

Experimental Part

1 Generalities

1.1 Apparatus

- Infrared spectra were recorded on a Bio-Rad FTS-135 spectrometer.
- ^1H NMR spectra were recorded at 200, 300 or 500 MHz on respectively a VARIAN GEMINI 200, VXR 200, GEMINI 300BB or BRUCKER AM-500, in a deuterated solvent with tetramethylsilane (TMS) or dimethylsulfoxide (DMSO) as internal standard. Chemical shifts are given in ppm; coupling constants are given in Hz.
- ^{13}C NMR spectra were recorded at 50, 75 or 125 MHz on respectively a VARIAN GEMINI 200, VXR 200 or GEMINI 300 or on a BRUCKER AM-500, in a deuterated solvent used as internal standard (CDCl_3 : 77 ppm; DMSO-d_6 : 39.5 ppm).
- NMR spectra recorded on the BRUCKER AM-500 were performed by Dr. R. Touillaux at the Université catholique de Louvain.
- ^{15}N NMR spectra (50 MHz) were recorded on a BRUCKER 500 (probe BBI [Broad Band Inverse]) with CH_3NO_2 used as external standard ($\delta = 375$ ppm). These experiments were carried out by Dr. D. Chapon at the Université catholique de Louvain.
- Mass spectra were recorded on a VARIAN MAT-44 or a FINNIGAN MAT TSQ 70 spectrometer in the laboratory of Professor de Hoffmann and Professor Habib-Jiwan at the Université catholique de Louvain.
- High resolution mass spectra (HRMS) were performed by Professor Flammang at the Université de Mons-Hainaut.
- Elemental analyses were realized in the laboratory of Dr Stone at University College, London
- High Performance Liquid Chromatography (HPLC) were carried out on WATERS 600-E apparatus equipped with gradient pumps and an oven MERCK Lichrojet (with Peltier effect), and a UV-visible detector. Integrations were carried out on an electronic integrator HITACHI D-2500 or D-7500 on a Beckman Gold integrated system equipped with a detector (PDA).
- Optical rotations were measured on a PERKIN-ELMER 241 MC Polarimeter. Concentrations are given in g/100 mL.
- Melting points were measured with a Büchi apparatus (oil bath) and are uncorrected.
- Bulb-to-bulb distillations were performed with a Büchi GKR 50 or GKR 51.
- X-Ray diffraction analyses were carried out on an automatic diffractometer HUBER (radiation $\text{MoK}\alpha$) by Pr. Dr. B. Tinant at the Université catholique de Louvain.

1.2 Techniques

- All reactions were realized under argon atmosphere unless otherwise stated.
- For reactions at 0 °C, flasks were placed in an ice bath; for reactions at -78 °C, flasks were placed in a dry-ice / *iso*-propanol bath; intermediate temperatures were realized by adding the desired quantity of dry-ice to *iso*-propanol; for longer reaction times flasks were placed in an *iso*-propanol bath cooled by a Haake EK90 cryostat.
- Evaporation of solvents was performed at ~ 35°C with a rotary evaporator connected to a water pump (~16 mmHg) unless otherwise stated.
- Flash chromatographies were performed on silica gel "60 Merck 40-63 μm ". Solvents used were of technical grade and distilled prior to use. R_f values were determined on silicagel plates Merck 60 F₂₅₄ on aluminum support. Spots were visualized using UV light ($\lambda = 254$ nm) or revealed using an aqueous potassium permanganate solution.

- *n*-butyllithium in hexanes was titrated in dry THF using 2,5-dimethoxybenzylic alcohol or diphenylacetic acid.
- CH_2Cl_2 was dried over CaH_2 and distilled.
- THF, diethyl ether and toluene were dried over Na / benzophenone and distilled.
- Triethylamine was dried over CaH_2 and distilled.
- Copper(II) triflate was dried by heating overnight at 150 °C under reduced pressure.

1.3 Abbreviations and symbols

1.3.1 Reagents and solvents

AcOEt	ethyl acetate
Boc ₂ O	di- <i>tert</i> -butyl dicarbonate
CH ₂ Cl ₂	dichloromethane
DIPRA	diisopropylamine
DMF	dimethylformamide
DMSO	dimethylsulfoxide
Et ₃ N	triethylamine
Et ₂ O	diethyl ether
EtOH	ethanol
MeOH	methanol
<i>n</i> -BuLi	<i>n</i> -butyllithium
NBS	<i>N</i> -bromosuccinimide
THF	tetrahydrofuran
TBDMSCl	<i>tert</i> -butyldimethylsilyl chloride
TIPSCl	tri- <i>iso</i> -propylsilyl chloride
TMS	tetramethylsilane
TMSCl	trimethylsilyl chloride

1.3.2 Abbreviations

E.A.	elemental analysis
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
b.p.	boiling point
br s	broad singlet
CI	chemical ionization
d	doublet
dd	doublet of doublet
Δ	heating at reflux or difference
EI	electronic impact
eq.	equivalents
Et	ethyl
IR	infrared
m	massif
Me	methyl
M.F.	molecular formula
m.p.	melting point
M.S.	mass spectrometry
mult	multiplet
M.W.	molecular weight
NMR	nuclear magnetic resonance
Ph	phenyl
q	quartet
R _f	ratio of fronts
r.t.	room temperature
s	singlet
st	stretching

TFA
TLC
 t_r

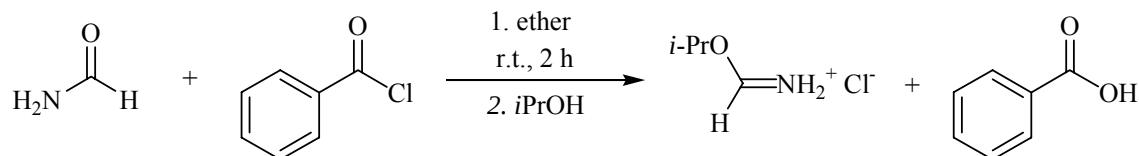
trifluoroacetic acid
thin layer chromatography
retention time

2 Synthesis of the 2-azadienes

2.1 Preparation of 1-isopropoxy-3-*tert*-butyldimethylsilyloxy-2-aza-1,3-butadiene **29a**

2.1.1 Synthesis of isopropyl formimidate chloride **93**

Reference: Ohme, R.; Schmitz, E. *Angew. Chem. Int. Ed.* **1967**, 6, 566



In a three-necked flask, equipped with an addition funnel and a condenser, dried under vacuum, 34.8 mL (42.1 g, 299.5 mmol, 1 eq.) of freshly distilled benzoyl chloride in solution in 350 mL of dry ether. A mixture of 29.9 mL (18.0 g, 299.5 mmol, 1 eq.) of dry isopropanol and 11.9 mL (13.5 g, 299.5 mmol, 1 eq.) of formamide (previously dried and distilled) was added dropwise over a period of one hour. After two hours stirring at 25 °C, the white solid formed was filtered, washed with three portions of dry ether, then dried under vacuum.

R.N. : [16694-44-3]

Physical aspect: white powder

F.B.: C₄H₁₀ClNO

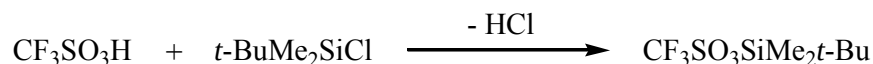
M.W.: 123.58

Yield: 31.4 g (85 %)

¹H NMR (200 MHz, CDCl₃, T = 25 °C) δ 11.70 (s, 2H, NH₂⁺), 8.80 (s, 1H, HC=N), 5.40 (sept., 1H, ³J = 7.1 Hz, (CH₃)₂CH), 1.50 (d, 6H, ³J = 7.1 Hz, (CH₃)₂CHO) ppm

2.1.2 Synthesis of *tert*-butyldimethylsilyl trifluoromethanesulfonate **207**

Reference: Emde, H.; Domsch, D.; Feger, H.; Frick, U.; Goetz, A. *Synthesis* **1982**, 1-26



To *tert*-butyldimethylsilyl chloride (24.0 g, 159.2 mmol, 1 eq.), trifluoromethanesulfonic acid (14.2 mL, 159.2 mmol, 1 eq.) was added dropwise, under agitation and under dry atmosphere. After addition is complete, the reacting mixture is then refluxed until the end of HCL emission (approximately 3 hours). The *tert*-butyldimethylsilyl triflate was then distilled under reduced pressure.

R.N. : [69739-34-0]

Physical aspect: colourless liquid

F.B.: C₇H₁₅F₃O₃SSi

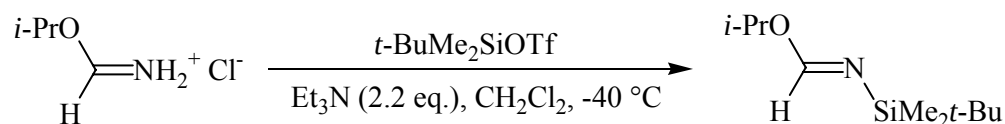
M.W.: 264.33

Yield: 33.6 g (80 %)

¹H NMR (200 MHz, CDCl₃, T = 25 °C) δ 1.01 (s, 9H, Me₃C), 0.47 (s, 6H, Me₂Si) ppm

2.1.3 Synthesis of *N*-*tert*-butyldimethylsilyl isopropyl formimidate **92**

Reference: Ghosez, L.; Bayard, Ph.; Nshimyumukiza, P.; Gouverneur, V.; Sainte, F.; Beaudegnies, R.; Rivera, M.; Frisque-Hesbain, A.-M. and Wynants, C. *Tet.* **1995**, 51, 11021-11042



A three-necked flask, equipped with a magnetic stirrer and an addition funnel, previously dried under vacuum, was charged with 7.0 g (56.6 mmol, 1 eq.) of isopropyl formimidate chloride and 65 mL of dry CH₂Cl₂. The suspension was cooled to -40 °C, and 17.3 mL (12.6 g, 124.6 mmol, 2.2 eq.) of triethylamine was added in one portion. A solution of 13.0 mL (15.0 g, 56.6 mmol, 1 eq.) of *tert*-butyldimethylsilyl triflate in 35 mL of CH₂Cl₂ was added dropwise. During the addition, the temperature must imperatively be maintained at -40 °C. After complete addition, 100 mL of dry petroleum ether was added at once and the cooling bath was removed. When the mixture had reached room temperature, the precipitate of triethylammonium chlorhydrate formed was filtered on celite, then rinsed three times with three portions of petroleum ether. The solvents were removed under reduced pressure. 100 mL of dry ether was added, and the residual triethylammonium triflate was removed by filtration. The ethereal solution was evaporated under vacuum. The residue contained compound **92** which was too unstable to be purified. It can however be easily kept at -20 °C without decomposition. It was used as such in the acylation step.

R.N. : [172095-72-6]

Physical aspect: colourless liquid

F.B.: C₁₀H₂₃NOSi

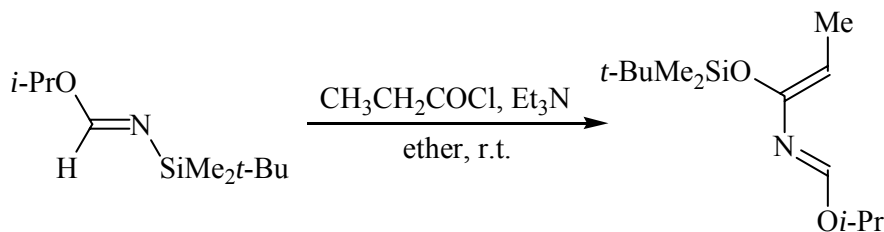
M.W.: 201.38

Yield: 10.38 g (91 %) (lit.: 90 %)

¹H NMR (200 MHz, CDCl₃, T = 25 °C) δ 7.64 (s, 1H, HC=N), 5.08 (sept., 1H, ³J = 6.3 Hz, (CH₃)₂CHO), 1.25 (d, 6H, ³J = 6.3 Hz, (CH₃)₂CHO), 0.90 (s, 9H, SiC(CH₃)₃), 0.09 (s, 6H, Si(CH₃)₂) ppm

2.1.4 Synthesis of 1-isopropoxy-3-*tert*-butyldimethylsilyloxy-2-aza-1,3-butadiene **29a**

Reference: Ghosez, L.; Bayard, Ph.; Nshimyumukiza, P.; Gouverneur, V.; Sainte, F.; Beaudegnies, R.; Rivera, M.; Frisque-Hesbain, A.-M. and Wynants, C. *Tet.* **1995**, *51*, 11021-11042



To a solution of 4.0 g (19.9 mmol, 1 eq.) of compound **92** in 20 mL of dry ether, was added at once 13.8 mL (10.0 g, 99.3 mmol, 5 eq.) of triethylamine. To this mixture, was added dropwise 1.76 mL (1.88 g, 19.9 mmol, 1 eq.) of propionyl chloride diluted in 10 mL of dry ether. Stirring was maintained for two hours at room temperature. The precipitate of triethylamine hydrochloride was filtered on celite and washed with two portions of ether. The filtrate was concentrated under reduced pressure and the crude product was obtained as a yellowish oil.

Purification: bulb-to-bulb distillation under vacuum (100 °C/0.03 mm Hg)

R.N. : [137910-10-2]

Physical aspect: colourless oil

F.B.: C₁₀H₁₄N₂O₂Si

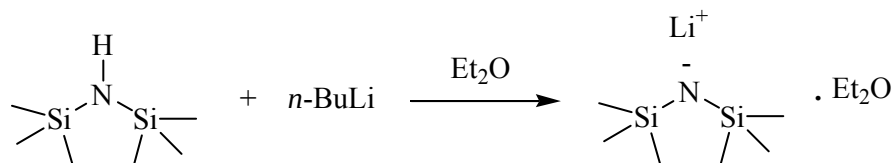
M.W.: 222.31

Yield: 3.5 g (68 %) (lit.: 77 %)

¹H NMR (200 MHz, CDCl₃, T = 25 °C) δ 7.67 (s, 1H, CH=N), 5.01 (sept., 1H, ³J = 6.2 Hz, Me₂CH), 4.15 (q, 1H, ³J = 6.8 Hz, MeCH=C), 1.56 (d, 3H, ³J = 6.8 Hz, Me), 1.26 (d, 6H, ³J = 6.2 Hz, Me₂CH), 0.95 (s, 9H, *t*-Bu), 0.15 (s, 6H, Si(CH₃)₂) ppm

2.2 Preparation of 1-phenyl-3-trimethylsilyloxy-2-aza-1,3-pentadiene **33b**2.2.1 Synthesis of lithium hexamethyldisilazane **208**

Reference: Amondo-Neizer, F. H.; Shaw, R. A.; Skolvin, D. O.; Smith, B. C. *J. Chem. Soc.* **1965**, 2997



In a round bottom flask, equipped with an addition funnel, a magnetic stirring bar and a condenser, oven dried and placed under an argon atmosphere, hexamethyldisilazane (12.3

mL, 57.1 mmol, 1 eq.) and 40 mL of ether were introduced. Then, *n*-butyllithium (24 mL, 60.0 mmol, 1.05 eq., 2.5 M in hexane) was added dropwise on the solution cooled to 0 °C. After addition was complete, the reacting mixture was refluxed during 30 minutes. The solvents were evaporated under reduced pressure and the residue washed with dry hexane. The white powder was then filtered and dried under vacuum.

