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Enantioselective synthesis of aziridine 2,2-dicarboxylates. Part 1: Copper(II)-bisoxazoline complex-catalysed Michael reaction on alkylidene malonates

Giuliana Cardillo,* Serena Fabbroni, Luca Gentilucci, Massimo Gianotti, Rossana Perciaccante and Alessandra Tolomelli

Dipartimento di Chimica 'G. Ciamician', Università di Bologna, Via Selmi 2, 40126 Bologna, Italy

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Abstract—The preparation of aziridine-2,2-dicarboxylates via 1,4-addition of *N*,*O*-bis(trimethylsilyl)hydroxylamine to α,β-unsaturated malonates in the presence of chiral Lewis acids is reported. Good enantioselectivity was observed for conjugate addition catalysed by [Cu(*S*,*S*)-Bn-(box)](OTf)$_2$ on isobutylidene and 3-methylbutylidene malonate.

1. Introduction

Aziridines are important heterocyclic compounds which are useful intermediates in the synthesis of a variety of nitrogen containing molecules.[1] Aziridine-carboxylates in particular, have been recently introduced in peptidomimetics either as modified amino acid moieties[2] or as turned scaffolds, and were tested in the inhibition of different enzymes.[3] In a programme directed toward the synthesis and biological evaluation of protease inhibitors, we have turned our attention to the synthesis of aziridine-2,2-dicarboxylates via a two step methodology involving the 1,4-addition of hydroxylamino derivatives to alkylidene malonates, followed by cyclisation to aziridine. Asymmetric conjugate additions are amongst the most useful methods for creating new stereogenic centres in the β-position.[4] Of the great number of unsaturated electrophiles, alkylidene and arylidene malonates have been described as good Michael acceptors in conjugate additions catalysed by chiral ligand–metal complexes. Evans[5] reported enantioselective C–C bond formation through the conjugate addition of silyl enolates to malonates, Jørgensen[6] described the enantioselective alkylation with heteroaromatic compounds and Sibi[7] reported the enantioselective conjugate addition of organomagnesium amides to enamidomalonates. Furthermore, the asymmetric conjugate addition of dialkylzinc onto aryl and alkylidene malonates by using catalytic copper complexes has been recently presented by Alexakis.[8] Following our initial report on the asymmetric version of the copper catalysed conjugate addition of hydroxylamino derivatives on alkylidene malonates,[9] we wish to report here the full details of the enantioselective preparation of aziridine-2,2-dicarboxylates[10] via 1,4 addition of *N*,*O*-bis(trimethylsilyl)hydroxylamine[11] to α,β-unsaturated malonates in the presence of chiral Lewis acids.

2. Results and discussion

The procedure involves the conjugate addition of commercially available *N*,*O*-bis(trimethylsilyl)hydroxylamine to the unsaturated substrate followed by cyclisation under very mild basic conditions.[12] The hydroxylamine derivative reacts both as a nucleophile, during the addition step, and as an electrophile during the cyclisation to aziridine, the OTMS group behaving as a good leaving group (Scheme 1).[13] The presence of a chiral Lewis acid as catalyst gives the opportunity to induce chirality in the process during the nucleophilic attack to alkylidene malonates. Cu(OTf)$_2$ shows good catalytic activity and the use of benzyl bisoxazoline as ligand turned out to furnish the best results.

The conjugate additions were carried out in CH_2Cl_2 at different temperatures. The results are reported in Table 1. When the reaction temperature exceeded 0°C a

* Corresponding author. E-mail: cardillo@ciam.unibo.it

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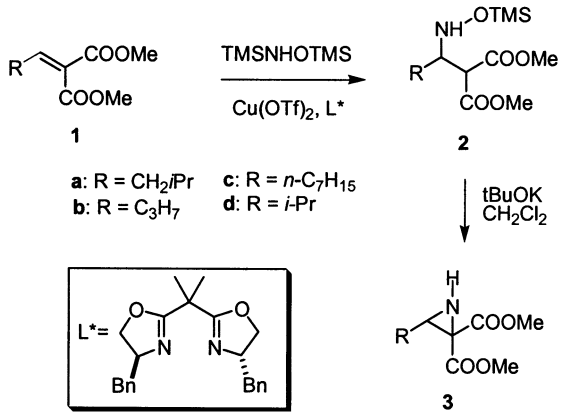

Scheme 1. [Cu(*S*,*S*)-Bn-(box)](OTf)$_2$ catalysed conjugate addition of *N*,*O*-bis(trimethylsilyl)hydroxylamine to **1** and cyclisation to aziridine **3**.

