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Asymmetric Formation of C-N Bonds in Chiral Enol Ethers[1]

Stefania Fioravanti, M. Antonietta Loreto, Lucio Pellacani, Paolo A. Tardella

Dipartimento di Chimica, Università "La Sapienza", P le Aldo Moro 2, I-00185 Roma, Italy

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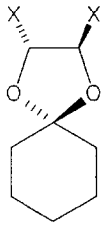
Abstract: *Attack of EtO_2CN on an enol ether carrying (S,S)-hydrobenzoin as chiral auxiliary gives diastereoselective aziridination with diastereomeric excess > 95%. Easy subsequent hydrolysis gives partially racemised α-amino ketone* **4**. *Other chiral auxiliaries does not allow isolation of intermediate aziridines and the α-amino ketone is isolated with a 75 25 enantiomeric ratio The thermolysis of EtO_2CN_3 in most of the same enol ethers gives the acetals of the α-amino ketone with prevailing opposite configuration at the new formed chiral centre*

Our attention has recently been focused on attempts of asymmetric induction during the formation of C-N bonds by (ethoxycarbonyl)nitrene (EtO_2CN) or ethyl azidoformate (EtO_2CN_3) on enamines[2,3] and silyl ketene acetals[4] containing a suitable chiral auxiliary A stereospecific introduction of an amino function by nitrene addition to enol ethers has been recently attempted by Danishefsky,[5] while the reaction between enol ethers and dibenzyl azodicarboxylate has been described by Leblanc.[6]

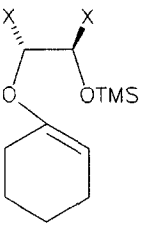
In this paper we report the results obtained in the reaction of EtO_2CN and chiral enol ethers. Substrates **2** have been prepared by a modification of a reported procedure[7] by treating the acetals **1** prepared from cyclohexanone and chiral 1,2-diols with TfOTMS Increasing steric hindrance in the diol required longer reaction times and higher molar ratio TfOTMS/acetal (see experimental)

We first tried the photolysis of EtO_2CN_3 in enol ethers but under these conditions the only reaction product detected and isolated was the starting acetal deriving from ring closure On the contrary the thermolysis at 120 °C (route A of Table 1) of an equimolar mixture of EtO_2CN_3 and enol ethers **2a-c** gave a functionalisation product, namely the acetals of 2-(ethoxycarbonylamino)cyclohexanone **3**.[8] Only minor traces of the amino ketone **4** have been found, except in the case of **2d** where it is the only detectable product The starting acetals **1** are also obtained as main products We showed that, under the above conditions the acetals **1** did not react, although related acetals have been reported to be reactive toward the same reagent [9]

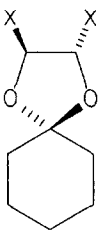
In order to obtain directly the amino ketone **4** we turned our attention to the reaction of ethyl *N*-{[(4-nitrophenyl)sulphonyl]oxy}carbamate at room temperature (route B of Table 1) An excess of this reagent (ranging from 2 5 to 7 equivalents) and an equimolar amount of triethylamine in the presence of the chiral enol ethers **2** gave, after HPLC, 2-(ethoxycarbonylamino)cyclohexanone **4** as the main product [3] Under these reaction conditions we obtained the best results (36% yields, 75% of the major stereoisomer) starting with enol ether **2c** In addition, in this case we were able to isolate the expected intermediate, the aziridine



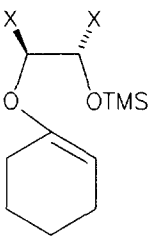
1 a,b



2 a,b



1 c,d



2 c,d

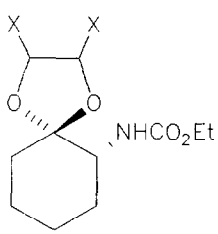
a X = Me, **b** X = CH_2OMe, **c** X = Ph, **d** X = CH_2OBn

5, in 19% yield and in a very high diastereomeric excess (>95%· GC, HPLC, ^{13}C NMR). We confirmed the following hydrolysis step to be responsible for partial racemization[10] giving the observed ratios of the amino ketone **4** and its enantiomer