R.N. : [18400-61-8]

Physical aspect: white powder

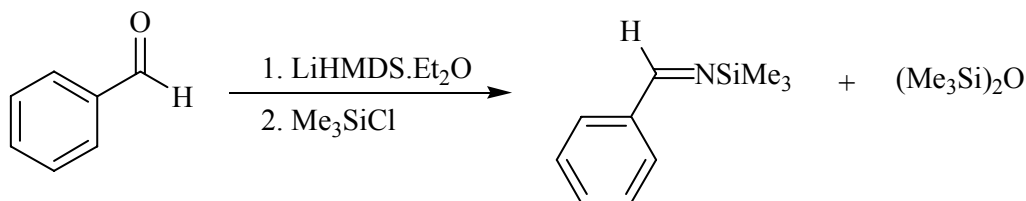
F.B.: C₁₀H₂₈LiNOSi₂

M.W.: 241.45

Yield: 11.4 g (82.5 %)

2.2.2 Synthesis of *N*-trimethylsilyl benzaldimine **94**

Reference: Ghosez, L.; Bayard, Ph.; Nshimyumukiza, P.; Gouverneur, V.; Sainte, F.; Beaudegnies, R.; Rivera, M.; Frisque-Hesbain, A.-M. and Wynants, C. *Tet.* **1995**, *51*, 11021-11042



A three-necked flask fitted with an addition funnel and a magnetic stirrer, previously dried under vacuum, was charged with 11.23 g (46.49 mmol, 1 eq.) of LiHMDS.Et₂O and 20 mL of dry ether. At the suspension cooled to 0 °C, a solution of 4.82 mL (5.03 g, 46.49 mmol, 1 eq.) of benzaldehyde freshly distilled in 10 mL of ether was added dropwise. After one hour stirring at this temperature, 5.90 mL (5.05 g, 46.49 mmol, 1 eq.) of trimethylsilyl chloride was added at once with the aid of a syringe through the septum. The cooling bath was removed, and the mixture was stirred at room temperature during two hours. The precipitate of lithium chloride was filtered (fast) on celite. The solvent was evaporated under reduced pressure (rotavapor equipped with a P₂O₅ tube). This product must be kept under argon at -20 °C.

Purification: bulb-to-bulb distillation under vacuum (60 °C/0.05 mm Hg)

R.N. : [17599-61-0]

Physical aspect: yellow oil

F.B.: C₁₀H₁₅NSi

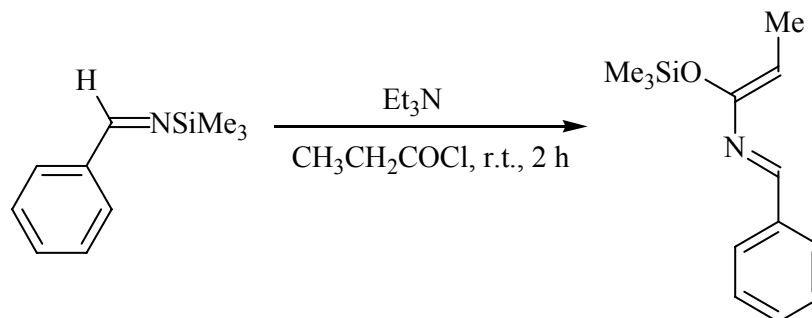
M.W.: 177.32

Yield: 6.57 g (80 %) (lit.: 95 %)

¹H NMR (200 MHz, CDCl₃, T = 25 °C) δ 8.90 (s, 1H, HC=N), 7.70 (mult, 2H, Ho), 7.30 (m, 3H, Hm+Hp), 0.20 (s, 9H, (CH₃)₃Si) ppm

2.2.3 Synthesis of 1-phenyl-3-trimethylsilyloxy-2-aza-1,3-pentadiene **33b**

Reference: Ghosez, L.; Bayard, Ph.; Nshimyumukiza, P.; Gouverneur, V.; Sainte, F.; Beaudegnies, R.; Rivera, M.; Frisque-Hesbain, A.-M. and Wynants, C. *Tet.* **1995**, *51*, 11021-11042



The same procedure as **29a** was used but, with the following conditions:

- *N*-silylated imine **94**: 2.32 g (13.08 mmol, 1 eq.) in 23 mL Et₂O
- Triethylamine: 3.64 mL (2.65 g, 26.16 mmol, 2 eq.)
- Propionyl chloride: 1.14 mL (1.21 g, 13.08 mmol, 1 eq.) in 5 mL Et₂O

Purification: bulb-to-bulb distillation under vacuum (100 °C/0.03 mm Hg)

R.N. : [121767-21-3]

Physical aspect: bright yellow oil

F.B.: C₁₃H₁₉NOSi

M.W.: 233.38

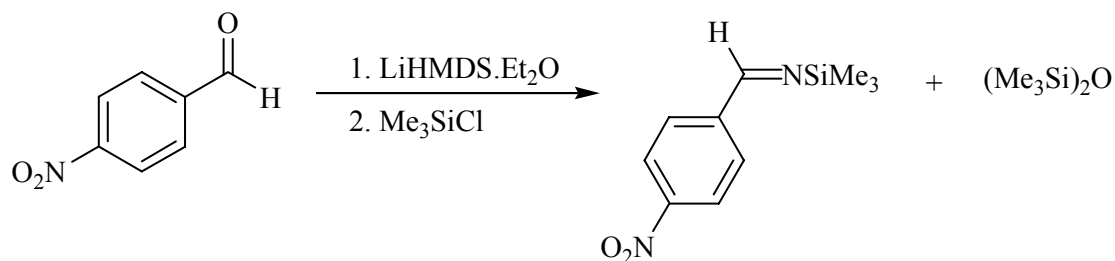
Yield: 1.81 g (59 %) (lit.: 67 %)

¹H NMR (200 MHz, CDCl₃, T = 25 °C) δ 8.31 (s, 1H, CH=N), 7.8 (mult, 2H, Ho), 7.4 (m, 3H, Hm+Hp), 5.25 (q, 1H, ³J = 7.3 Hz, MeCH=C), 1.77 (d, 3H, ³J = 7.3 Hz, Me), 0.27 (s, 9H, (CH₃)₃Si) ppm

2.3 Preparation of 1-(*para*-nitrophenyl)-3-trimethylsilyloxy-2-aza-1,3-pentadiene **33c**

2.3.1 Synthesis of *N*-trimethylsilyl *para*-nitrobenzalimine **209**

Reference of the product: Ntirampebura, D. *Dissertation UCL* **2001**



To a suspension of *para*-nitrobenzaldehyde (16.0 g, 105.6 mmol, 1 eq.) in 50 mL of ether cooled to 0 °C, LiHMDS.Et₂O (25.5 g, 105.6 mmol, 1 equiv.) dissolved in 50 mL of ether was added *via* cannula. After one hour stirring at this temperature, chlorotrimethylsilane (13.4 mL, 105.6 mmol, 1 eq.) was added in one portion with a syringe through the septum. The cold bath was removed and the mixture was stirred at room temperature for 2 hours. The lithium chloride precipitate was filtered on celite and the solvent was evaporated under reduced pressure (rotavapor equipped with a P₂O₅ tube). A yellow solid was obtained and used in the next step without any purification.

R.N. : [160313-81-5]

Physical aspect: yellow solid

F.B.: C₁₀H₁₄N₂O₂Si

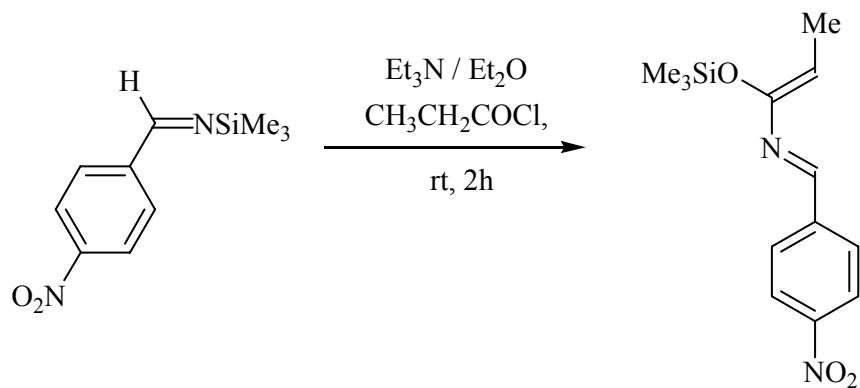
M.W.: 222.31

Yield: 19.8 g (84 %) (lit.: 87 %)

¹H NMR (200 MHz, CDCl₃, T = 25 °C) δ 9.2 (s, 1H, HC=N), 8.2 (d, 2H, ³J = 7.8 Hz), 7.8 (d, 2H, ³J = 7.8 Hz), 0.20 (s, 9H, (CH₃)₃Si) ppm

2.3.2 Synthesis of 1-(*para*-nitrophenyl)-3-trimethylsilyloxy-2-aza-1,3-pentadiene **33c**

Reference of the product: Ntirampebura, D. *Dissertation UCL 2001*



The same procedure as **29a** was used but, with the following conditions:

- *N*-silylated imine **209**: 4 g (13.9 mmol, 1 eq.) in 30 mL Et₂O
- Triethylamine: 4 mL (2.9 g, 1.6 eq.)
- Propionyl chloride: 1.56 mL (17.9 mmol, 1 eq.) in 10 mL Et₂O

Purification: flash chromatography (hexane/ether: 90/10)

Physical aspect: yellow solid

F.B.: C₁₃H₁₈N₂O₂Si

M.W.: 278.38

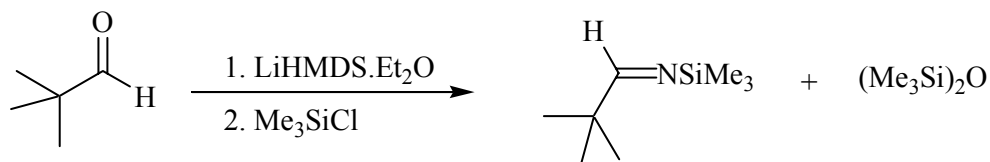
Yield: 3.0 g (60 %) (lit.:64 %)

¹H NMR (300 MHz, CDCl₃, T = 25 °C) δ 8.33 (s, 1H, HC=N), 8.28 (d, 2H, ³J = 7.8 Hz, Hm), 7.95 (d, 2H, ³J = 7.8 Hz, Ho), 5.43 (q, 1H, ³J = 7.3 Hz, MeCH=C), 1.82 (d, 3H, ³J = 7.3 Hz, Me), 0.29 (s, 9H, (CH₃)₃Si) ppm

2.4 Preparation of the 2,2-dimethyl-5-trimethylsilyloxy-4-aza-3,5-heptadiene **33a**

2.4.1 Synthesis of *N*-trimethylsilyl-2,2-dimethyl propionaldimine **210**

Reference: Ghosez, L.; Bayard, Ph.; Nshimyumukiza, P.; Gouverneur, V.; Sainte, F.; Beaudegnies, R.; Rivera, M.; Frisque-Hesbain, A.-M. and Wynants, C. *Tet.* **1995**, *51*, 11021-11042



The same procedure as **94** was used but, with the following conditions:

- LiHMDS.Et₂O: 30.0 g (124.2 mmol, 1 eq.) in 60 mL Et₂O
- Trimethylacetaldehyde: 13.8 mL (124.2 mmol, 1 eq.)
- Chlorotrimethylsilane: 16.1 mL (124.2 mmol, 1 eq.)

Purification: bulb-to-bulb distillation under vacuum (37-40 °C / 12 torr)

R.N.: [61860-99-9]

Physical aspect: colourless liquid

F.B.: C₈H₁₉NSi

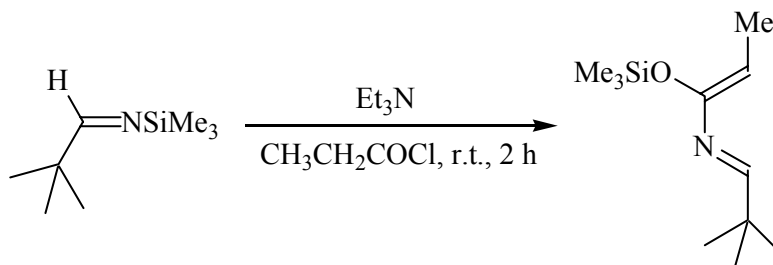
M.W.: 157.33

Yield: 13.7 g (70 %) (lit.: 75 %)

¹H NMR (200 MHz, CDCl₃, T = 25 °C) δ 8.20 (s, 1H, CH=N), 0.95 (s, 9H, *t*-Bu), 0.10 (s, 9H, (CH₃)₃Si) ppm

2.4.2 Synthesis of 2,2-dimethyl-5-trimethylsilyloxy-4-aza-3,5-heptadiene **33a**

References: Ghosez, L.; Bayard, Ph.; Nshimyumukiza, P.; Gouverneur, V.; Sainte, F.; Beaudegnies, R.; Rivera, M.; Frisque-Hesbain, A.-M. and Wynants, C. *Tet.* **1995**, *51*, 11021-11042



The same procedure as **29a** was used but, with the following conditions:

- *N*-silylated imine **210**: 13.0 g (82.6 mmol, 1 eq.) in 50 mL Et₂O
- Triethylamine: 56.3 mL (404.9 mmol, 4.9 eq.)
- Propionyl chloride: 7.3 mL (82.6 mmol, 1 eq.) in 60 mL Et₂O

Purification: bulb-to-bulb distillation under vacuum (70 °C/0.5 mm Hg)

R.N.: [172095-52-2]

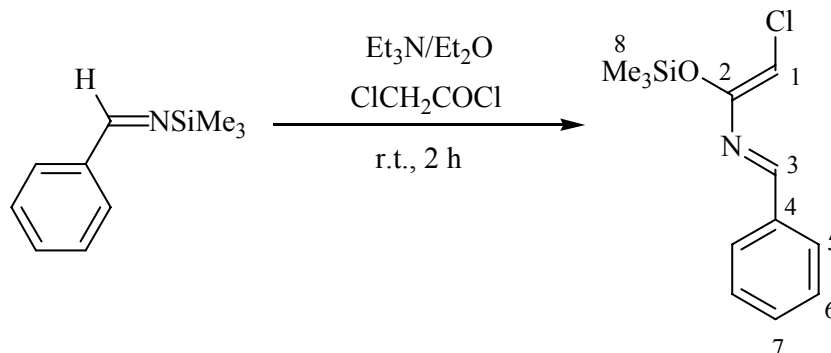
Physical aspect: colourless oil

F.B.: C₁₁H₂₃NOSi

M.W.: 213.39

Yield: 5.5 g (31 %) (lit.: 66 %)

¹H NMR (300 MHz, CDCl₃, T = 25 °C) δ 7.66 (s, 1H, CH=N), 4.90 (q, 1H, ³J = 7.0 Hz, MeCH=C), 1.67 (d, 3H, ³J = 7.0 Hz, Me), 1.12 (s, 9H, *t*-Bu), 0.24 (s, 9H, (CH₃)₃Si) ppm

2.5 Synthesis of the 4-chloro-1-phenyl-3-trimethylsilyloxy-2-aza-1,3-butadiene **33e**

To a solution of 2.5 g (14.1 mmol, 1 eq.) of imine **94** in 50 mL of dry ether, was added at once 2.93 mL (21.1 mmol, 1.5 eq.) of triethylamine. To this mixture, was added dropwise 1.12 mL (14.1 mmol, 1 eq.) of chloroacetyl chloride diluted in 3 mL of dry ether. Stirring was maintained for two hours at room temperature. The precipitate of triethylamine hydrochloride

was filtered on celite and washed with two portions of ether. The filtrate was concentrated under reduced pressure and the crude product was obtained as a yellow oil.