Table 1. 1,4-Addition of *N*,*O*-bis(trimethylsilyl) hydroxylamine to **1**

Entry	Reagent	Cat.(%)	*T* (°C)	Yield[a] **2** (%)
1	**1a**	10	−10	52
2	**1a**	12	−10	71
3	**1b**	10	−10	46
4	**1b**	10	−15	45
5	**1c**	10	−10	73
6	**1d**	10	−40	70
7	**1d**	8	−10	82
8[b]	**1d**	10	−10	75

[a] Isolated yields after flash chromatography on silica gel.
[b] This reaction occurs with 80% e.e.

considerable amount of oxime and dimethyl malonate, resulting from decomposition, were obtained.

Determination of the enantiomeric excess of the 1,4-adduct by HPLC analysis was found to be difficult, since we could not achieve an acceptable separation of the enantiomers. Only compound **2d** showed good resolution of the two enantiomers (Fig. 1). The chromatograms of racemic adduct **2d** (Fig. 1A) and of the enriched mixture (80% e.e.) produced in the conjugate addition catalysed by [Cu(*S*,*S*)-Bn-(box)](OTf)$_2$ are reported (Fig. 1B). The e.e. of the 1,4-adducts **2a–c** could be easily established from the analysis of cyclised compounds **3a–c**.

Table 2. Cyclisation of enantiomerically enriched adduct **2** to aziridine **3**

Entry[a]	Reagent	Yield[b] **3** (%)	E.e.[c] **3** (%)
1	**2a**	72	74
2	**2a**	70	36
3	**2b**	75	42
4	**2b**	77	38
5	**2c**	65	67
6	**2d**	71	40
7	**2d**	68	78
8	**2d**	70	80

[a] Each entry corresponds to the cyclisation of the products of the corresponding entry in Table 1.
[b] Isolated yields after flash chromatography on silica gel.
[c] The e.e. values were determined by HPLC analysis on a chiral column (see Section 4).

The isolated adducts **2a–d** were indeed easily transformed into the corresponding aziridines **3a–d** upon treatment with a catalytic amount of potassium *tert*-butoxide in CH_2Cl_2 (Table 2). HPLC analysis of the aziridine-2,2-dicarboxylates **3a–d** allowed the accurate determination of the e.e. of these compounds.[9]

In Fig. 2 the racemic aziridine **3d** (Fig. 2A) and the mixture obtained by cyclisation of enriched **2d** with 80% e.e. (Fig. 2B) are compared. Moreover, when [Cu(*R*,*R*)-Bn-(box)](OTf)$_2$ was utilised as the chiral Lewis acid, after cyclisation of the addition product, the enantiomer of aziridine **3d** was obtained as the major product in 82% e.e. (Fig. 2C).

The data reported in Table 2 allows us to evaluate that the optimal conditions for asymmetric conjugate addition (shown in Table 1), are 10% of chiral bisoxazoline at −10°C. Moreover, the conjugate addition reaction

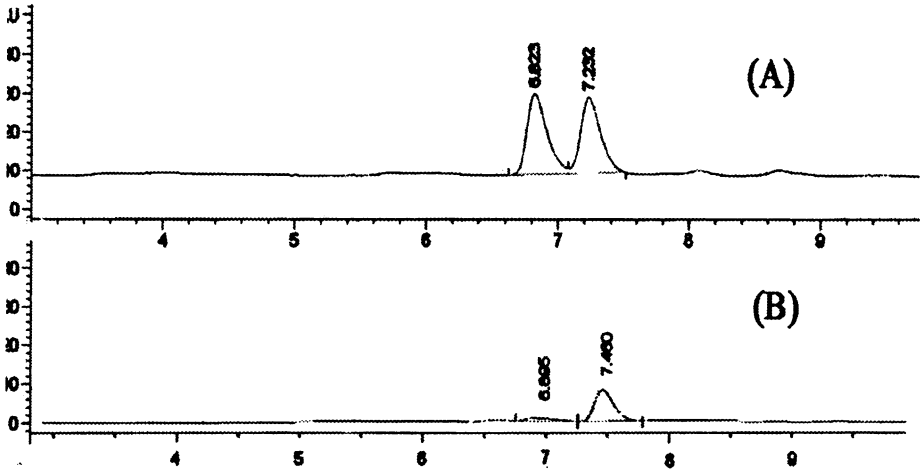

Figure 1. HPLC analysis of racemic and enantiomerically enriched **2d**.