As far as the stereochemical outcome[11] of the reaction we studied is concerned, we note that in all cases in the reaction at room temperature the amino ketone **4** of (*S*) configuration prevailed, while the thermolysis of EtO_2CN_3 gave the acetal **3** with the new chiral centre having mainly an (*R*) configuration, except in the case of **2d** where the main product was the amino ketone **4** of (*S*) configuration, under both conditions [12]

Since at 120 °C we should not expect a 1,3-cycloaddition reaction of the azide, especially because several attempts of reactions run at reflux in benzene for a long time did not give any product, (although some enol ethers react with azidoformate slowly to give imines),[13] we might assume the reaction to proceed via nitrene even in this case The opposite stereochemical result observed for the thermolysis on substrates **2a-c** could be due, assuming an intermediate like **5** is formed, to a preferential protonation[14,15] of the supposed enol ether **6**[16,17] (from the same face from which nitrene attacks) followed by ring closure giving the observed acetal ratio The temperature and the absence of triethylamine could favour the cyclization.

We wish to underline that the room temperature amination reaction reported in this paper is a further case of a highly diastereoselective reaction carried out on chiral enol ethers[18] by means of highly reactive reagents



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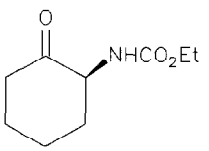

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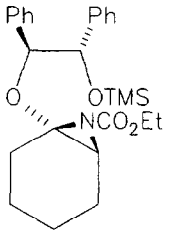

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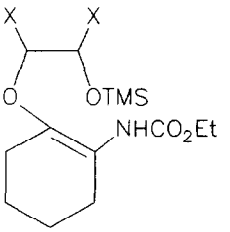

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Only the major stereoisomer is shown for compounds 3, 4, and 5

Table 1 Amination Reaction of Chiral Enol Ethers

enol ether 2	chiral auxiliary configuration	X	route	molar ratio (2 reagent)	chemical yield (%)[a]	products 3 (2*R*) (%)[b]	4 (2*S*) (%)[b]
a	*R,R*	Me	A	1 1	14	69	
			B	1 2.5	24		68
b	*R,R*	CH_2OMe	A	1 1	14	63	
			B	1 4	27		63
c	*S,S*	Ph	A	1 1	13[c]	62	
			B	1.5	36[d]		75
d	*S,S*	CH_2OBn	A	1 1	10		76
			B	1 7	28		60

[a] isolated products, [b] determined by GC, for product 4 after conversion into the diastereomeric acetals,[2] [c] GC ratio, [d] in addition to 19% of aziridine 5

EXPERIMENTAL SECTION

GC analyses were performed on a Carlo Erba GI gas-chromatograph with a SPB-20 glass capillary column (30 m x 0.75 mm) GC-MS was done on HP 5970 Chemstation Mass Selective Detector connected with a HP 5890 gas-chromatograph using a 15 m capillary column coated with fluid methyl silicone HRMS (EI) and MS (FAB) were obtained on a Kratos MS 80 spectrometer. ^1H and ^{13}C NMR (in $CDCl_3$) were obtained on a Varian XL-300 spectrometer with $CHCl_3$ and $CDCl_3$ respectively, as internal standards IR spectra (in CCl_4) were done on a Perkin-Elmer 457 instrument Optical rotations were recorded at the Sodium D line with a Perkin-Elmer 241 polarimeter (1-cm cell) The separation by HPLC were done with a Violet Clar 002 instrument equipped with a IOTA Jobin-Yvon differential refractometer Solvents were HPLC-grade. CH_2Cl_2 was distilled over $CaCl_2$ Ethyldiisopropylamine and triethylamine were dried by standing over KOH and then distillation under nitrogen Chiral diols were commercial products (Fluka, Aldrich) Ethyl *N*-{[(4-nitrophenyl)sulphonyl]oxy}carbamate[19] and ethyl azidoformate (EtO_2CN_3, *CAUTION! it can decompose explosively at 160 °C and its vapours are toxic)*[20] were prepared by standard procedures