Purification: bulb-to-bulb distillation under reduced pressure (145 °C/9 10⁻² mbar)

Physical aspect: viscous yellow oil

F.B.: C₁₂H₁₆ClNOSi

M.W.: 253.80

Yield: 0.75 g (21 %)

I.R.: (film, cm⁻¹): 3064, 3033, 2959, 2901, 1811, 1762, 1682 (st C=C), 1622 (aromatics C=C), 1456 (st C=N), 1255, 851 (C-Cl)

¹H NMR (200 MHz, CDCl₃, T = 25 °C) δ 8.22 (s, 1H, H³), 7.66-7.61 (mult, 2H, H⁵), 7.29-7.26 (m, 3H, H⁶+H⁷), 5.83 (s, 1H, H¹), 0.20 (s, 9H, H⁸) ppm

¹³C NMR (75 MHz, CDCl₃, T = 25 °C) δ 155.21 (C³), 153.47 (C²), 135.67 (C⁴), 131.45 (C⁷), 129.18 (C⁵), 128.87 (C⁶), 101.65 (C¹), 1.30 (C⁸) ppm

M.S. (C.I. /CH₄-N₂O): 255.6 (M⁺ • (³⁷Cl), 30 %), 253.7 (M⁺ • (³⁵Cl), 63 %), 217.9 (M⁺ • ⁻³⁵Cl, 6 %), 194.9 (48 %), 178.9 (76 %), 165.6 ([M+H]⁺ • -Me₃SiO[•], 80 %), 149.8 (54 %), 146.8 (100 %), 106.8 (38 %), 73 (Me₃Si⁺, 4 %)

2.6 Synthesis of the 4-fluoro-1-phenyl-3-trimethylsilyloxy-2-aza-1,3-butadiene **33f**

2.6.1 Synthesis of fluoroacetyl chloride **211**

Reference: Truce, William E. *J. Am. Chem. Soc.* **1948**, 70, 2828



In a round bottom flask connected to a P₂O₅ tube, sodium fluoroacetate (10.0 g, 99.0 mmol, 1 eq.) and phosphorus pentachloride (23.1 g, 14.5 mL, 108.9 mmol, 1.1 eq.) were introduced. The mixture was heated at 90 °C until completion of the distillation of fluoroacetyl chloride.

Physical aspect: colourless liquid

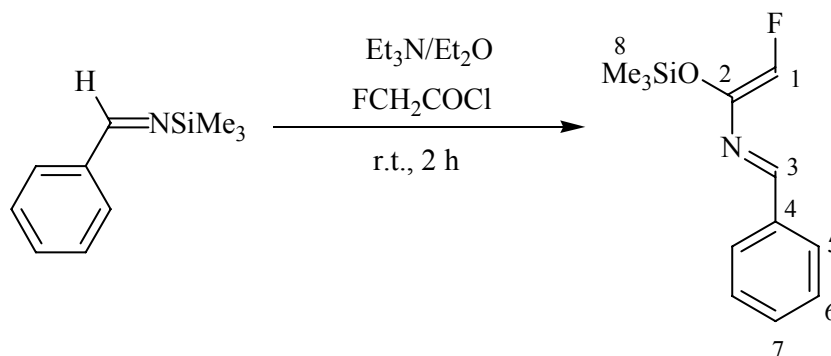
R.N.: [359-06-8]

F.B.: C₂H₂ClFO

M.W.: 95.98

Yield: 9.2 g (96 %)

¹H NMR (200 MHz, CDCl₃, T = 25 °C) δ 5.05 (d, 2H, ²J_{H-F} = 46.7 Hz) ppm

2.6.2 Synthesis of 4-fluoro-1-phenyl-3-trimethylsilyloxy-2-aza-1,3-butadiene **33f**

The same procedure as **33e** was used but, with the following conditions:

- N-silylated imine **94**: 5.0 g (28.2 mmol, 1 eq.) in 60 mL Et₂O
- Triethylamine: 39.19 mL (281.9 mmol, 10 eq.)
- Fluoroacetyl chloride: 2.72 mL (28.2 mmol, 1 eq.) in 10 mL Et₂O

Rem.: the mixture is stirred at room temperature during 3 hours.

Purification: bulb-to-bulb distillation under reduced pressure (100 °C/4.9 10⁻³ mbar). The azadiene was obtained as a mixture of two isomers: *Z/E* : 80/20

Physical aspect: yellowish oil

F.B.: C₁₂H₁₆FNOSi

M.W.: 237.34

Yield: 1.25 g (19 %)

I.R.: (film, cm⁻¹): 3064 (aryl-H), 2960, 1760, 1665 (characteristic absorption of enol ether and st C=N), 1451, 1323 (st C-F)

¹H NMR (300 MHz, CDCl₃, T = 25 °C):

Z isomer: δ 8.41 (s, 1H, H³), 7.84-7.90 (mult, 2H, Ho), 7.38-7.45 (m, 3H, Hm+Hp), 6.87-7.14 (d, 1H, ²J_{H-F} = 78.45 Hz, H¹), 0.31 (s, 9H, Me₃Si) ppm

E isomer: δ 8.37 (s, 1H, H³), 7.84-7.90 (mult, 2H, Ho), 7.38-7.45 (m, 3H, Hm+Hp), 6.44-6.70 (d, 1H, ²J_{H-F} = 78.45 Hz, H¹), 0.29 (s, 9H, Me₃Si) ppm

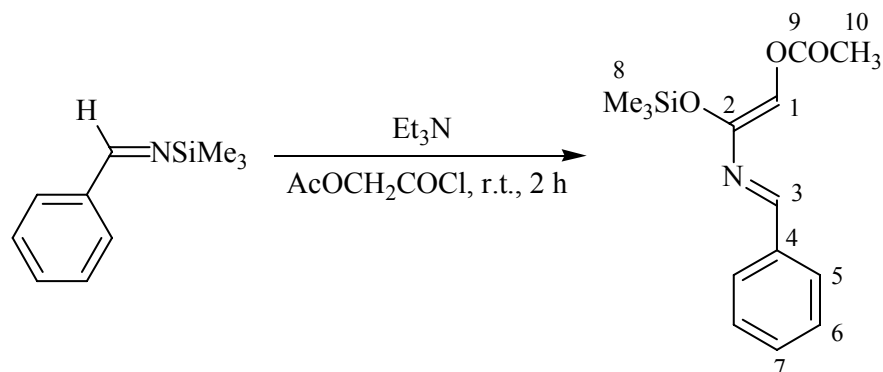
¹³C NMR (75 MHz, CDCl₃, T = 25 °C) δ 155.5 (C³), 143.5 (C²), 136.2 (C⁴), 131.6 (C⁷), 129.2 (C⁵), 128.9 (C⁶), 128.6 (C¹), 2.1 (C⁸) ppm

M.S. (C.I. /CH₄-N₂O): 266 ([M+C₂H₅]⁺, 6 %), 238 ([M+H]⁺, 100 %), 237 (M⁺, 96 %)

HRMS (C.I.): Calculated for C₁₂H₁₆FNOSi: 237.097896

Found: 237.098521

2.7 Synthesis of the 4-acetoxy-1-phenyl-3-trimethylsilyloxy-2-aza-1,3-butadiene **33h**



The same procedure as **33e** was used but, with the following conditions:

- *N*-silylated imine **94**: 2.0 g (11.28 mmol, 1 eq.) in 20 mL Et_2O
- Triethylamine: 7.84 mL (5.70 g, 56.39 mmol, 5 eq.)
- Acetoxyacetyl chloride: 1.25 mL (1.59 g, 11.28 mmol, 1 eq.) in 3 mL Et_2O

Rem.: the mixture is stirred at room temperature during 4 hours.

Purification: bulb-to-bulb distillation under vacuum ($145\text{ }^\circ\text{C}/1.2\cdot 10^{-2}\text{ mbar}$)

Physical aspect: yellow oil

F.B.: $\text{C}_{14}\text{H}_{19}\text{NO}_3\text{Si}$

M.W.: 277.39

Yield: 1.92 g (61 %)

I.R. (film, cm^{-1}): 3361, 3121, 3063, 3031, 2958, 2900, 2239, 2116, 1761 (st $\text{C}=\text{O}$), 1663 (st $\text{C}=\text{C}$), 1451 (st $\text{C}=\text{N}$), 1371 (st $\text{C}-\text{H}$ in OCOCH_3), 913, 851, 757, 692

^1H NMR (200 MHz, CDCl_3 , $T = 25\text{ }^\circ\text{C}$) δ 8.41 (s, 1H, H^3), 7.83-7.78 (mult, 2H, H^5), 7.44-7.41 (m, 4H, $\text{H}^6+\text{H}^7+\text{H}^1$), 2.23 (s, 3H, H^{10}), 0.29 (s, 9H, H^8) ppm

^{13}C NMR (50 MHz, CDCl_3 , $T = 25\text{ }^\circ\text{C}$) δ 167.10 (C^9), 154.5 (C^3), 143.1 (C^2), 136.3 (C^4), 131.1 (C^7), 129.2 (C^5), 128.9 (C^6), 122.4 (C^1), 21.0 (C^{10}), 0.6 (C^8) ppm

M.S. (C.I. / $\text{CH}_4\text{-N}_2\text{O}$): 279.4 ($[\text{M}+\text{H}]^+$, 48 %), 277.9 (M^+ , 100 %), 178.0 (8 %), 117.9 (9 %), 102.9 (10 %), 91.0 ($\text{Me}_3\text{SiOH}_2^+$, 38 %), 73.0 (Me_3Si^+ , 100 %)

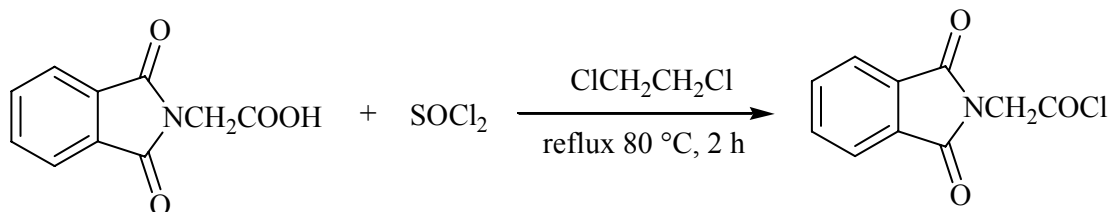
HRMS: Calculated for $\text{C}_{14}\text{H}_{19}\text{NO}_3\text{Si}$: 277.113840

Found: 277.113422

2.8 Preparation of the 1-phenyl-4-(*N*-phthalimido)-3-trimethylsilyloxy-2-aza-1,3-butadiene **33g**

2.8.1 Synthesis of *N*-phthaloylglycine chloride **213**

Reference: Kumli, F. *Dissertation* UCL-ORSY, 1996



In a three-necked round bottom flask, equipped with a magnetic stirring bar, a condenser and an addition funnel, oven dried and placed under argon atmosphere, *N*-phthaloylglycine (5.0 g, 24.1 mmol, 1 eq.) and 30 mL of dry dichloroethane were introduced. Thionyl chloride (2.65 mL, 36.2 mmol, 1.5 eq.) was then added, and the mixture refluxed at 80 °C for two hours. The solvent was evaporated under reduced pressure (rotavapor equipped with a P₂O₅ tube). The acid chloride obtained was engaged in the next step without any further purification.

Physical aspect: white solid

R.N.: [125427-99-8]

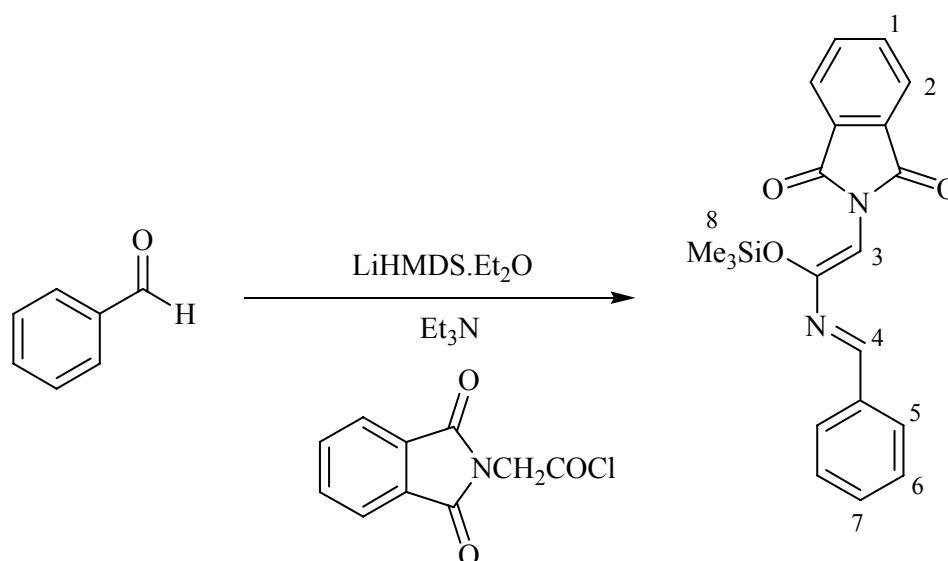
F.B.: C₁₀H₆ClNO

M.W.: 223.61

Yield: 4.5 g (83 %) (lit.: 90 %)

¹H NMR (200 MHz, CDCl₃, T = 25 °C) δ 7.87-7.95 (mult, 2H, Har), 7.77-7.85 (mult, 2H, Har), 4.85 (s, 2H, CH₂CO) ppm

2.8.2 Synthesis of the 1-phenyl-4-(*N*-phthalimido)-3-trimethylsilyloxy-2-aza-1,3-butadiene **33g**



Lithium hexamethyldisilazane (6.5 g, 26.8 mmol, 1 eq.) and 40 mL of dry ether were placed in a round bottom flask. After cooling of the mixture at 0°C, a solution of freshly distilled benzaldehyde (2.7 mL, 26.8 mmol, 1 eq.) in 15 mL of dry ether was added dropwise *via* the addition funnel. After addition of the aldehyde, the reaction was let for one hour at 0 °C. Trimethylsilyl chloride (3.6 mL, 26.8 mmol, 1 eq.) was added in one portion in order to remove the residual trimethylsilanolate. After 10 min. agitation at 0 °C, the solution was warmed at room temperature and stirred for one hour and a white precipitate appeared. The mixture was cooled to 0 °C and dry triethylamine (4.1 mL, 29.5 mmol, 1.1 eq.) was then added at once. After 5 min., through the dropping funnel was added at once a solution of *N*-phthaloylglycine chloride (6.0 g, 26.8 mmol, 1 eq.) in 60 mL of dry ether. The cooling bath was removed and the reaction was let at room temperature for an extra two hours. The triethylamine hydrochloride was filtered on celite and the solvent was removed under vacuum.

