantioselectivity obtained when other TADDOL phosphoramidites derived from bis(phenylethylamine) (Figure 1, **L9**, **L10**; Table 1, entries 11, 12) were used, nor when phenyl groups by 2-naphthyl substituents (Figure 1, **L11**; Table 1, entry 13) were substituted for them.

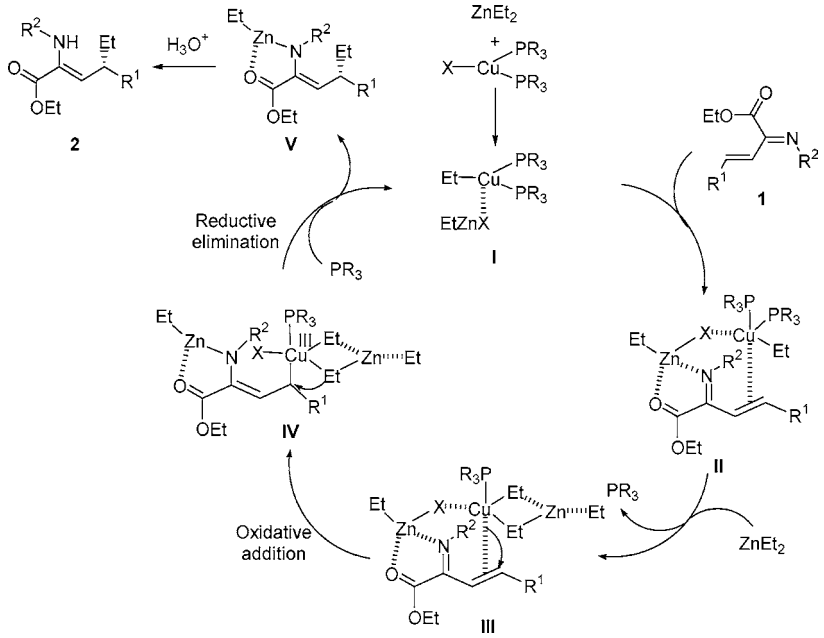
The dependence of the enantioselectivity of the process on the temperature and solvent is well-known. Therefore, we focused our efforts on exploring the optimal temperature and solvent for the conjugate addition of $ZnEt_2$ (Table 2).

Table 2. Temperature, Solvent, and Copper Source Effect on the Conjugate Addition of 1.5 equiv of $ZnEt_2$ to β,γ-Unsaturated α-Iminoester **1a** Using TADDOL-Derived Ligand **L7** (10%)

solv	CuX	temp (°C)	time (h)	1,4:1,2: double	er[8]
toluene	$Cu(OTf)_2$	0	2	98:1:1	87:13
toluene	$Cu(OTf)_2$	−30	2	92:1:7	89:11
toluene	$Cu(OTf)_2$	−40	2	90:3:7	91:9
toluene	$Cu(OTf)_2$	−50	4	82:16:2	92:8
toluene	$Cu(OTf)_2$	−80	16	81:19:<1	80:20
CH_2Cl_2	$Cu(OTf)_2$	−40	2	93:3:4	84:16
$CHCl_3$	$Cu(OTf)_2$	−40	4	73:5:22	80:20
Et_2O	$Cu(OTf)_2$	−40	4	61:31:8	79:21
^{t}BuOMe	$Cu(OTf)_2$	−40	16	99:1:<1	77:23
THF	$Cu(OTf)_2$	−40	16	47:31:22	80:20
toluene	$Cu(OAc)_2$	−40	2	92:<1:8	87:13
toluene	$Cu(acac)_2$	−40	2	95:<1:5	88:12
toluene	$Cu(CF_3COAcO)_2$	−40	2	93:<1:7	88:12
toluene	$Cu(PirazCO_2)_2$	−40	2	90:1:9	87:13
toluene	$Cu(CH_3CN)_4PF_6$	−40	2	92:<1:8	94:6
toluene	CuBr	−40	2	97:<1:3	89:11
toluene	CuI	−40	2	91:1:8	89:11
toluene	CuCN	−40	2	92:<1:8	90:10

An increase in enantioselectivity was observed when the temperature was lowered, but the rates of the quaternary carbon containing double addition and the kinetic 1,2-addition products were also raised. Unfortunately, compared to toluene no improvement in enantioselectivity and increased rates of 1,2 or/and double addition were observed when other

Scheme 2. Tentative Catalytic Cycle for 1,4-Addition of $ZnEt_2$ to α,β-Unsaturated Imines **1** Derived from α-Aminoacids



noncoordinating solvents (Table 2, CH_2Cl_2 and $CHCl_3$), weakly coordinating solvents (Table 2, Et_2O, ^{t}BuOMe), or more strongly coordinating solvents (Table 2, THF) were used. Toluene at −40 °C was determined as the best choice of solvent and temperature. Both Cu(I) and Cu(II) salts have been used with success as catalysts for Michael addition of organozinc to conjugated systems. This supposes that when Cu(II) sources are used, an in situ reduction to Cu(I) by $ZnEt_2$ takes place. A screening of several copper sources using the best solvent and temperature conditions showed only an improvement in enantioselectivity with respect to $Cu(OTf)_2$ when $Cu(CH_3CN)_4PF_6$ was used (Table 2).

Having optimized the catalyst, temperature, solvent, and copper source, for $ZnEt_2$ addition to α,β-unsaturated imine **1a** (R^1 = *p*-Me-Ph, R^2 = *p*-NO_2-Ph), the best conditions were applied for several α,β-unsaturated imines derived from α-aminoacids, and optically enriched α-dehydroaminoesters **2** were obtained[9] (Table 3). It should be also emphasized that the reduction of catalyst rate from 5% to 3% did not imply an excessive drop in the enantioselectivity of the process (Table 3).

