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Conjugate addition of hydroxylamino derivatives to alkylidene malonates in the presence of chiral Lewis acids

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Abstract—The conjugate addition of *O*-benzylhydroxylamine and *N*,*O*-bis(trimethylsilyl)hydroxylamine to alkylidene and arylidene malonates in the presence of Lewis acids affords the corresponding β-hydroxylamino derivatives in good yields. The use of $Cu(OTf)_2$ in the presence of chiral bisoxazoline ligands opens the possibility of performing this reaction in a catalytic and enantioselective way. © 2001 Elsevier Science Ltd. All rights reserved.

Recently, increasing interest has been focused on β-amino acids,[1a–d] which are important molecules present in natural and synthetic biologically active peptides and depsipeptides[1e–i] and can be easily converted into β-lactams.[2] The conjugate addition of nitrogen nucleophiles to α,β-unsaturated carboxylates has been demonstrated to be one of the most rapid and efficient methods for carbon–nitrogen bond formation in the β-position.[3] The 1,4-addition of hydroxylamine derivatives[4] is a topic of current interest in the area of C–N bond formation, since the resulting β-hydroxylamino derivatives are useful intermediates for the preparation of isoxazolidinones[5] and aziridines[6] and of β-amino acids[1] or β-lactams[2] after reduction of the N–O bond. In continuation of our studies on Lewis acid-induced conjugate addition reactions, we wish to report herein the addition of *O*-benzylhydroxylamine and *N*,*O*-bis(trimethylsilyl)hydroxylamine to substituted alkylidene malonates in the presence of chiral Lewis acids.[7] First of all the addition of *O*-benzylhydroxylamine to alkylidene malonates **1** and the effects of some Lewis acids were investigated. The reactions were carried out in CH_2Cl_2 starting at −40°C and allowing the temperature to slowly reach 0°C. The adducts were isolated in good yield by chromatography on silica gel. When the reaction temperature exceeded 0°C, decomposition occurred affording the corresponding oxime and dimethyl malonate. Furthermore, a large amount of catalyst and long reaction times also induce decomposition. Some selected results of the conjugate addition of *O*-benzylhydroxylamine on alkylidene and arylidene malonates in the presence of different Lewis acids are reported in Table 1.

Lewis acids such as $AlMe_2Cl$ and $BF_3{\cdot}Et_2O$ did not catalyze the conjugate addition for the preferential complex formation with hydroxylamine. Better results were obtained when the reaction was performed in the presence of either 10% $Cu(OTf)_2$ in CH_2Cl_2 (entry 1), 3% $Yb(OTf)_3$ in CH_2Cl_2 (entries 4 and 5) or when 5% $MgBr_2{\cdot}Et_2O$ was utilized as the catalyst in toluene (entry 3). When the reaction was performed in CH_2Cl_2 and $MgBr_2{\cdot}Et_2O$ was added as catalyst, a considerable amount of oxime and dimethyl malonate, deriving from decomposition, were obtained (entry 2).

On the basis of these results, we performed the *O*-benzylhydroxylamine addition to alkylidene or arylidene malonates in the presence of a Lewis acid and a chiral ligand.[8] We tested several chiral bisoxazolines, but no enantioselectivity could be obtained utilizing $Yb(OTf)_3$ or $MgBr_2{\cdot}Et_2O$. When (*S*)-(−)-2,2′-isopropylidenebis(4-benzyl-2-oxazoline) was used as the ligand and $Cu(OTf)_2$ as the Lewis acid, a poor enantiomeric excess was observed (Table 2).

The 1,4-addition of NH_2OBn on **1a** was very slow and inefficient at low temperature. Good yields were observed at 10°C, but low product enantiomeric excess were obtained (entry 1). The ethyl ester **1b** reacted at −18°C with good yield but without any enantioselectivity (entry 2). The addition performed on isopropylidene

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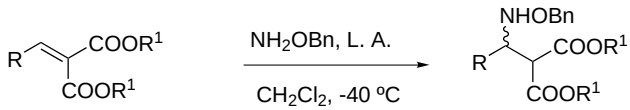
Table 1.



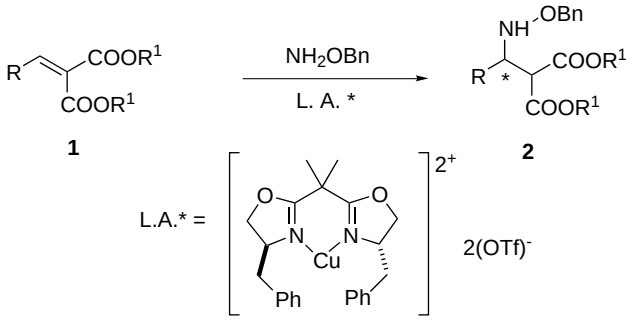
1 **2**

a: R = Ph, R^1 = Me
b: R = Ph, R^1 = Et

Entry	Compound	Lewis acid (%)	Solvent	Conversion[a] (%)	Yield[b] (%)
1	**1a**	$Cu(OTf)_2$ (10)	CH_2Cl_2	80	60
2	**1a**	$MgBr_2{\cdot}Et_2O$ (5)	CH_2Cl_2	99	30[c]
3	**1a**	$MgBr_2{\cdot}Et_2O$ (5)	Toluene	90	75
4	**1a**	$Yb(OTf)_3$ (3)	CH_2Cl_2	90	75
5	**1b**	$Yb(OTf)_3$ (3)	CH_2Cl_2	90	70

[a] Determined by ^{1}H NMR.
[b] Calculated on isolated product **2**, after flash chromatography.
[c] The rest being dimethyl malonate and oxime.