Purification: column chromatography

Reference of the product: Panunzio, M.; Martelli, G.; Bongini, A.; Bandini, E.; Campana, E.; Spunta, G. *Tetrahedron: Asymmetry* **2001**, *12*, 439-454.

Physical aspect: viscous yellow oil

F.B.: C₂₀H₂₀N₂O₃Si

M.W.: 364.47

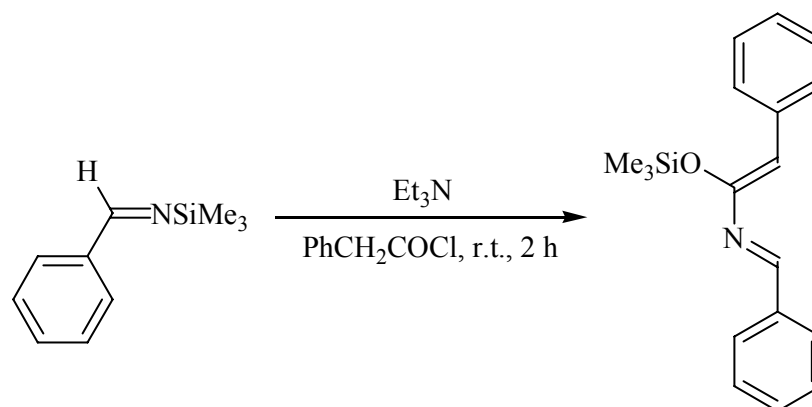
Yield: 7.2 g (73 %)

I.R. (film, cm⁻¹): 3080 (C=H arom.), 1717 (C=O), 1652 (C=N), 1609 (C=C arom.)

¹H NMR (200 MHz, CDCl₃, T = 25 °C) δ 8.57 (s, 1H, H⁴), 7.86-7.88 (mult, 2H, H²), 7.83-7.78 (mult, 2H, H¹), 7.71-7.74 (mult, 2H, H⁵), 7.44-7.41 (m, 3H, H⁶+H⁷), 5.92 (s, 1H, H³), 0.17 (s, 9H, H⁸) ppm

2.9 Synthesis of 1,4-diphenyl-3-trimethylsilyoxy-2-aza-1,3-butadiene **33i**

Reference: Ghosez, L.; Bayard, Ph.; Nshimyumukiza, P.; Gouverneur, V.; Sainte, F.; Beaudegnies, R.; Rivera, M.; Frisque-Hesbain, A.-M. and Wynants, C. *Tet.* **1995**, *51*, 11021-11042



The same procedure as **33e** was used but, with the following conditions:

- N-silylated imine **94**: 0.3 g (1.69 mmol, 1 eq.) in 6 mL Et_2O
- Triethylamine: 0.259 mL (0.188 g, 1.86 mmol, 1.1 eq.)
- Phenylacetyl chloride: 0.228 mL (0.267 g, 1.69 mmol, 1 eq.) in 0.6 mL Et_2O

Dry petroleum ether was used to rinse the celite. After evaporation of the solvents, dry petroleum ether was added on the residue in order to precipitate the triethylammonium chloride, and the suspension was filtered on the celite. This step was repeated until no more precipitate appeared. Finally, the solvent was evaporated under reduced pressure, and the product dried *in vacuo*.

R.N. : [172095-47-5]

Physical aspect: yellow-orange oil

F.B.: $\text{C}_{18}\text{H}_{21}\text{NOSi}$

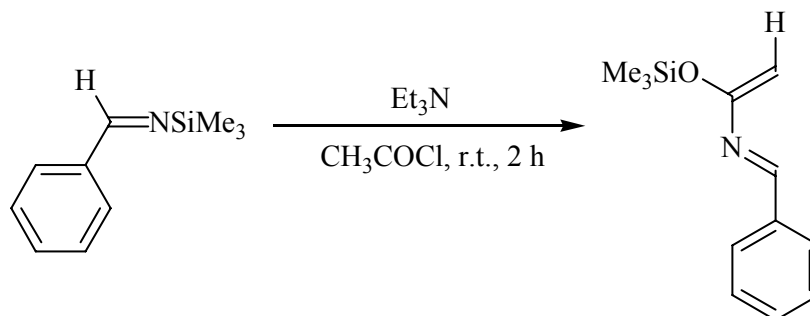
M.W.: 295.45

Yield: 0.47 g (crude: 95 %) (lit.: 96 % [crude])

^1H NMR (200 MHz, CDCl_3 , T = 25 °C) δ 8.49 (s, 1H, $\text{CH}=\text{N}$), 7.85-7.10 (m, 10H, Har), 5.90 (s, 1H, $\text{PhCH}=\text{C}$), 0.23 (s, 9H, $(\text{CH}_3)_3\text{Si}$) ppm

2.10 Synthesis of 1-phenyl-3-trimethylsilyloxy-2-aza-1,3-butadiene **33d**

Reference: Ghosez, L.; Bayard, Ph.; Nshimyumukiza, P.; Gouverneur, V.; Sainte, F.; Beaudegnies, R.; Rivera, M.; Frisque-Hesbain, A.-M. and Wynants, C. *Tet.* **1995**, *51*, 11021-11042



The same procedure as **33e** was used but, with the following conditions:

- *N*-silylated imine **94**: 1.5 g (8.46 mmol, 1 eq.) in 10 mL Et₂O
- Triethylamine: 1.411 mL (1.027 g, 10.15 mmol, 1.2 eq.)
- Acetyl chloride: 0.608 mL (0.671 g, 8.46 mmol, 1 equiv.) in 2.5 mL Et₂O

Dry petroleum ether was used to rinse the celite. After evaporation of the solvents, dry petroleum ether was added on the residue in order to precipitate the triethylammonium chloride, and the suspension was filtered on the celite. This step was repeated until no more precipitate appeared. Finally, the solvent was evaporated under reduced pressure, and the product dried *in vacuo*.

R.N. : [121767-19-9]

Physical aspect: bright yellow oil

F.B.: C₁₂H₁₇NOSi

M.W.: 219.35

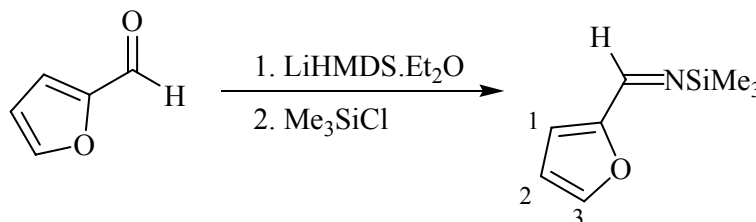
Yield: 1.20 g (crude: 65 %) (lit.: 72 %)

¹H NMR (200 MHz, CDCl₃, T = 25 °C) δ 8.49 (s, 1H, CH=N), 7.85 (mult, 2H, Ho), 7.45 (m, 3H, Hm+p), 4.68 (s, 1H), 4.31 (s, 1H), 0.30 (s, 9H, Me₃Si) ppm

2.11 Synthesis of 1-(2-furyl)-3-trimethylsilyloxy-2-aza-1,3-pentadiene **101**

2.11.1 Synthesis of *N*-trimethylsilyl-2-furfuraldimine **215**

Reference: Nshimyumukiza P. *Dissertation UCL* **1994**, Colvin, E. W.; Mc Garry, D.; Nugent, M. J. *Tetrahedron* **1988**, *44*, 4157



A three-necked flask fitted with an addition funnel and a magnetic stirrer, previously dried under vacuum, was charged with 15.1 g (62.5 mmol, 1 eq.) of LiHMDS.Et₂O and 20 mL of dry ether. At the suspension cooled to 0 °C, a solution of 5.2 mL (6.0 g, 62.5 mmol, 1 eq.) of

2-furfuraldehyde freshly distilled in 10 mL of ether was added dropwise. After one hour stirring at this temperature, 7.9 mL (6.8 g, 62.5 mmol, 1 eq.) of trimethylsilyl chloride was added at once with the aid of a syringe through the septum. The cooling bath was removed, and the mixture was stirred at room temperature during two hours. The precipitate of lithium chloride was filtered (fast) on celite. The solvent was evaporated under reduced pressure (rotavapor equipped with a P₂O₅ tube). This product must be kept under argon at -20 °C.

Purification: distillation under reduced pressure (54-55 °C/0.1 mbar)

R.N.: [83948-29-2]

Physical aspect: yellow oil

F.B.: C₈H₁₃NOSi

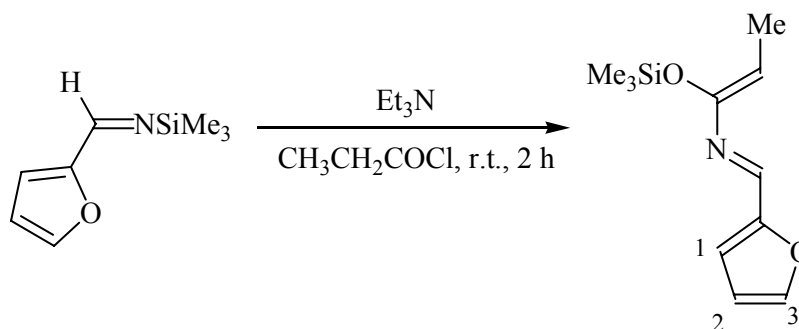
M.W.: 167.28

Yield: 6.38 g (61 %) (lit.: 65 %)

¹H NMR (200 MHz, CDCl₃, T = 25 °C) δ 8.72 (s, 1H, CH=N), 7.58 (s, 1H, H³), 6.87 (d, 1H, ³J_{H1-H2} = 3.4 Hz, H¹), 6.54 (dd, 1H, ³J_{H2-H1} = 3.4 Hz, ³J_{H2-H3} = 1.8 Hz, H²), 0.30 (s, 9H, (CH₃)₃Si) ppm

2.11.2 Synthesis of 1-(2-furyl)-3-trimethylsilyloxy-2-aza-1,3-pentadiene **101**

Reference: Ghosez, L.; Bayard, Ph.; Nshimyumukiza, P.; Gouverneur, V.; Sainte, F.; Beaudegnies, R.; Rivera, M.; Frisque-Hesbain, A.-M. and Wynants, C. *Tet.* **1995**, *51*, 11021-11042



The same procedure as **33e** was used but, with the following conditions:

- *N*-silylated imine **215**: 1.0 g (5.98 mmol, 1 eq.) in 8 mL Et₂O
- Triethylamine: 8.31 mL (6.05 g, 59.78 mmol, 10 eq.)
- Propionyl chloride: 0.57 mL (0.61 g, 6.58 mmol, 1.1 eq.) in 2 mL Et₂O

Dry petroleum ether was used to rinse the celite. After evaporation of the solvents, dry petroleum ether was added on the residue in order to precipitate the triethylammonium chloride, and the suspension was filtered on the celite. This step was repeated until no more precipitate appeared. Finally, the solvent was evaporated under reduced pressure, and the product dried *in vacuo*.

R.N. : [172095-56-6]

Physical aspect: yellow oil

F.B.: C₁₁H₁₇NO₂Si

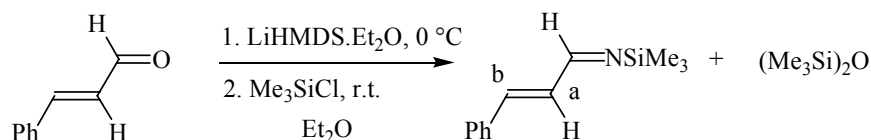
M.W.: 223.34

Yield: 0.84 g (63 % crude) (lit.: 71 % pure [5 equiv. Et₃N])

¹H NMR (200 MHz, CDCl₃, T = 25 °C) δ 8.10 (s, 1H, CH=N), 7.56 (d, 1H, ³J_{H3-H2} = 1.8 Hz, H³), 6.82 (d, 1H, ³J_{H1-H2} = 3.5 Hz, H¹), 6.51 (dd, 1H, ³J_{H2-H1} = 3.5 Hz, ³J_{H2-H3} = 1.8 Hz, H²), 5.35 (q, 1H, ³J_{Me} = 7.3 Hz, MeCH=C), 1.78 (d, 3H, ³J_(MeCH=C) = 7.3 Hz, Me), 0.29 (s, 9H, (CH₃)₃Si) ppm

2.12 Synthesis of silylated imine **116**

Reference: Ghosez, L.; Bayard, Ph.; Nshimyumukiza, P.; Gouverneur, V.; Sainte, F.; Beaudegnies, R.; Rivera, M.; Frisque-Hesbain, A.-M. and Wynants, C. *Tet.* **1995**, 51, 11021-11042



A three-necked flask fitted with an addition funnel and a magnetic stirrer, previously dried under vacuum, was charged with 6.0 g (24.85 mmol, 1 eq.) of LiHMDS.Et₂O and 7 mL of dry ether. At the suspension cooled to 0 °C, a solution of 3.13 mL (3.28 g, 24.85 mmol, 1 eq.) of *trans*-cinnamaldehyde freshly distilled in 10 mL of ether was added dropwise. After one hour stirring at this temperature, 3.15 mL (2.70 g, 24.85 mmol, 1 eq.) of trimethylsilyl chloride was added at once with the aid of a syringe through the septum. The cooling bath was removed, and the mixture was stirred at room temperature during two hours. The lithium chloride precipitate was filtered (fast) on celite. The solvent was evaporated under reduced pressure (rotavapor equipped with a P₂O₅ tube). This product must be kept under argon at -20 °C.