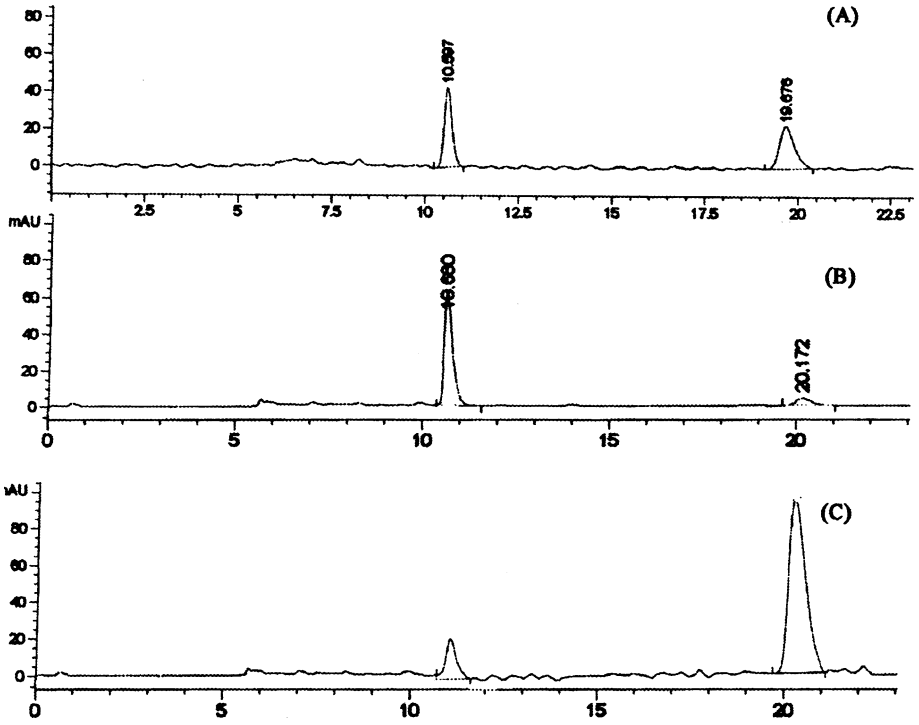

Figure 2. HPLC analysis of racemic and enantiomerically enriched **3d**.

carried out on linear alkylidene malonates **1b** and **1c** furnished low e.e while good enantioselectivities were observed for the branched malonates **1a** and **1d**.

3. Conclusion

In conclusion, the preparation of aziridine-2,2-dicarboxylates via 1,4-addition of *N*,*O*-bis(trimethylsilyl)-hydroxylamine to α,β-unsaturated malonates in the presence of chiral Lewis acids has been reported. Good results of enantioselectivity were observed when the conjugate additions on isobutylidene and 3-methylbutylidene malonates were catalysed by [Cu(*S*,*S*)-Bn-(box)](OTf)$_2$.

4. Experimental

4.1. General procedures

Unless stated otherwise, chemicals were obtained from commercial sources and used without further purification. CH_2Cl_2 was distilled from P_2O_5. Flash chromatography was performed on Merck silica gel 60 (230–400 mesh). NMR Spectra were recorded with a INOVA Varian spectrometer 300 MHz or with a Gemini Varian spectrometer 200 MHz. Chemical shifts were reported as δ values relative to the solvent peak of $CDCl_3$ set at $\delta = 7.27$ (^{1}H NMR) or $\delta = 77.0$ (^{13}C NMR). Infrared spectra were recorded with an FT-IR Nicolet 205 spectrometer. GC–MS analysis were performed on HP5890 series II chromatograph with HP5971 mass detector. Optical rotation powers were recorded with Perkin–Elmer polarimeter 343. HPLC analysis were performed on HP1090 liquid chromatograph equipped with UV detector. CHIRALCEL-OD chiral column, isocratic analysis with 90:10 hexane/isopropanol as eluent, 0.5 mL/min solvent flow, UV detector at 214.4 and 220.4 nm. MS analysis were performed with a HP 1100 series mass spectrometer single quadrupole with electrospray ionisation interface (ESI). Alkylidene malonates **1** were prepared following a previously reported protocol.[14]

4.2. General procedure for the conjugate addition of *N*,*O*-bis(trimethylsilyl)hydroxylamine to alkylidene malonates 1

A mixture of $Cu(OTf)_2$ (0.1 mmol, 0.036 g) and bisoxazoline (0.12 mmol, 0.032 g) was stirred under vacuum for 2 h and then, after replacing vacuum with nitrogen atmosphere, dry dichloromethane (10 ml) was added. The prepared green catalyst mixture was stirred for 15 min before use. Then malonate **1** (1 mmol) was added and the solution was cooled to the selected temperature (see Table 1). After stirring the reaction mixture for 15 minutes, *N*,*O*-bis(trimethylsilyl)hydroxylamine (2 mmol, 0.43 ml) was finally added. The reaction was monitored through TLC. The solution was quenched with diluted HCl (5 ml), washed with NH_4OH (10 ml), dried over Na_2SO_4 and solvent removed under reduced pressure Adduct **2** was easily purified by flash chromatography on silica gel (cyclohexane/ethyl acetate, 1:1 as eluant). The spectroscopic data for compounds **2a–d** (^{1}H NMR, ^{13}C NMR, IR) are in agreement with the data previously reported.[9]

4.2.1. 2-(1-Trimethylsilyloxyamino-3-methylbutyl)-malonic acid dimethyl ester 2a. Starting from 0.2 g of **1a**, 0.215 g of product were obtained (yield 52%). E.e. 74%. $[\alpha]_D^{20} = -26.4$ (*c* 0.7, $CHCl_3$).