Based on previous mechanistic studies concerning conjugate addition of organozinc to enones[10] we propose a catalytic cycle as shown in Scheme 2, with an initial alkyl transfer from Et_2Zn to the copper salt, followed by formation of the π-complex **I** between the soft Cu species and the double bond of the α,β-unsaturated imine, where the imine nitrogen and the carbonyl oxygen are chelated with the hard Lewis acid EtZnX, forming a five-membered ring. Coordination of both copper and zinc with the counteranion in species **I** would be essential for the exclusive formation of the *Z*-enamine, since by means of such coordination the necessary less stable pseudo-*cis* configuration is fixed in the α,β-unsaturated system. Then a second molecule of $ZnEt_2$ is captured by the Cu species with simultaneous release of one of the phosphoramidite ligand molecules to form a highly nucleophilic Cu/Zn cluster **III**, which undergoes an oxidative

Table 3. Conjugate Addition of $ZnEt_2$ to Several β,γ-Unsaturated α-Iminoesters **1** Using TADDOL-Derived Phosphoramidite **L13** (10%) and $Cu(CH_3CN)_4PF_6$ (5%)

compd	R^1	R^2	yield[c] (%)	1,4:1,2: double	er[8]
2a	*p*-Me-Ph	*p*-NO_2-Ph	89	92:<1:8	94:6
2b	*p*-MeO-Ph	*p*-NO_2-Ph	87	98:1:1	89:11
2c[a]	*p*-Me-Ph	*p*-Me-Ph	85	99:<1:1	88:12
2d[a]	*p*-NO_2-Ph	*p*-Me-Ph	83	96:3:1	91:9
2d[a,b]	*p*-NO_2-Ph	*p*-Me-Ph	85	95:3:2	88:12

[a] Methyl ester instead of ethyl ester. [b] Using 3% of copper-phosphoramidite catalyst. [c] After chromatography.

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(9) **General procedure** for the asymmetric conjugate addition of $ZnEt_2$ to α,β-unsaturated imines **1** derived from α-aminoacids: A solution of $Cu(CH_3CN)PF_6$ (1.86 mg, 5 μmol) and phosphoramidite ligand **L7** (5.40 mg, 10 μmol) in toluene (500 μL) was stirred at room temperature for 1 h. The resulting copper-phosphoramidite complex solution was cooled to −40 °C, and the corresponding α,β-unsaturated imine **1** (100 μmol) was then added. The resulting solution was stirred at −40 °C for 15 minutes, and a 1.5 M solution of $ZnEt_2$ in toluene (100 μL, 150 μmol) was then added over a period of 2 h. The resulting dark solution was quenched with a saturated aqueous solution of NH_4Cl (1 mL) and stirred vigorously until a clear mixture was obtained. The resulting mixture was warmed to room temperature and extracted with Et_2O (3 mL), which was dried over $MgSO_4$ and concentrated at low pressure. The crude residue was purified by chromatography (SiO_2, Et_2O/pentane 1:3) to afford α-dehydroaminoesters **2**.

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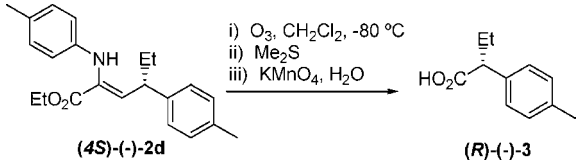
addition of the organocopper reagent to the double bond to afford the σ-complex **IV**. Finally, a reductive elimination with concomitant formation of the C−C bond yields the enolate **V** (probably in the thermodynamically more stable dimeric form), which can be quenched with water to give α-dehydroaminoester **2**.

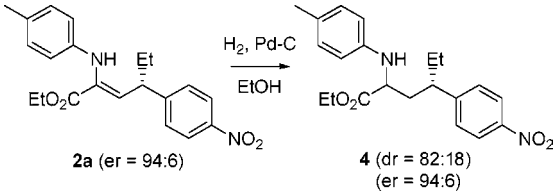
In order to stablish the absolute configuration of the stereogenic center, enamine **2a** was submitted to ozonlysis to afford aldehyde, which was oxidized to the known carboxylic acid (*R*)-**3**,[11] revealing a *S* configuration for **2d** (Scheme 3).

Scheme 3. Ozonolysis of the α-Dehydroaminoester (4*S*)-**2d**



It is well-known that α-dehydroaminoesters are efficient starting materials for the preparation of optically active substituted aminoesters by catalytic hydrogenation.[12] In our case, the presence of a stereogenic center in the γ position can work as a chiral inductor, and when α-dehydroaminoester **2a** was submitted to palladium-catalyzed hydrogenation conditions, α-aminoester **4** was obtained with a diastereomeric ratio of 82:18. The suprafacial (*syn*) addition of hydrogen is the most accepted mechanism for metal-catalyzed hydrogenations, in which the reaction occurs between species that are adsorbed on the surface (Langmuir−Hinshelwood mechanism).[13] Therefore, the enamine is expected to approach the molecular hydrogen, which is adsorbed on the palladium surface, bearing both substituents at the stereogenic center pointing out of the catalyst, which would explain the diastereoselectivity observed for the hydrogenation.

Scheme 4. Hydrogenation of α-Dehydroaminoester **2a**



In conclusion, a highly enantioselective synthesis of α-dehydroaminoacid derivatives **2** containing a stereogenic center in the γ position is reported. α-Dehydroaminoesters **2** are also efficient synthons for the preparation of optically active substituted α-aminoesters.

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Supporting Information Available: Full characterization and procedures for the synthesis of α-dehydroaminoesters **2**, carboxylic acid **3**, and aminoester **4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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