Purification: bulb-to-bulb distillation under vacuum (125 °C/0.05 mm Hg)

R.N. : [83948-28-1]

Physical aspect: yellow oil

F.B.: C₁₂H₁₇NSi

M.W.: 203.35

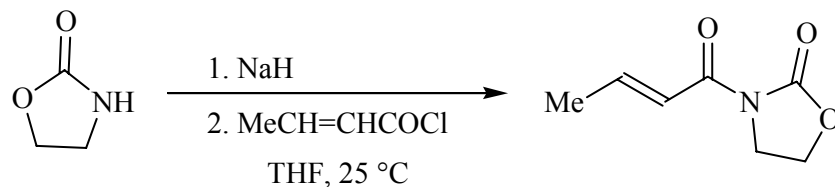
Yield: 4.59 g (91 %) (lit.: 95 %)

¹H NMR (200 MHz, CDCl₃, T = 25 °C) δ 8.70 (d, 1H, HC=N, J_{Ha} = 8.1 Hz), 7.50 (mult., 2H, Ho), 7.35 (m, 3H, Hm+Hp), 7.10 (d, 1H, Hb, ³J_{Ha} = 15.9 Hz), 6.83 (dd, 1H, Ha), 0.24 (s, 9H, (CH₃)₃Si) ppm

3 Synthesis of the dienophiles

3.1 Synthesis of the 3-crotonoyl-1,3-oxazolidin-2-one **88**

Reference: Davies, S.G.; Edwards, A.J.; Walters, I.A.S. *Recl. Trav. Chim. Pays-Bas* **1995**, *114*, 175-183



A three-necked flask of 250 mL, equipped with an addition funnel, a condenser and a magnetic stirrer, is dried under vacuum. In the flask, were introduced 2.10 g (53 mmol, 1.1 eq.) of sodium hydride (60 % in paraffin), and 50 mL of dry tetrahydrofuran. A suspension of 4.6 g (53 mmol, 1.1 eq.) of 1,3-oxazolidin-2-one in 25 mL THF were added dropwise. After one hour stirring at room temperature, a solution of 4.58 mL (48 mmol, 1 eq.) of crotonyl chloride in 25 mL THF were added dropwise. After two hours stirring at reflux, the mixture was quenched with 50 mL water. The THF was evaporated under reduced pressure and the aqueous phase was extracted with 3X50 mL dichloromethane. The organic layers were combined and dried over MgSO_4 . After evaporation of the solvent under reduced pressure, we obtained a yellow oil which becomes solid.

R.N. : [109299-92-5]

Purification: flash chromatography (Et_2O /hexane) followed by a recrystallization (Et_2O /hexane at 0 °C)

Physical aspect: white powder

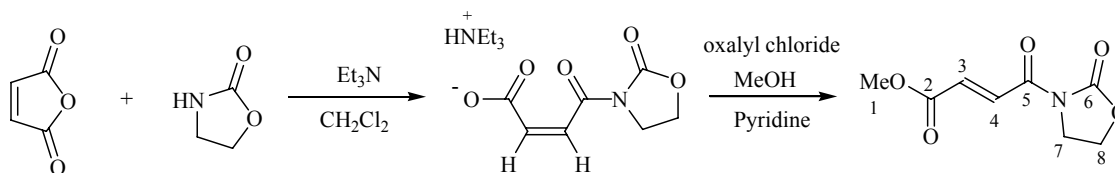
F.B.: $\text{C}_7\text{H}_9\text{NO}_3$

Yield: 4.48 g (60 %) (lit.: 46 %)

^1H NMR (300 MHz, CDCl_3 , T = 25 °C) δ 7.24-7.05 (m, 2H, $\text{MeCH}=\text{CH}$), 4.41 (t, 2H, CH_2O , $^3J_{\text{HH}} = 8.0$ Hz), 4.05 (t, 2H, CH_2N , $^3J_{\text{HH}} = 8.0$ Hz), 1.95 (d, 3H, $\text{CH}_3\text{CH}=\text{CH}$, $^3J_{\text{MeH}} = 5.4$ Hz) ppm

3.2 Synthesis of the 3-((E)-3-(methoxycarbonyl)propenoyl)-1,3-oxazolidin-2-one **91**

Reference: Knol, J.; Feringa, B. L. *Synlett* **1995**, 1025-1026, Narasaka, K.; Iwasawa, N.; Inoue, M.; Yamada, T.; Nakashima, M. and Sugimori, J. *J. Am. Chem. Soc.* **1989**, *111*, 5340-5345



The triethylammonium salt was prepared by reaction of 2-oxazolidinone (1.0 g, 11.25 mmol, 1 eq.) and maleic anhydride (1.14 g, 11.25 mmol, 1 eq.) in dry dichloromethane (20 mL) in

the presence of triethylamine (1.72 mL, 12.38 mmol, 1.1 eq.) at room temperature for 16 hours. This solution was used without further purification.

To the cooled solution (0 °C) of the triethylammonium salt, containing five drops of dry DMF, was added oxalyl chloride (1.0 mL, 11.25 mmol, 1 eq.) and the mixture was stirred for 3 hours at room temperature. After recooling (0 °C), a pyridine solution of methanol (0.91 mL, 22.51 mmol, 2 eq. in 5.1 mL pyridine) was added and the dark brown mixture was stirred for 1 hour at room temperature followed by filtration over silica gel with a ethyl acetate/petroleum ether (40-60) mixture.

Purification: flash chromatography (ethyl acetate/petroleum ether : 40/60)

Physical aspect: white-beige solid

F.B.: C₈H₉NO₅

M.W.: 199

Yield: 0.10 g (45 %) (lit.: 45 %)

¹H NMR (200 MHz, CDCl₃, T = 25 °C) δ 8.16 (d, 1H, ³J = 15.6 Hz, CHCOOCH₃), 6.96 (d, 1H, ³J = 15.6 Hz, CHCOoxaz), 4.49 (t, 2H, CH₂O, ³J = 8.0 Hz), 4.11 (t, 2H, CH₂N, ³J = 8.0 Hz), 3.83 (s, 3H, CO₂CH₃) ppm

¹³C NMR (50 MHz, CDCl₃, T = 25 °C) δ 165.4 (C²), 163.9 (C⁵), 153.3 (C⁶), 133.9 (C⁴), 132.2 (C³), 62.5 (C⁷), 52.5 (C¹), 42.3 (C⁸) ppm

M.S. (C.I./CH₄-N₂O) : 200 ([M+H]⁺, 100 %), 168 ([M+H-CH₃O]⁺, 71 %), 140 ([M-CO₂Me]⁺, 25 %)

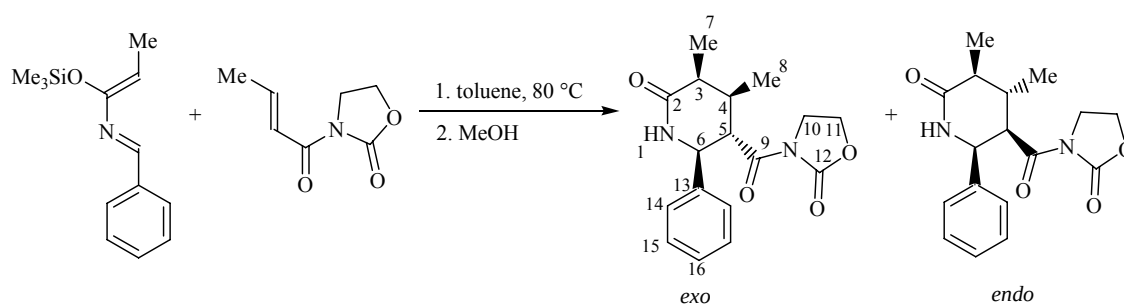
4 Synthesis of 2-piperidones via thermal [4+2] cycloadditions

General procedure

In a two-necked flask of 25 mL, equipped with a magnetic stirrer and a condenser; is dried under vacuum. In the flask, the dienophile and the diene in solution in a dry solvent are introduced. The reaction is carried out at the temperature and the time required. Then, a large excess of MeOH is added on the mixture and is shaken for minimum 30 minutes. After evaporation of the solvents under reduced pressure, the cycladduct is purified by a flash chromatography and/or recrystallized.

4.1 Synthesis of the 3,4-dimethyl-5-[(2-oxo-1,3-oxazolidin-3-yl)carbonyl]-6-phenyltetrahydropyridin-2(1H)-one **104 exo**

Reference: Jnoff, E. *Dissertation, UCL-ORSY*, **1999**, Jnoff, E.; Ghosez, L. *J. Am. Chem. Soc.* **1999**, *121*, 2617-2618



Prepared according to the general procedure with **88** (0.15 g, 0.967 mmol, 1 eq.) in 2 mL toluene and **33b** (0.451 g, 1.934 mmol, 2 eq.), 80 °C, 5 h 30. Composition of the crude mixture: *exo/endo*: 90/10. Only the *exo* isomer was isolated.

Purification: recrystallization in AcOEt/hexane

Physical aspect: white powder

R.N.: [222638-06-4]

F.B.: C₁₇H₂₀N₂O₄

M.W.: 316.36

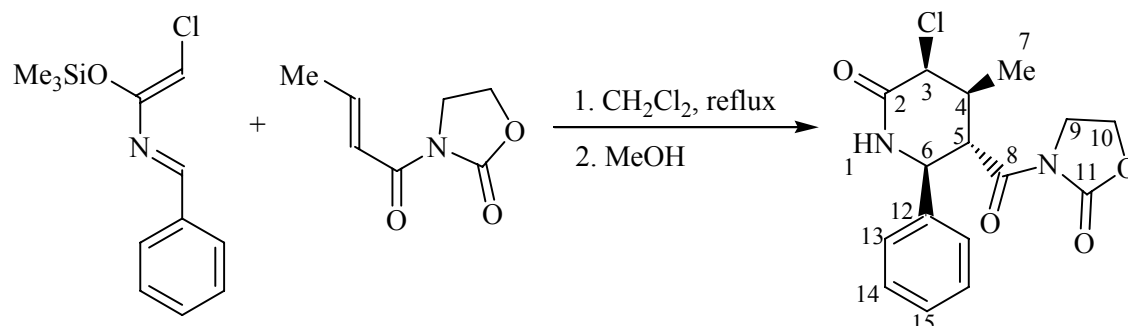
Yield: 0.239 g (78 %) (lit.: 90 %)

¹H NMR (300 MHz, CDCl₃, T = 25 °C)

Proton	δ (ppm)	Mult.	Integ.	J (Hz)
14, 15, 16	7.40-7.25	m	5	/
1	5.64	s	1	/
6	4.76	d	1	³ J ₆₋₅ = 10.4
5	4.58	dd	1	³ J ₅₋₆ = 10.4, ³ J ₅₋₄ = 10.3
11	4.27	m	1	/
11'	4.06	m	1	/
10	3.92	m	1	/
10'	3.72	m	1	/
3	2.65	qd	1	³ J ₃₋₇ = 7.4, ³ J ₃₋₄ = 5.0
4	2.59-2.48	mult	1	³ J ₄₋₃ = 5.0, ³ J ₄₋₅ = 10.3, ³ J ₄₋₈ = 6.9
7	1.37	d	3	³ J ₇₋₃ = 7.4
8	0.98	d	3	³ J ₈₋₄ = 6.9

¹³C NMR (75 MHz, CDCl₃, T = 25 °C) δ 175.4 (C²), 173.3 (C⁹), 152.7 (C¹²), 139.2 (C¹³), 128.9 (C¹⁴), 128.8 (C¹⁵), 127.0 (C¹⁶), 61.6 (C¹¹), 60.5 (C⁶), 46.3 (C⁵), 42.4 (C¹⁰), 40.4 (C³), 35.1 (C⁴), 15.1 (C⁷), 12.9 (C⁸) ppm

4.2 Synthesis of the 3-chloro-4-methyl-5-[(2-oxo-1,3-oxazolidin-3-yl)carbonyl]-6-phenyltetrahydropyridin-2(1H)-one **105 exo**



Prepared according to the general procedure with dienophile **88** (0.35 g, 1.404 mmol, 1 eq.) in 4 mL CH_2Cl_2 and azadiene **33e** (0.723 g, 2.808 mmol, 2 eq.), room temperature, 1 night. Only the *exo* isomer was formed.

Purification: flash chromatography (AcOEt)

Rf: 0.46 (AcOEt)

Physical aspect: white solid

F.B.: $\text{C}_{16}\text{H}_{17}\text{ClN}_2\text{O}_4$

M.W.: 336.77

Yield: 0.520 g (99 %)

HPLC: Chiralcel AD, *i*-PrOH/hexane (15/85), 2 mL/min, $\lambda = 220$ nm, $t_r = 16.6$ min. and $t_r = 26.7$ min.

I.R.: (KBr, cm^{-1}): 3182 (NH), 2924-3062 (CH aliph.), 1768 (CO oxazolidinone), 1703 (CO imide), 1678 (CO lactam), 1388, 1100 (st C-Cl), 829

^1H NMR (500 MHz, CDCl_3 , T = 25 °C)

Proton	δ (ppm)	Mult.	Integ.	J (Hz)
13, 14, 15	7.4-7.3	m	5	/
1	5.72	br s	1	/
5	4.97	dd	1	$^3J_{5-6} = 11.0$, $^3J_{5-4} = 11.0$
6	4.76	d	1	$^3J_{6-5} = 11.0$
3	4.39	d	1	$^3J_{3-4} = 3.9$
10	4.26	ddd	1	$^2J_{10-10'} = 9.1$, $^3J_{10-9} = 9.1$, $^3J_{10-9'} = 6.1$
10'	4.03	ddd	1	$^2J_{10'-10} = 9.1$, $^3J_{10'-9} = 7.2$, $^3J_{10'-9'} = 9.1$
9	3.91	ddd	1	$^2J_{9-9'} = 11.1$, $^3J_{9-10} = 9.1$, $^3J_{9-10'} = 7.2$
9'	3.73	ddd	1	$^2J_{9'-9} = 11.1$, $^3J_{9'-10} = 6.1$, $^3J_{9'-10'} = 9.1$
4	2.75	mult	1	$^3J_{4-7} = 6.3$, $^3J_{4-5} = 11.0$, $^3J_{4-3} = 3.9$
7	1.14	d	3	$^3J_{7-4} = 6.3$

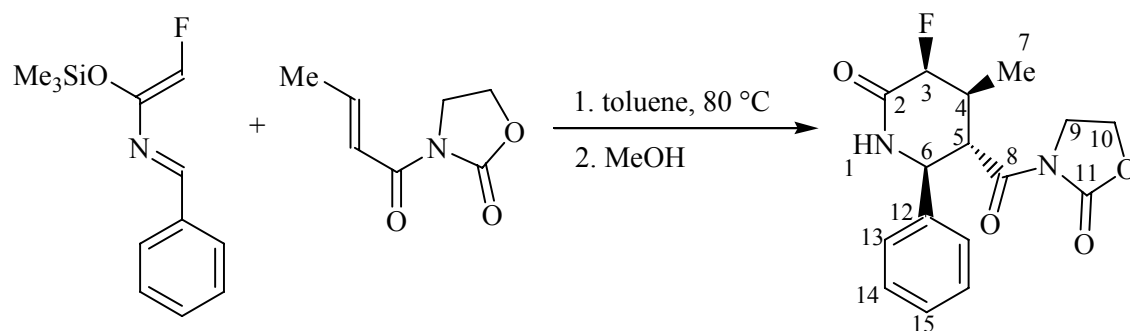
^{13}C NMR (125 MHz, CDCl_3 , $T = 25\text{ }^\circ\text{C}$) δ 172.43 (C^2), 167.35 (C^8), 152.10 (C^{11}), 138.16 (C^{12}), 129.11 (C^{15}), 128.89 (C^{14}), 127.04 (C^{13}), 61.46 (C^{10}), 61.08 (C^6), 59.08 (C^3), 45.08 (C^5), 42.37 (C^9), 36.69 (C^4), 15.18 (C^7) ppm

M.S. (C.I./ $\text{CH}_4\text{-N}_2\text{O}$) : 339 ($[\text{M}+\text{H}]^+$, ^{37}Cl , 24 %), 337 ($[\text{M}+\text{H}]^+$, ^{35}Cl , 100 %), 336 (M^+ , 5 %), 259 ($[\text{M}-\text{C}_6\text{H}_5]^+$, 6 %), 210 (24 %), 185 (24 %), 120 (100 %), 92 (46 %)

HRMS (C.I.): Calculated for $\text{C}_{16}\text{H}_{18}\text{ClN}_2\text{O}_4$: 337.094551

Found: 337.095510

4.3 Synthesis of the 3-fluoro-4-methyl-5-[(2-oxo-1,3-oxazolidin-3-yl)carbonyl]-6-phenyltetrahydropyridin-2(1*H*)-one **106** *exo*



Prepared according to the general procedure with dienophile **88** (0.2 g, 1.289 mmol, 1 eq.) in 3 mL toluene and azadiene **33f** (0.612 g, 2.578 mmol, 2 eq.), $80\text{ }^\circ\text{C}$, 6 h. Only the *exo* isomer was formed.