General Procedure for Acetalation

To a solution of cyclohexanone (10 mmol) in benzene (10 ml), diol (20 mmol) and pyridinium *p*-toluensulphonate (0,5 mmol) were added The mixture was refluxed under nitrogen and water was removed azeotropically with a Dean Stark trap Progress of the reaction was monitored by GC (2-5 h)

When the reaction was complete, the mixture was concentrated *in vacuo* and the residue diluted with CH_2Cl_2, washed with water, saturated $NaHCO_3$ solution, saturated NaCl solution, dried over anhydrous Na_2SO_4, filtered and concentrated The crude product being homogeneous by GC was directly used.

1a . yield 83% , $[\alpha]_D$ -5 50 (*c* 2 00, CH_2Cl_2), IR 1100 cm^{-1}, ^1H NMR δ 1 17 (d, 6 H, CH_3), 1 25-1 36 (m, 2 H, ring CH_2), 1 52-1 54 (m, 8 H, ring CH_2), 3 50-3 60 (m, 2 H, $CHCH_3$), ^{13}C NMR δ 17 04 (CH_3), 23 88, 25 19, 36 88, 77 86 (CH), 108 12 (C), MS *m/z* 170 (M^+, 10), 127 (88), 126 (13), 98 (15), 67 (14), 56 (11), 55 (100), 43 (36), 42 (20), 41 (41), HRMS, 170 1313 (M^+), calcd for $C_{10}H_{18}O_2$, 170 1306

1b yield 62% , $[\alpha]_D$ +8 25 (*c* 0 97, CH_2Cl_2), IR 1100 cm^{-1}, ^1H NMR δ 1 34-1 44 (m, 2 H, ring CH_2), 1 58-1 68 (m, 8 H, ring CH_2), 3 41 (s, 6 H, CH_3), 3 52-3.53 (m, 4 H, CH_2O), 3 95-3 97 (m, 2 H, CH), ^{13}C NMR δ 23 77, 25 07, 36 52, 59 44 (CH_3), 73 70 (CH_2O), 77 00 (CH), 110 29 (C), MS *m/z* 230 (M^+, 12), 201 (17), 187 (70), 115 (74), 87 (11), 85 (32), 81 (10), 71 (10), 69 (18), 59 (18), 55 (68), 53 (11), 45 (100), HRMS, 230 1528 (M^+), calcd for $C_{12}H_{22}O_4$, 230 1518

1c yield 78% , $[\alpha]_D$ -5 55 (*c* 0 90, CH_2Cl_2), IR 1120 cm^{-1}, ^1H NMR δ 1 38-1 46 (m, 2 H, ring CH_2), 1 63-1 72 (m, 4 H, ring CH_2), 1 82-1 88 (m, 4 H, ring CH_2), 4 67 (s, 2 H, CH), 7.13-7 18 (m, 5 H), 7 23-7 25 (m, 5 H), ^{13}C NMR δ 23 85, 25 18, 36 76, 85 16 (CH), 109 94 (C), 126 7+ 128 16 +128 37 (aromatic CH), 137 06 (aromatic C), MS *m/z* 294 (M^+, 3), 189 (13), 188 (100), 179 (24), 178 (13), 167 (38), 165 (16), 107 (11), 105 (16), 97 (11), 91 (57), 90 (12), 89 (16), 79 (14), 77 (18), 67 (14), 55 (30), 42 (15), 41 (21), HRMS, 294 1618 (M^+), calcd for $C_{20}H_{22}O_2$, 294 1620

1d · yield 81% , $[\alpha]_D$ -9 27 (*c* 1 94, CH_2Cl_2), IR 1100 cm^{-1}, ^1H NMR δ 1 25-1 35 (m, 2 H, ring CH_2), 1 50-1 62 (m, 8 H, ring CH_2), 3 52-3 54 (m, 4 H, CH_2O), 3 90-3 99 (m, 2 H, CH), 4 50 (s, 4 H, CH_2Ph), 7 17-7 25 (m, 10 H), ^{13}C NMR δ 23 83, 25 10, 36.55, 70 90 (CH_2O), 73 43 (CH_2Ph), 77 22 (CH), 110 15 (C), 127 57 + 128 32 (aromatic CH), 138 06 (aromatic C), MS *m/z* 382 (M^+, 2), 339 (8), 105 (8), 92 (9), 91 (100), 69 (8), HRMS, 382 2148 (M^+), calcd for $C_{24}H_{30}O_4$, 382 2144