4.2.2. 2-(1-Trimethylsilyloxyaminobutyl)malonic acid dimethyl ester 2b. Starting from 0.186 g of **1b**, 0.134 g of product **2b** was obtained (yield 46%). E.e. 42%. $[\alpha]_D^{20} = -19.6$ (*c* 1.3, $CHCl_3$).

4.2.3. 2-(1-Trimethylsilyloxyaminooctyl)malonic acid dimethyl ester 2c. Starting from 0.242 g of **1c**, 0.252 g of product **2c** was obtained (yield 73%). E.e. 67%. $[\alpha]_D^{20} = -16.4$ (*c* 0.7, $CHCl_3$).

4.2.4. 2-(1-Trimethylsilyloxyamino-2-methylpropyl)-malonic acid dimethyl ester 2d. Starting from 0.186 g of **1d**, 0.238 g of product **2d** was obtained (yield 75%). E.e. 80%. $[\alpha]_D^{20} = -55.0$ (*c* 0.6, $CHCl_3$). HPLC separation on CHIRALCEL-OD chiral column, isocratic analysis with 90:10 hexane/isopropanol as eluent, 0.5 mL/min solvent flow, UV detector at 214.4 and 220.4 nm, major isomer 7.3 min, minor isomer 6.7 min.

4.3. General procedure for the ring closure of 2 to aziridine 3

To a stirred solution of **2** (1 mmol) in dry CH_2Cl_2 at rt under nitrogen atmosphere, *t*BuOK (0.25 mmol, 0.25 mL, solution 1 M in THF) was added in one portion. After stirring for 4 h, the reaction was quenched with water, extracted twice with CH_2Cl_2, dried over Na_2SO_4 and solvent removed under reduced pressure. Aziridine **3** was isolated by flash chromatography on silica gel (cyclohexane/diethyl ether, 7:3 as eluent). The spectroscopic data for compound **3a–d** (^{1}H NMR, ^{13}C NMR, IR) are in agreement with the data previously reported.[9]

4.3.1. 3-Isobutylaziridine-2,2-dicarboxylic acid dimethyl ester 3a. Starting from 0.305 g of **2a**, 0.155 g of product **3a** was obtained (yield 72%). E.e. 74%. $[\alpha]_D^{20} = -35.2$ (*c* 0.7, $CHCl_3$). HPLC separation on CHIRALCEL-OD chiral column, isocratic analysis with 90:10 hexane/isopropanol as eluent, 0.5 mL/min solvent flow, UV detector at 214.4 and 220.4 nm, major isomer 9.2 min, minor isomer 14.2 min. MS-ESI m/z 216 (M+1)

4.3.2. 3-Propylaziridine-2,2-dicarboxylic acid dimethyl ester 3b. Starting from 0.291 g of **2b**, 0.151 g of product **3b** was obtained (yield 75%). E.e. 42%. $[\alpha]_D^{20} = -25.7$ (*c* 0.7, $CHCl_3$). HPLC separation on CHIRALCEL-OD chiral column, isocratic analysis with 90:10 hexane/isopropanol as eluent, 0.5 mL/min solvent flow, UV detector at 214.4 and 220.4 nm, major isomer 11.0 min, minor isomer 19.3 min. MS-ESI m/z 202 (M+1)

4.3.3. 3-Heptylaziridine-2,2-dicarboxylic acid dimethyl ester 3c. Starting from 0.347 g of **2c**, 0.167 g of product **3c** was obtained (yield 65%). E.e. 67%. $[\alpha]_D^{20} = -21.6$ (*c* 0.9, $CHCl_3$). HPLC separation on CHIRALCEL-OD chiral column, isocratic analysis with 90:10 hexane/isopropanol as eluent, 0.5 mL/min solvent flow, UV detector at 214.4 and 220.4 nm, major isomer 9.98 min, minor isomer 14.4 min. MS-ESI m/z 258 (M+1)

4.3.4. 3-Isopropylaziridine-2,2-dicarboxylic acid dimethyl ester 3d. Starting from 0.291 g of **2d**, 0.140 g of product **3d** was obtained (yield 70%). E.e. 80%. $[\alpha]_D^{20} = -58.2$ (*c* 0.9, $CHCl_3$). HPLC separation on CHIRALCEL-OD chiral column, isocratic analysis with 90:10 hexane/isopropanol as eluent, 0.5 mL/min solvent flow, UV detector at 214.4 and 220.4 nm, major isomer 10.4 min, minor isomer 18.7 min. MS-ESI m/z 202 (M+1)

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