Purification: flash chromatography (AcOEt), then recrystallized in AcOEt/hexane

Rf: 0.53 (AcOEt)

Physical aspect: white solid

M.P.: $190\text{--}191\text{ }^\circ\text{C}$

F.B.: $\text{C}_{16}\text{H}_{17}\text{FN}_2\text{O}_4$

M.W.: 320.32

Yield: 0.16 g (39 %)

HPLC: Chiralcel AD, *i*-PrOH/hexane (20/80), 2 mL/min, $\lambda = 220\text{ nm}$, $t_r = 12.4\text{ min.}$ and $t_r = 19.6\text{ min.}$

I.R.: (KBr, cm^{-1}): 3260 (NH), 2884–2971 (CH aliph.), 1776 (CO oxazolidinone), 1696 (CO imide), 1657 (CO lactam), 1389, 1217 (C-F)

¹H NMR (500 MHz, CDCl₃, T = 25 °C)

Proton	δ (ppm)	Mult.	Integ.	J (Hz)
13, 14, 15	7.38-7.28	m	5	/
1	5.92	br s	1	/
3	4.85	d	1	² J _{3-F} = 47.0, ³ J ₃₋₄ = 3.5
6	4.77	d	1	/
5	4.73	mult	1	³ J ₅₋₄ = 10.4
10	4.24	ddd	1	² J _{10-10'} = 9.0, ³ J ₁₀₋₉ = 9.0, ³ J _{10-9'} = 6.1
10'	4.00	ddd	1	² J _{10'-10} = 9.0, ³ J _{10'-9} = 7.4, ³ J _{10'-9'} = 9.0
9	3.90	ddd	1	² J _{9-9'} = 11.2, ³ J ₉₋₁₀ = 9.0, ³ J _{9-10'} = 7.4
9'	3.68	ddd	1	² J _{9'-9} = 11.2, ³ J _{9'-10} = 6.1, ³ J _{9'-10'} = 9.0
4	2.55	mult	1	³ J _{4-F} = 31.5, ³ J ₄₋₇ = 7.0, ³ J ₄₋₅ = 10.4, ³ J ₄₋₃ = 3.5
7	1.16	d	3	⁴ J _{7-F} = 1.3, ³ J ₇₋₄ = 7.0

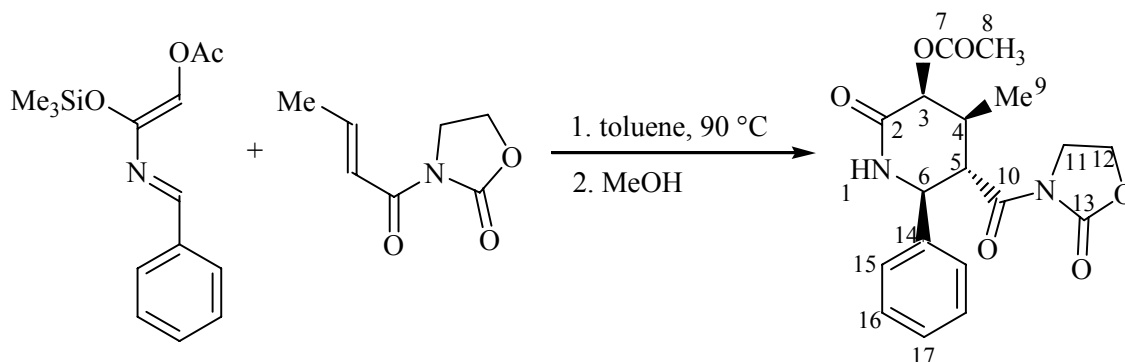
¹³C NMR (125 MHz, CDCl₃, T = 25 °C) δ 172.38 (C²), 166.01 (C⁸), 152.08 (C¹¹), 137.76 (C¹²), 129.16 (C¹⁵), 128.90 (C¹⁴), 127.05 (C¹³), 88.29 (C³) (¹J_{3-F} = 179 Hz), 61.44 (C¹⁰), 60.65 (C⁶), 45.72 (C⁵), 42.36 (C⁹), 36.61 (C⁴) (²J_{4-F} = 20.2 Hz), 13.30 (C⁷) (³J_{7-F} = 6.7 Hz) ppm

M.S. (C.I./CH₄-N₂O) : 322 ([M+2H]⁺, 5 %), 321 ([M+H]⁺, 33 %), 216 (7 %), 122 (44 %), 188 ([M+H-F-C₄H₄NO₃]⁺, 14 %), 169 (100 %), 140 (63 %)

HRMS (C.I.): Calculated for C₁₆H₁₈FN₂O₄: 321.125214

Found: 321.125061

4.4 Synthesis of the 3-acetoxy-4-methyl-5-[(2-oxo-1,3-oxazolidin-3-yl)carbonyl]-6-phenyltetrahydropyridin-2(1*H*)-one **107** *exo*



Prepared according to the general procedure with dienophile **88** (0.21 g, 1.353 mmol, 1 eq.) in 4 mL toluene and azadiene **33h** (0.751 g, 2.707 mmol, 2 eq.), 90 °C, 1 night. Only the *exo* isomer was formed.

Purification: flash chromatography (AcOEt/cyclohexane : 2/1, AcOEt), then recrystallized in AcOEt/hexane

Rf: 0.48 (AcOEt)

Physical aspect: white solid

M.P.: 197-199 °C

F.B.: C₁₈H₂₀FN₂O₆

M.W.: 360.36

Yield: 0.2 g (41 %)

HPLC: Chiralcel AD, *i*-PrOH/hexane (20/80), 2 mL/min, λ = 220 nm, t_r = 9.6 min. and t_r = 17.9 min.

I.R.: (KBr, cm⁻¹): 3203 (NH), 3090, 2935-2969 (CH aliph.), 1777 (CO oxazolidinone), 1743 (CO ester), 1698 (CO imide), 1673 (CO lactam), 1386-1401 (st C-H in OCOCH₃), 1228

¹H NMR (500 MHz, CDCl₃, T = 25 °C)

Proton	δ (ppm)	Mult.	Integ.	J (Hz)
15, 16, 17	7.33	m	5	/
1	5.87	br s	1	/
3	5.60	d	1	³ J ₃₋₄ = 4.1
6	4.80	d	1	³ J ₆₋₅ = 10.2
5	4.70	dd	1	³ J ₅₋₆ = 10.2, ³ J ₅₋₄ = 10.2
12	4.26	ddd	1	² J _{12-12'} = 9.3, ³ J ₁₂₋₁₁ = 9.3, ³ J _{12-11'} = 6.1
12'	4.04	ddd	1	² J _{12'-12} = 9.3, ³ J _{12'-11} = 7.5, ³ J _{12'-11'} = 9.3
11	3.91	ddd	1	² J _{11-11'} = 11.0, ³ J ₁₁₋₁₂ = 9.3, ³ J _{11-12'} = 7.5
11'	3.69	ddd	1	² J _{11'-11} = 11.0, ³ J _{11'-12} = 6.1, ³ J _{11'-12'} = 9.3
4	2.61	mult	1	³ J ₄₋₃ = 4.1, ³ J ₄₋₅ = 10.2, ³ J ₄₋₉ = 6.8
8	2.21	s	3	/
9	1.03	d	3	³ J ₉₋₄ = 6.8

The different coupling were checked by selective irradiations.

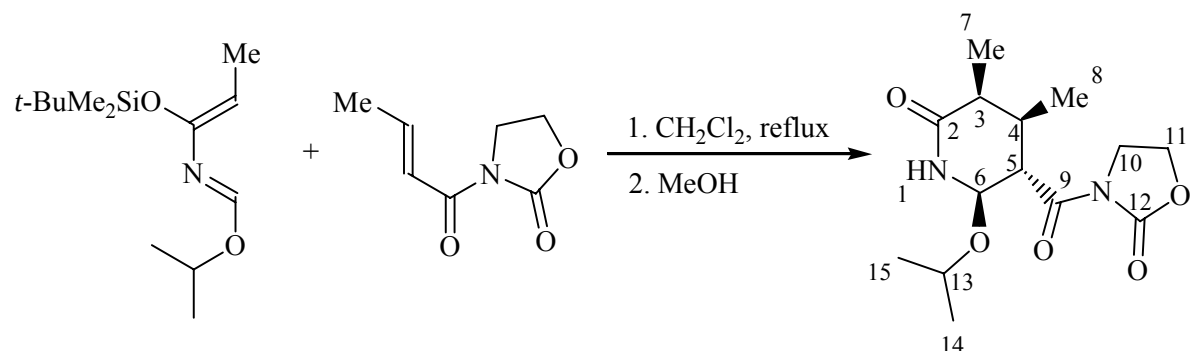
¹³C NMR (125 MHz, CDCl₃, T = 25 °C) δ 172.46 (C²), 169.96 (C¹⁰), 167.30 (C⁷), 152.42 (C¹³), 138.09 (C¹⁴), 129.05 (C¹⁷), 128.92 (C¹⁶), 127.08 (C¹⁵), 69.91 (C³), 61.52 (C¹²), 59.91 (C⁶), 47.01 (C⁵), 42.38 (C¹¹), 36.09 (C⁴), 20.57 (C⁸), 13.86 (C⁹) ppm

M.S. (C.I./CH₄-N₂O) : 389 ([M+C₂H₅]⁺, 13 %), 362 ([M+2H]⁺, 25 %), 361 ([M+H]⁺, 100 %), 319 (22 %), 303 (22 %)

E.A.:

Element	% calculated	% found	Δ
C	59.99	59.87	0.12
H	5.59	5.61	0.02
N	7.77	7.74	0.03

4.5 Synthesis of the 6-isopropoxy-3,4-dimethyl-5-[(2-oxo-1,3-oxazolidin-3-yl)carbonyl]tetrahydropyridin-2(1*H*)-one **108** *exo*



Prepared according to the general procedure with dienophile **88** (0.10 g, 0.64 mmol, 1 eq.) in 2 mL CH₂Cl₂ and 2-azadiene **29a** (0.33 g, 1.29 mmol, 2 eq.), room temperature, 1 hour; then reflux, 1 night. After the addition of MeOH, the solution was stirred for 2 hours. Only the *exo* isomer was formed.

Purification: recrystallization in AcOEt/hexane, ice bath

Rf: 0.31 (AcOEt)

Physical aspect: white solid

M.P.: 50-52 °C

F.B.: C₁₄H₂₂N₂O₅

M.W.: 298.33

Yield: 0.16 g (80 %)

HPLC: Chiralcel AD, EtOH/hexane (40/60), 1 mL/min, λ = 220 nm, t_r = 7.0 min. and t_r = 9.5 min.

I.R.: (KBr, cm⁻¹): 3360 (st NH), 2973 (st CH aliph.), 2932 (st O-CH), 1780 (CO oxazolidinone), 1698 (CO imide), 1665 (CO lactam), 1482, 1388

¹H NMR (200 MHz, CDCl₃, T = 25 °C)

Proton	δ (ppm)	Mult.	Integ.	J (Hz)
1	6.71	br s	1	/
6	5.07	d	1	³ J ₆₋₅ = 7.3
11	4.46	t	2	/
5	4.34	dd	1	³ J ₅₋₆ = 7.3, ³ J ₅₋₄ = 10.2
10	4.08	t	2	/
13	3.74	mult	1	³ J ₁₃₋₁₄ = 6.2, ³ J ₁₃₋₁₅ = 6.0
3	2.52-2.36	mult	1	³ J ₃₋₇ = 7.3
4	2.35-2.21	mult	1	³ J ₄₋₈ = 7.0, ³ J ₄₋₅ = 10.2
7	1.25	d	3	³ J ₇₋₃ = 7.3

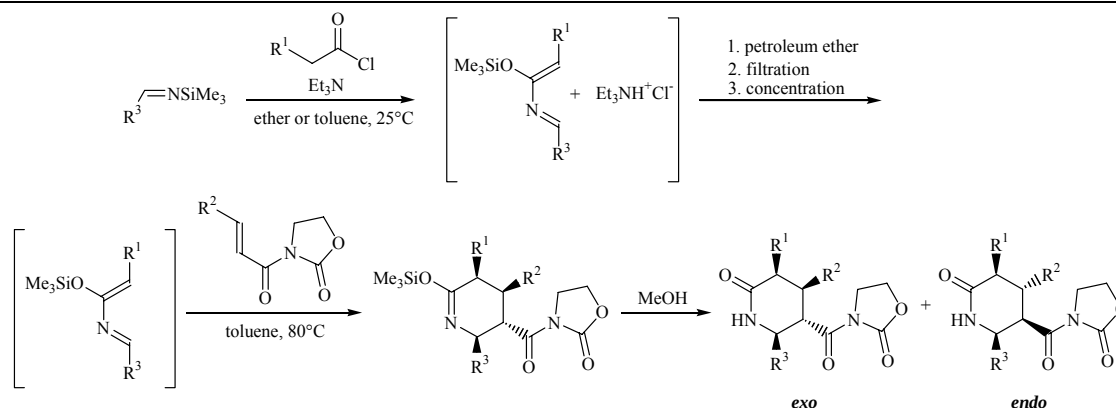
Proton	δ (ppm)	Mult.	Integ.	J (Hz)
14	1.17	d	3	$^3J_{14-13} = 6.2$
15	1.06	d	3	$^3J_{15-13} = 6.0$
8	0.99	d	3	$^3J_{8-4} = 7.0$

^{13}C NMR (50 MHz, CDCl_3 , $T = 25^\circ\text{C}$) δ 175.2 (C^2), 173.6 (C^9), 153.2 (C^{12}), 84.0 (C^6), 71.3 (C^{13}), 62.0 (C^{11}), 46.0 (C^5), 42.9 (C^{10}), 40.0 (C^3), 33.5 (C^4), 23.4 (C^{15}), 22.3 (C^{14}), 14.9 (C^8), 12.2 (C^7) ppm

M.S. (C.I./ $\text{CH}_4\text{-N}_2\text{O}$) : 299 ($[\text{M}+\text{H}]^+$, 27 %), 255 ($[\text{M}-\text{C}_3\text{H}_7]^+$, 34 %), 239 ($[\text{M}-\text{C}_3\text{H}_7\text{O}]^+$, 14 %)

HRMS: Calculated for $\text{C}_{14}\text{H}_{23}\text{N}_2\text{O}_5$: 299.160697
Found: 299.162929

5 Synthesis of 2-piperidones via a thermal three-components process



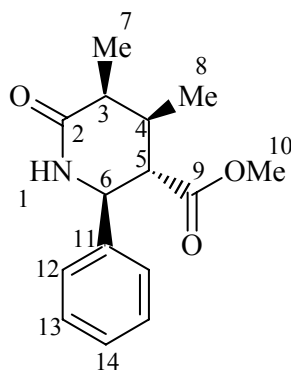
General procedure

In a 25 mL flask, equipped with a magnetic stirrer, dried under vacuum, the silylated imine, triethylamine and dry toluene are introduced. The acid chloride in solution in toluene is added dropwise and the mixture is maintained at room temperature under strong agitation during two hours. Petroleum ether is then added and the mixture is filtered through celite. The precipitate is washed with three portions of petroleum ether, and the organic layer is evaporated under vacuum in order to remove the excess of triethylamine.