Preparation of Enol Ethers

Enol ethers were obtained according to literature methods for opening of cyclic acetals[7] with the modifications (reaction times, molar ratios of acetal TfOTMS ethyldiisopropylamine, respectively) indicated in parenthesis

2a (4 h, 1 1 2 1 3) yield 78% , $[\alpha]_D$ -25 0 (*c* 0 60, CH_2Cl_2), IR 1665 cm^{-1}, ^1H NMR δ 0 13 [s, 9 H, $Si(CH_3)_3$], 1 11 (d, 3 H, CH_3), 1 13 (d, 3 H, CH_3), 1 50-1 58 (m, 2 H, ring CH_2), 1 63-1.71 (m, 2 H, ring CH_2), 2 02-2 10 (m, 4 H, ring CH_2), 3 81-3 89 (m, 1 H, $CHCH_3$), 3 92-3 94 (m, 1 H, $CHCH_3$), 4.64-4 66 (m, 1 H, CH), ^{13}C NMR δ 0 24 [$Si(CH_3)_3$], 13 74 (CH_3), 18 00 (CH_3), 22 34, 22 57, 23 15, 27 75, 69 32 ($CHCH_3$), 74 08 ($CHCH_3$), 94 63 (CH), 152 51 (CO), MS *m/z* 242 (M^+, 0 4), 145 (20), 144 (18), 75 (37), 73 (100), 55 (12), 45 (15), 41 (20), HRMS, 242 1710 (M^+), calcd for $C_{13}H_{26}O_2Si$, 242 1701

2b (22 h, 1 2 2 2) yield 96% , $[\alpha]_D$ -4 76 (*c* 2 10, CH_2Cl_2), IR 1670 cm^{-1}, ^1H NMR δ 0 14 [s, 9 H, $Si(CH_3)_3$], 1 56-1 72 (m, 4 H, ring CH_2), 1 97-2 11 (m, 4 H, ring CH_2), 3 31 (s, 3 H, CH_3), 3 34 (s, 3 H, CH_3), 3 36-3 59 (m, 4 H, CH_2O), 3 96-4 02 (m, 1 H, $CHCH_2$), 4 09-4 30 (m, 1 H, $CHCH_2$), 4 72-4 80 (m, 1 H, CH), ^{13}C NMR δ 0 31 [$Si(CH_3)_3$], 21 61, 22 93, 23 54, 27 95, 59 00 (CH_3), 59 06 (CH_3), 70 40 (CH_2O), 70 63 (CH_2O), 74 02 ($CHCH_2$), 75 32 ($CHCH_2$), 96 29 (CH), 153 57 (CO), MS *m/z* 257 (0 8), 172 (11), 159 (55), 147 (20), 129 (21), 115 (15), 89 (50), 79 (11), 75 (51), 74 (10), 73 (100), 59 (23), 55 (13), 45 (76), 41 (23), HRMS, 302 1924 (M^+), calcd for $C_{15}H_{30}O_4Si$, 302 1913

2c (48 h, 1.2 6 2.9). yield 87% ; $[\alpha]_D$ -11 54 (*c* 0.26, CH_2Cl_2); IR 1665 cm^{-1}, ^1H NMR δ 0 12 [s, 9 H, $Si(CH_3)_3$], 1.36-1.48 (m, 2 H, ring CH_2), 1.52-1.69 (m, 2 H, ring CH_2), 1.82-1.95 (m, 2 H, ring CH_2), 2 06-2.12 (m, 2 H, ring CH_2), 4.49-4.52 (m, 1 H, CH), 4.86 (d, 1 H, CHPh), 4 96 (d, 1H, CHPh), 7.13-7 26 (m, 10 H); ^{13}C NMR δ 0.06 [$Si(CH_3)_3$], 22.55, 22 84, 23 48, 27 91, 78.34 (CHPh), 82 82 (CHPh), 96.77 (CH), 126 98 + 127.05 + 127.19 + 127 22 + 127.30 + 127 50 (aromatic CH), 139 07 (aromatic C), 153.425 (CO); MS *m/z* 269 (13), 180 (14), 179 (87), 170 (12), 79 (10), 75 (16), 73 (100), 45 (12), 41 (12).