Table 2.



1 **2**

a: R = Ph, R^1 = Me **b**: R = Ph, R^1 = Et
c: R = *i*Pr, R^1 = Me **d**: R = *i*Pr R^1 = Et

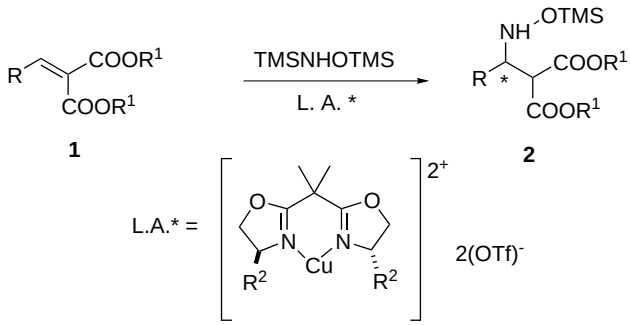
Entry	Reactant	Solvent	*t* (h)	*T* (°C)	Yield%[a] (e.e.%[b])
1	**1a**	CH_2Cl_2	12	10[c]	66 (20)
2	**1b**	CH_2Cl_2	12	−18	57 (0)
3	**1c**	CH_2Cl_2	5	−10	60 (0)
4	**1d**	CH_2Cl_2	5	0	77 (26)
5	**1d**	CH_2Cl_2	5	−10	64 (20)
6	**1d**	CH_2Cl_2	5	−20	71 (29)
7	**1d**	THF	5	−10	53 (18)
8	**1d**	$PhMe/CH_2Cl_2$	5	−10	55 (14)

[a] Calculated on isolated product **2**, after flash chromatography.
[b] Determined for **2a** by ^{1}H NMR using Eu* shift reagents and for **2b–d** by HPLC using a CHIRALCEL-OD column.
[c] In the presence of the chiral catalyst, no decomposition of the reaction product was observed even at T>0°C.

ethyl malonate **1d** afforded compound **2d** in 71% yield and 29% e.e. The use of different solvents, such as THF and toluene, did not affect the selectivity of the reaction (entries 7 and 8). With the aim of increasing the enantioselectivity of the process, the bulkier *N*,*O*-bis(trimethylsilyl)hydroxylamine[9] was used as nucleophile. The results obtained are reported in Table 3.

The reaction was performed by stirring $Cu(OTf)_2$ (10%) and bisoxazoline (12%) under vacuum for 2 h and then adding dichloromethane. The resulting green catalyst solution was stirred for 2 h before use. Malonate **1** was added and the solution was cooled to the selected temperature. *N*,*O*-Bis(trimethylsilyl)hydroxylamine was added after stirring the reaction mixture for 15 min and

Table 3.



c: R = *i*Pr, R^1 = Me
d: R = *i*Pr, R^1 = Et
e: R = CH_2*i*Pr, R^1 = Me

Entry	Reactant	R^2	Solvent	*T* (°C)	Yield%[a] (e.e.%[b])
1	**1c**	Ph	CH_2Cl_2	−10	52 (20)
2	**1c**	*i*-Pr	CH_2Cl_2	−10	35 (52)
3	**1c**	Bn	CH_2Cl_2	0	54 (40)
4	**1c**	Bn	CH_2Cl_2	−10	73 (**76**)
5	**1c**	Bn	CH_2Cl_2	−20	96 (34)
6	**1c**	Bn	CH_2Cl_2	−40	100 (38)
7	**1d**	Bn	CH_2Cl_2	−10	62 (22)
8	**1e**	Bn	CH_2Cl_2	−10	52 (**74**)

[a] Calculated on isolated product **2**, after flash chromatography.
[b] Determined by HPLC using a CHIRALCEL-OD column.

the reaction was monitored by TLC. The work up with dilute aqueous HCl and NH_4OH, allowed a clean product mixture to be obtained, the components of which were easily separable by flash chromatography on silica gel. The best yields and e.e.s were obtained at −10°C utilizing alkylidene methyl esters **1c** and **1e** (entries 4 and 8), while the reaction performed on ethyl ester **1d** furnished product with a lower e.e. (entry 7). The reaction performed with Ph-box (entry 1) afforded adduct **2c** only in 20% e.e. The use of *i*-Pr- and Bn-box increased the enantiomeric excess (entries 2 and 3) and both bisoxazolines exhibited identical facial selectivity. It is significant that these two bisoxazolines display opposite facial selectivity in respect to Ph-box. These results are in accord with the stereochemical model reported by Evans et al.[7d] for the alkylidene malonate/bisoxazoline system. On the basis of their model we suggest the (*R*)-configuration for the major product from the reactions catalyzed by [Cu(*S*,*S*)-Bn-box](OTf)$_2$. According to the results presented herein, the use of Cu(OTf)$_2$ in the presence of bisoxazoline ligands opens the possibility to perform the conjugate addition of hydroxylamino derivatives to alkylidene and arylidene malonates in a catalytic and enantioselective way. We showed that the conjugate addition of either *O*-benzylhydroxylamine or *N*,*O*-bis(trimethylsilyl)hydroxylamine occurs on alkylidene or arylidene malonates in the presence of chiral Lewis acids affords β-hydroxylamino derivatives in good yields. Further studies in this area are now being carried out in our laboratory.

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