The crude azadiene dissolved in toluene is introduced in a 25 mL flask, equipped with a condenser and a magnetic stirrer. The dienophile is then added, and the mixture is shaken at 85°C during the time required. The mixture is then treated with an excess of methanol during minimum 20 minutes. The solvents are evaporated and the product is purified by a flash chromatography and/or a recrystallization.

5.1 Synthesis of methyl 4,5-dimethyl-6-oxo-2-phenylpiperidine-3-carboxylate **109** *exo*

Reference: Inoff, E. *Dissertation, UCL-ORSY, 1999*

**exo**

Prepared according to the general procedure with the following quantities and conditions:

- *N*-(trimethylsilyl)benzaldimine **94**: 0.5 g (2.820 mmol, 2 eq.) in 2.5 mL toluene
- Triethylamine: 0.588 mL (4.230 mmol, 3 eq.)
- Propionyl chloride: 0.245 mL (2.820 mmol, 2 eq.) in 1 mL toluene
- Methyl (*E*)-but-2-enoate: 0.150 mL (1.410 mmol, 1 eq.) in 3.5 mL toluene
- reaction time: 18 h 30 at 85 °C
- composition of the crude mixture: *exo/endo*: 100/0
- flash chromatography (AcOEt/cyclohexane: 1/1, AcOEt)

Reference of the product: Bayard, Ph. *Dissertation, UCL-ORSY, 1991*

Physical aspect: white powder

F.B.: C₁₅H₁₉NO₃

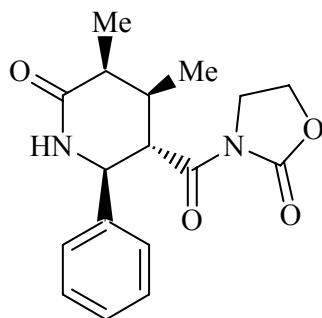
M.W.: 261.32

Yield: 0.213 g (58 %) (lit.: 60 %)

¹H NMR (300 MHz, CDCl₃, T = 25 °C)

Proton	δ (ppm)	Mult.	Integ.	J (Hz)
12, 13, 14	7.40-7.20	m	5	/
1	5.57	s	1	/
6	4.71	d	1	³ J ₆₋₅ = 10.4
10	3.56	s	3	/
5	2.61	dd	1	³ J ₅₋₆ = 10.4, ³ J ₅₋₄ = 10.4
3	2.58	qd	1	³ J ₃₋₇ = 7.2, ³ J ₃₋₄ = 5.0
4	2.47	m	1	³ J ₄₋₃ = 5.0, ³ J ₄₋₅ = 10.4
7	1.29	d	3	³ J ₇₋₃ = 7.2
8	0.98	d	3	/

5.2 Synthesis of the 3,4-dimethyl-5-[(2-oxo-1,3-oxazolidin-3-yl)carbonyl]-6-phenyltetrahydropyridin-2(1H)-one **104** *exo*



Prepared according to the general procedure with the following quantities and conditions:

- *N*-(trimethylsilyl)benzaldimine **94**: 0.5 g (2.820 mmol, 2 eq.) in 2.5 mL toluene
- Triethylamine: 0.588 mL (4.230 mmol, 3 eq.)
- Propionyl chloride: 0.245 mL (2.820 mmol, 2 eq.) in 1 mL toluene
- *N*-crotonyl-2-oxazolidinone **88**: 0.219 g (1.410 mmol, 1 eq.) in 3.5 mL toluene
- reaction time: 5 h 30 at 85 °C
- composition of the crude mixture: *exo/endo*: 90/10
- flash chromatography (AcOEt/cyclohexane: 2/1, AcOEt)

Rem.: in this case, after the first filtration through celite, the solvents are completely evaporated, the residue is redissolved in petroleum ether, and refiltered through celite.

Only the *exo* isomer was isolated and characterised.

Reference of the product: Jnoff, E. *Dissertation, UCL-ORSY*, **1999**, Jnoff, E.; Ghosez, L. *J. Am. Chem. Soc.* **1999**, *121*, 2617-2618

Physical aspect: white powder

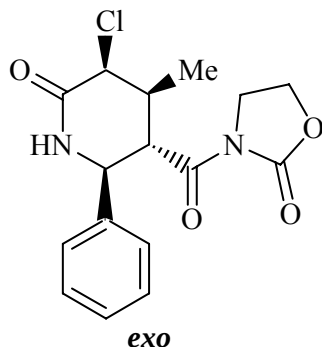
R.N.: [222638-06-4]

F.B.: C₁₇H₂₀N₂O₄

M.W.: 316.36

Yield: 0.270 g (60 %)

5.3 Synthesis of the 3-chloro-4-methyl-5-[(2-oxo-1,3-oxazolidin-3-yl)carbonyl]-6-phenyltetrahydropyridin-2(1*H*)-one **105** *exo*



Prepared according to the general procedure with the following quantities and conditions:

- *N*-(trimethylsilyl)benzaldimine **94**: 0.5 g (2.820 mmol, 1.5 eq.) in 2.5 mL toluene
- Triethylamine: 0.431 mL (3.102 mmol, 1.65 eq.)
- Chloroacetyl chloride: 0.224 mL (2.820 mmol, 1.5 eq.) in 1 mL toluene
- *N*-crotonyl-2-oxazolidinone: 0.292 g (1.880 mmol, 1 eq.) in 3.5 mL toluene
- reaction time: 5 h 30 at 85 °C
- composition of the crude mixture: only the *exo* isomer was detected
- flash chromatography (AcOEt/cyclohexane: 2/1, AcOEt)

Physical aspect: white solid

F.B.: C₁₆H₁₇ClN₂O₄

M.W.: 336.77

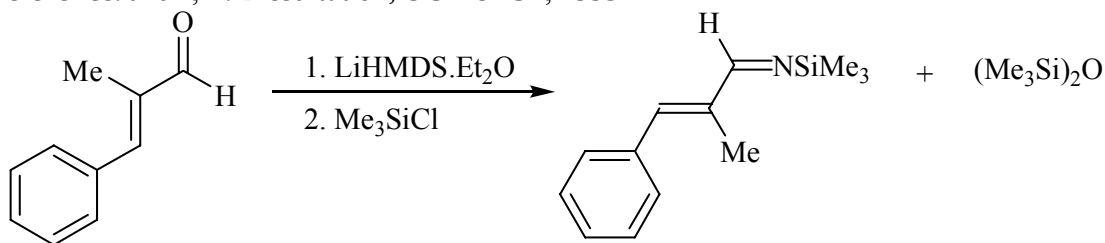
Yield: 0.155 g (24 %)

The spectroscopic and spectrometric data are described for the reaction at the point 2.2.2.

5.4 Synthesis of the 3,4-dimethyl-6-[(*E*)- α -methylstyryl]-5-[(2-oxo-1,3-oxazolidin-3-yl)carbonyl]tetrahydropyridin-2(1*H*)-one **111** *exo*

5.4.1 Synthesis of the *N*-[(*Z-E*)-2-methyl-3-phenyl-2-propenylidene]-*N*-(trimethylsilyl)amine **110**

Reference: Jnoff, E. *Dissertation, UCL-ORSY, 1999*



A three-necked flask fitted with an addition funnel and a magnetic stirrer, previously dried under vacuum, was charged with 5.5 g (22.9 mmol, 1 eq.) of LiHMDS.Et₂O and 7 mL of dry ether. At the suspension cooled to 0 °C, a solution of 3.2 mL (22.9 mmol, 1 eq.) of α -methyl-*trans*-cinnamaldehyde freshly distilled in 5 mL of ether was added dropwise. After one

hour stirring at this temperature, 2.9 mL (22.9 mmol, 1 eq.) of trimethylsilyl chloride was added at once with the aid of a syringe through the septum. The cooling bath was removed, and the mixture was stirred at room temperature during two hours. The precipitate of lithium chloride was filtered (fast) on celite. The solvent was evaporated under reduced pressure (rotavapor equipped with a P₂O₅ tube). This product must be kept under argon at -20 °C.

Purification: bulb-to-bulb distillation under vacuum (125 °C/1.8 10⁻² mbar)

R.N. : [172095-77-1]

Physical aspect: yellow oil

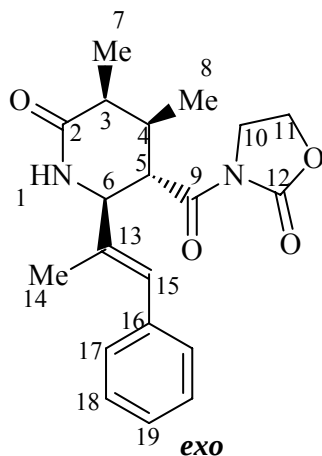
F.B.: C₁₃H₁₉NSi

M.W.: 217.38

Yield: 4.6 g (92 %) (lit.: 86 %)

¹H NMR (200 MHz, CDCl₃, T = 25 °C) δ 8.68 (s, 1H, H-C=N), 7.50-7.25 (m, 5H, Har), 6.93 (s, 1H, PhCH=CCH₃), 2.13 (s, 3H, PhCH=CCH₃), 0.25 (s, 9H, (CH₃)₃Si) ppm

5.4.2 Synthesis of the 3,4-dimethyl-6-[(*E*)-α-methylstyryl]-5-[(2-oxo-1,3-oxazolidin-3-yl)carbonyl]tetrahydropyridin-2(1*H*)-one **111** *exo*



Prepared according to the general procedure with the following quantities and conditions:

- *N*-silylated imine **110**: 0.5 g (2.300 mmol, 3 eq.) in 2.5 mL toluene
- Triethylamine: 1.066 mL (7.667 mmol, 10 eq.)
- Propionyl chloride: 0.2 mL (2.300 mmol, 3 eq.) in 1 mL toluene
- *N*-crotonyl-2-oxazolidinone **88**: 0.119 g (0.767 mmol, 1 eq.) in 3.5 mL toluene
- reaction time: 5 h 30 at 85 °C
- composition of the crude mixture: *exo/endo*: >90/10
- flash chromatography (AcOEt/cyclohexane: 2/1, AcOEt)

Only the *exo* isomer was isolated and characterised:

Reference of the product: Jnoff, E. *Dissertation, UCL-ORSY*, **1999**, Jnoff, E.; Ghosez, L. *J. Am. Chem. Soc.* **1999**, *121*, 2617-2618

R.N.: [222638-11-1]

Physical aspect: white powder

F.B.: C₂₀H₂₄N₂O₄

M.W.: 356.42

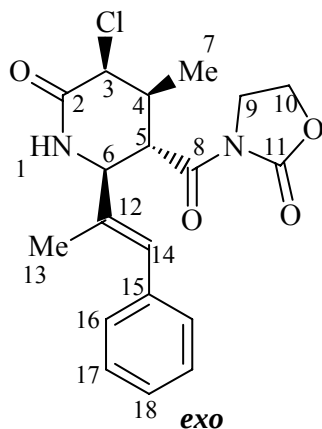
Yield: 0.210 g (77 %)

¹H NMR (300 MHz, CDCl₃, T = 25 °C)

Proton	δ (ppm)	Mult.	Integ.	J (Hz)
17, 18, 19	7.36-7.20	m	5	/
15	6.39	s	1	/
1	5.67	br s	1	/
5	4.59	dd	1	/
6, 11	4.42-4.33	m	2	/
11'	4.25	mult	1	/
10, 10'	4.13-3.89	mult	2	/
3, 4	2.50	m	2	/
14	1.90	d	3	/
7	1.29	d	3	³ J ₇₋₃ = 7.2
8	0.98	d	3	³ J ₈₋₄ = 6.6

¹³C NMR (50 MHz, CDCl₃, T = 25 °C) δ 175.99 (C²), 173.96 (C⁹), 153.48 (C¹²), 136.64 (C¹⁶), 135.34 (C¹³), 129.70 (C¹⁵), 129.25 (C¹⁷), 129.10 (C¹⁸), 127.41 (C¹⁹), 64.94 (C⁶), 61.93 (C¹¹), 42.82 (C¹⁰), 41.88 (C⁵), 40.43 (C³), 34.57 (C⁴), 15.43 (C⁸), 12.90 (C¹⁴), 12.77 (C⁷) ppm

5.5 Synthesis of the 3-chloro-4-methyl-6-[(*E*)-1-methyl-2-phenylethenyl]-5-[(2-oxo-1,3-oxazolan-3-yl)carbonyl]tetrahydropyridin-2(1*H*)-one **115** *exo*



Prepared according to the general procedure with the following quantities and conditions:

- *N*-silylated imine **110**: 0.841 g (3.867 mmol, 3 eq.) in 3 mL toluene
- Triethylamine: 0.654 mL (4.705 mmol, 3.65 eq.)
- Chloroacetyl chloride: 0.308 mL (3.867 mmol, 3 eq.) in 1 mL toluene

- *N*-crotonyl-2-oxazolidinone **88**: 0.2 g (1.289 mmol, 1 eq.) in 3 mL toluene
- reaction time: 5 h 30 at 85 °C
- composition of the crude mixture: only the *exo* isomer is detected
- flash chromatography (AcOEt/cyclohexane: 1/1, 2/1, AcOEt)

Rf: 0.51 (AcOEt)

Physical aspect: white solid

M.P.: 196-198 °C

F.B.: C₁₉H₂₁ClN₂O₄

M.W.: 376.83

Yield: 0.362 g (75 %)

HPLC: Chiralcel AD, EtOH/hexane (15/85), 2 mL/min, λ = 254 nm, t_r = 10.5 min. and t_r = 16.4 min.