2d (24 h, 1 2 7 3): yield 98% , $[\alpha]_D$ +6.8 (*c* 4.40, CH_2Cl_2), IR 1670 cm^{-1} ; ^1H NMR δ 0 11 [s, 9 H, $Si(CH_3)_3$], 1 48-1 60 (m, 4 H, ring CH_2), 2 00-2 09 (m, 4 H, ring CH_2), 3.40-3.72 (m, 4 H, CH_2O), 4.07-4.25 (m, 2 H, $CHCH_2$), 4 48-4 50 (m, 4 H, CH_2Ph), 4 71-4 78 (m, 1 H, CH), 7 25-7 35 (m, 10 H), ^{13}C NMR δ 0 16 [$Si(CH_3)_3$], 22 45, 22 77, 23 37, 27.79, 67 86 (CH_2Ph), 70 85 (CH_2O) , 71 51(CH_2O), 73 21($CHCH_2$), 75.19 ($CHCH_2$), 96.20 (CH), 127 56 + 127 62 + 127.7 + 128 40 + 128 41 (aromatic CH), 138 57 (aromatic C), 153 78 (CO), MS *m/z* 355 (10), 265 (6), 129 (10), 91 (100), 73 (13), HRMS, 454 2551 (M^+), calcd for $C_{27}H_{38}O_4Si$, 454 2539

Thermolysis of Ethyl Azidoformate with Enol Ethers

EtO_2CN_3 (10 mmol) and enol ether **2** (10 mmol) in CH_2Cl_2 (10 ml) were heated at 120 °C . When the azide band disappeared in the IR spectrum (*ca* 4 h), the solvent was evaporated *in vacuo* and the residue was separated by HPLC (hexane/ethyl acetate 7·3) giving the products in the yields and the ratios indicated in Table 1 In all cases the acetals **1** are obtained (up to 50%)

(2R)-2-(Ethoxycarbonylamino)cyclohexanone (1R,2R)-1,2-Bis(methoxymethyl)ethylene Acetal (**3b**) $[\alpha]_D$ +8 3 (*c* 0.24, CH_2Cl_2), IR 3440 cm^{-1}, 1720 cm^{-1}, ^1H NMR δ 1 14-2 01 (m overlapped with t at δ 1 24, 11 H, CH_2CH_3, ring CH_2), 3 39 (s, 3 H, CH_3O), 3 46 (s, 3 H, CH_3O), 3 41-3 88 (m, 4 H, CH_2O), 3 97-4 28 (m overlapped with q at δ 4.1, 5 H, CHN, CH_2CH_3, CHO), 6 11 (d, 1 H, NH); ^{13}C NMR δ 14 62 (CH_2CH_3), 23 37, 23 99, 31 50, 36 66, 55 91, 59 23, 59 30 (CH_3O), 60 29 (CH_2CH_3), 71.27 (CH_2O), 73 41 (CH_2O), 76 45 ($CHCH_2$), 77 89 ($CHCH_2$), 110 08 (C), 156 35 (CO_2), MS *m/z* 317 (M^+, 12), 187 (95), 128 (12), 115 (100), 85 (43), 84 (35), 71 (20), 70 (12), 69 (24), 68 (12), 67 (17), 59 (10), 57 (10), 56 (31), 55 (43), 45 (79), 43 (22), 42 (13), 41 (35), HRMS, 317.1833 (M^+), calcd for $C_{15}H_{27}NO_6$, 317 1838.

(2S)-2-(Ethoxycarbonylamino)cyclohexanone (1R,2R)-1,2-Bis(methoxymethyl)ethylene Acetal : $[\alpha]_D$ -7 8 (*c* 0.45, CH_2Cl_2), IR 3445 cm^{-1}, 1730 cm^{-1}, ^1H NMR δ 1 18-2 00 (m overlapped with t at δ 1 27, 11 H, CH_2CH_3, ring CH_2), 3 39 (s, 3 H, CH_3O), 3 42 (s, 3 H, CH_3O), 3 50-3 56 (m, 4 H, CH_2O), 4 05-4 17 (m overlapped with q at δ 4 13, 5 H, CHN, CH_2CH_3, CH), 4 94 (d, 1 H, NH), ^{13}C NMR δ 14 68 (CH_2CH_3), 22 84, 23 86, 30 84, 36 02, 54 23, 59 44 (CH_3O), 59 50 (CH_3O), 60 37 (CH_2CH_3), 70 44 (CH_2O), 74.55 (CH_2O), 77 42 ($CHCH_2$), 78 85 ($CHCH_2$), 110 42 (C), 156 35 (CO_2), MS *m/z* 317 (M^+, 13), 188 (11), 187 (96), 128 (12), 115 (100), 85 (44), 84 (37), 71 (23), 70 (13), 69 (26), 68 (11), 67 (17), 59 (12), 56 (28), 55 (44), 53 (10), 45 (72), 43 (22), 42 (13), 41 (35), HRMS, 317 1842 (M^+), calcd for $C_{15}H_{17}NO_6$, 317 1838

(2R)-2-(Ethoxycarbonylamino)cyclohexanone (1S,2S)-Diphenylethylene Acetal (**3c**) MS *m/z* 181 (15), 180 (100), 179 (28), 178 (58), 165 (10), 140 (10), 77 (11), 67 (10), 56 (17), 55 (10), 41 (10)

(2S)-2-(Ethoxycarbonylamino)cyclohexanone (1S,2S)-Diphenylethylene Acetal MS *m/z* 181 (15), 180 (100), 179 (27), 178 (50), 165 (10), 140 (10), 56 (15)

Reaction of Ethyl N-{*[(4-Nitrophenyl)sulphonyl]oxy*}*carbamate with Enol Ethers*

To a solution of enol ether **2** (10 mmol), triethylamine (25-70 mmol) and CH_2Cl_2 (25 ml) under an atmosphere of N_2 was added ethyl *N*-{[(4-nitrophenyl)sulphonyl]oxy}carbamate (25-70 mmol) in 1h at

room temperature The reaction mixture was stirred a further 2 h and then diluted with petroleum ether (bp 30-50 °C). After filtration, the solvent was evaporated under reduced pressure and the residue was separated by HPLC (hexane/ethyl acetate 8:2) giving 2-(ethoxycarbonylamino)cyclohexanone **4** in the yields and in the enantiomeric ratios indicated in Table 1 With **1c** as starting material another product was collected and identified as **5** · yield 19% , $[\alpha]_D$ -6 6 (*c* 0.45, CH_2Cl_2); IR 1715 cm^{-1}, ^1H NMR δ 0.10 [s, 9 H, $Si(CH_3)_3$], 1.09-1 94 (m overlapped with t at δ 1.3, 11 H, CH_2CH_3, ring CH_2), 3.60 (t, 1 H, CHN), 4.16 (q, 2 H, CH_2CH_3), 4.60 (d, 1 H, CHPh), 4 94 (d, 1 H, CHPh), 6.97-7 25 (m, 10 H); ^{13}C NMR δ 0 17 [$Si(CH_3)_3$], 14 63 (CH_2CH_3), 21.94, 24 27, 33 70, 53.40 (CHN), 60.68 (CH_2CH_3), 77.20 (CHPh), 79.81 (CHPh), 98 03 (CN), 127 05, 127.28, 127.55, 127 62, 127 68, 127.89 (aromatic CH), 139 78 (aromatic C), 156.00 (CO); MS *m/z* 271 (0 6), 180 (17), 179 (95), 77 (18), 75 (25), 74 (10), 73 (100), 45 (17); MS (FAB) *m/z* 454 ($M^+ + 1$)

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