I.R.: (KBr, cm⁻¹): 3206 (st NH), 2979 and 2921 (CH aliph.), 1781 (CO oxazolidinone), 1684 (CO imide), 1478-1457, 1387, 754

¹H NMR (500 MHz, CDCl₃, T = 25 °C)

Proton	δ (ppm)	Mult.	Integ.	J (Hz)
17	7.33	dd	2	/
18	7.25	m	1	/
16	7.22	d	2	/
14	6.34	d	1	⁴ J ₁₄₋₁₃ = 1.2
1	5.87	br s	1	/
5	4.93	t	1	³ J ₅₋₆ = 11.0, ³ J ₅₋₄ = 11.0
6	4.40	d	1	³ J ₆₋₅ = 11.0
10	4.36	ddd	1	² J _{10-10'} = 9.0, ³ J ₁₀₋₉ = 9.0, ³ J _{10-9'} = 6.3
3	4.30	d	1	³ J ₃₋₄ = 3.1
10'	4.22	ddd	1	² J _{10'-10} = 9.0, ³ J _{10'-9} = 7.0, ³ J _{10'-9'} = 9.0
9	4.02	ddd	1	² J _{9-9'} = 11.2, ³ J ₉₋₁₀ = 9.0, ³ J _{9-10'} = 7.0
9'	3.92	ddd	1	² J _{9'-9} = 11.2, ³ J _{9'-10} = 6.3, ³ J _{9'-10'} = 9.0
4	2.70	mult	1	³ J ₄₋₃ = 3.1, ³ J ₄₋₅ = 11.0, ³ J ₄₋₇ = 6.8
13	1.95	s	3	/
7	1.12	d	3	³ J ₇₋₄ = 6.8

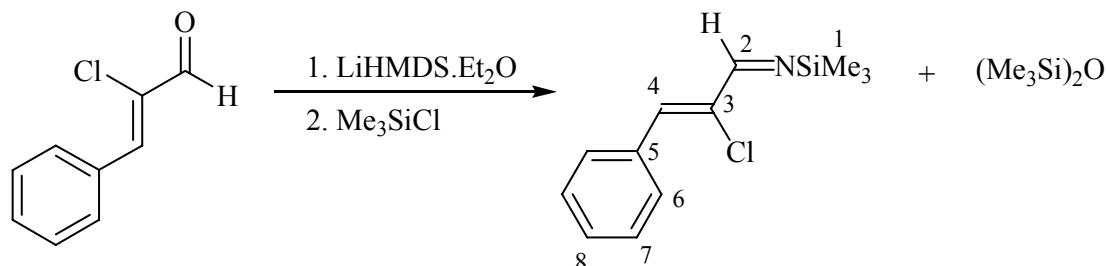
¹³C NMR (125 MHz, CDCl₃, T = 25 °C) δ 172.98 (C²), 167.63 (C⁸), 152.74 (C¹¹), 136.12 (C¹⁵), 134.95 (C¹²), 129.42 (C¹⁴), 128.75 (C¹⁶), 128.28 (C¹⁷), 127.23 (C¹⁸), 65.16 (C⁶), 61.63 (C¹⁰), 58.74 (C³), 42.60 (C⁹), 41.06 (C⁵), 35.92 (C⁴), 15.34 (C⁷), 12.62 (C¹³) ppm

M.S. (C.I./CH₄-N₂O) : 377 ([M+H]⁺, 1 %), 245 (27 %), 209 (73 %), 181 ([M-C₃H₄NO₂-C₆H₅]⁺, 100 %)

HRMS (C.I.): Calculated for $C_{19}H_{21}ClN_2O_4$: 376.118324
Found: 376.118985

5.6 Synthesis of the 6-[(*E*)- α -chlorostyryl]-4-methoxycarbonyl-3-methyl-5-[(2-oxo-1,3-oxazolidin-3-yl)carbonyl]tetrahydropyridin-2(1*H*)-one **114** *exo*

5.6.1 Synthesis of *N*-[*(Z,Z)*-2-chloro-3-phenyl-2-propenylidene](trimethyl)silanamine **112**



A three-necked flask fitted with an addition funnel and a magnetic stirrer, previously dried under vacuum, was charged with 10.0 g (41.4 mmol, 1 eq.) of LiHMDS.Et₂O and 30 mL of dry ether. At the suspension cooled to 0 °C, a solution of 7.1 g (41.4 mmol, 1 eq.) of α -chloro-cinnamaldehyde freshly distilled in 15 mL of ether was added dropwise. After one hour stirring at this temperature, 5.3 mL (41.4 mmol, 1 eq.) of trimethylsilyl chloride was added at once with the aid of a syringe through the septum. The cooling bath was removed, and the mixture was stirred at room temperature during two hours. The precipitate of lithium chloride was filtered (fast) on celite. The solvent was evaporated under reduced pressure (rotavapor equipped with a P₂O₅ tube). This product must be kept under argon at -20 °C.

Purification: bulb-to-bulb distillation under vacuum (125 °C/6.3 10⁻³ mbar)

Physical aspect: yellow oil

F.B.: C₁₂H₁₆ClNSi

M.W.: 237.80

Yield: 7.2 g (73 %)

I.R.: (film, cm⁻¹): 3396, 3057-3026 (st CH in arom.), 2956, 2897, 1633 (st C=C), 1493 (st C=N), 1251, 842 (st alkyl-Cl)

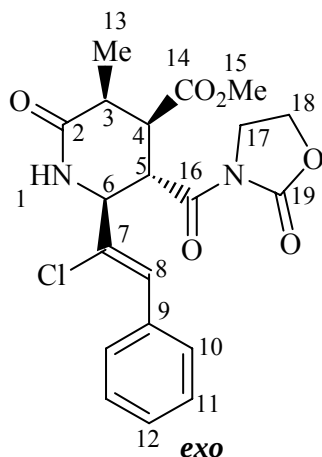
¹H NMR (200 MHz, CDCl₃, T = 25 °C) δ 8.54 (s, 1H, H-C=N), 7.89-7.84 (mult, 2H, Ho), 7.44-7.30 (m, 3H, Hm+p), 7.22 (s, 1H, PhCH=CCl), 0.28 (s, 9H, (CH₃)₃Si) ppm

¹³C NMR (50 MHz, CDCl₃, T = 25 °C) δ 165.1 (C²), 135.9 (C⁵), 130.8 (C³), 130.4 (C⁴), 128.9 (C⁷), 128.6 (C⁸), 125.0 (C⁶), 1.0 (C¹)ppm

M.S. (C.I./CH₄-N₂O) : 256 ([M+H₂O]⁺, 42 %), 240 ([M (³⁷Cl)+H]⁺, 44 %), 238 ([M (³⁵Cl)+H]⁺, 57 %)

HRMS (C.I.): Calculated for $C_{12}H_{17}ClNSi$: 238.082432
Found: 238.081881

5.6.2 Synthesis of the 6-[(*E*)- α -chlorostyryl]-4-methoxycarbonyl-3-methyl-5-[(2-oxo-1,3-oxazolidin-3-yl)carbonyl]tetrahydropyridin-2(1*H*)-one **114** *exo*



Prepared according to the general procedure with the following quantities and conditions:

- *N*-silylated imine **112**: 1.0 g (4.21 mmol, 3 eq.) in 14 mL toluene
- Triethylamine: 1.95 mL (14.02 mmol, 10 eq.)
- Propionyl chloride: 0.37 mL (4.21 mmol, 3 eq.) in 3 mL toluene
- *N*-fumaroyl-2-oxazolidinone **91**: 0.28 g (1.40 mmol, 1 eq.) in 10 mL toluene
- reaction time: 5 h 30 at 85 °C
- composition of the crude mixture: only the *exo* isomer is detected
- flash chromatography (AcOEt/cyclohexane: 3/1, AcOEt)

Rf: 0.50 (AcOEt)

Physical aspect: beige solid

M.P.: 160-161 °C

F.B.: $C_{20}H_{21}ClN_2O_6$

M.W.: 420.84

Yield: 0.46 g (79 %)

HPLC: Chiralcel AD, *i*-PrOH/hexane (60/40), 0.2 mL/min, λ = 254 nm, t_r = 36.9 min. and t_r = 39.5 min.

I.R.: (KBr, cm^{-1}): 3187 (st NH), 3072 (CH aliph.), 2963-2940, 1779 (CO oxazolidinone), 1767, 1726 (CO ester), 1695 (CO imide), 1689 (CO lactam), 1397

¹H NMR (200 MHz, CDCl₃, T = 25 °C)

Proton	δ (ppm)	Mult.	Integ.	J (Hz)
10	7.64-7.59	mult	2	/
11, 12	7.39-7.35	m	3	/
8	6.67	s	1	/
1	5.89	br s	1	/
5	5.17	t	1	³ J ₅₋₆ = 10.8
6	4.50	d	1	³ J ₆₋₅ = 10.2
18	4.36	mult	1	/
18', 17	4.20-4.00	m	2	/
17'	3.88	mult	1	/
15	3.72	s	3	/
4	3.50	mult	1	³ J ₄₋₃ = 5.4, ³ J ₄₋₅ = 11.5
3	3.06	dd	1	³ J ₃₋₁₃ = 7.1, ³ J ₃₋₄ = 5.4
13	1.31	d	3	³ J ₁₃₋₃ = 7.1

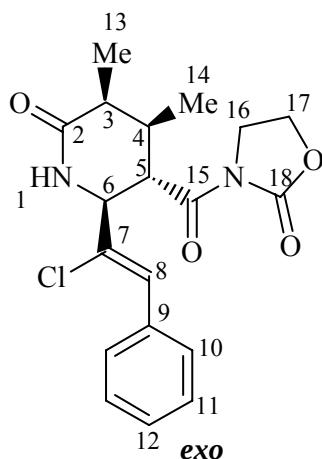
¹³C NMR (50 MHz, CDCl₃, T = 25 °C) δ 173.7 (C²), 173.4 (C¹⁶), 171.5 (C¹⁴), 153.1 (C¹⁹), 133.3 (C⁷), 129.9 (C⁹), 129.7 (C¹¹), 129.2 (C¹²), 128.9 (C¹⁰), 128.5 (C⁸), 64.0 (C⁶), 61.8 (C¹⁸), 52.6 (C¹⁵), 46.2 (C⁴), 43.0 (C¹⁷), 37.6 (C³), 36.9 (C⁵), 14.7 (C¹³) ppm

M.S. (C.I./CH₄-N₂O) : 449 ([M (³⁵Cl)+C₂H₅]⁺, 5 %), 423 ([M (³⁷Cl)+H]⁺, 8 %), 421 ([M (³⁵Cl)+H]⁺, 31 %)

HRMS (E.I.): Calculated for C₂₀H₂₁ClN₂O₆: 420.109632

Found: 420.108814

5.7 Synthesis of the 6-[(Z)-1-chloro-2-phenylethenyl]-3,4-dimethyl-5-[(2-oxo-1,3-oxazolidin-3-yl)carbonyl]-2-piperidinone **113** *exo*



Prepared according to the general procedure with the following quantities and conditions:

- *N*-silylated imine **112**: 0.5 g (2.10 mmol, 3 eq.) in 8 mL toluene
- Triethylamine: 0.97 mL (7.01 mmol, 10 eq.)
- Propionyl chloride: 0.18 mL (2.10 mmol, 3 eq.) in 3 mL toluene
- *N*-crotonyl-2-oxazolidinone: 0.11 g (0.70 mmol, 1 eq.) in 4 mL toluene
- reaction time: 5 h 30 at 85 °C

- composition of the crude mixture: only the *exo* isomer is detected
- flash chromatography (AcOEt/cyclohexane: 3/1, AcOEt)

Rf: 0.5 (AcOEt)

Physical aspect: beige solid

M.P.: 177-178 °C

F.B.: C₁₉H₂₁ClN₂O₄

M.W.: 376.83

Yield: 0.14 g (53 %)

HPLC: Chiralcel AD, *i*-PrOH/hexane (30/70), 1 mL/min, λ = 220 nm, t_r = 12.5 min. and t_r = 27.4 min.

I.R.: (KBr, cm⁻¹): 3345 (st NH), 2978-2928 (st CH aliph.), 1781 (CO oxazolidinone), 1686 (CO imide), 1655 (CO lactam), 1388

¹H NMR (500 MHz, CDCl₃, T = 25 °C)

Proton	δ (ppm)	Mult.	Integ.	<i>J</i> (Hz)
10	7.60	d	2	/
11	7.35	mult	2	/
12	7.30	mult	1	/
8	6.65	s	1	/
1	6.12	br s	1	/
5	4.76	dd	1	³ <i>J</i> ₅₋₆ = 9.8, ³ <i>J</i> ₅₋₄ = 9.8
6	4.67	d	1	³ <i>J</i> ₆₋₅ = 9.8
17	4.36	mult	1	³ <i>J</i> _{17-17'} = 9.3, ³ <i>J</i> ₁₇₋₁₆ = 9.3, ³ <i>J</i> _{17-16'} = 6.3
17'	4.27	mult	1	³ <i>J</i> _{17'-17} = 9.3, ³ <i>J</i> _{17'-16} = 7.5, ³ <i>J</i> _{17'-16'} = 9.3
16	4.00	mult	1	³ <i>J</i> ₁₆₋₁₇ = 9.3, ³ <i>J</i> _{16-17'} = 7.5, ³ <i>J</i> _{16-16'} = 11.0
16'	3.94	mult	1	³ <i>J</i> _{16'-17} = 6.3, ³ <i>J</i> _{16'-17'} = 9.3, ³ <i>J</i> _{16'-16} = 11.0
3	2.50	mult	1	³ <i>J</i> ₃₋₁₃ = 7.3, ³ <i>J</i> ₃₋₄ = 4.6
4	2.40	mult	1	³ <i>J</i> ₄₋₁₄ = 7.0, ³ <i>J</i> ₄₋₅ = 9.8, ³ <i>J</i> ₄₋₃ = 4.6
13	1.28	d	3	³ <i>J</i> ₁₃₋₃ = 7.3
14	0.98	d	3	³ <i>J</i> ₁₄₋₄ = 7.0

¹³C NMR (125 MHz, CDCl₃, T = 25 °C) δ 175.4 (C²), 173.2 (C¹⁵), 152.8, (C¹⁸) 133.2 (C⁹), 130.6 (C⁷), 129.2 (C¹⁰), 128.6 (C¹²), 128.3 (C¹¹), 128.2 (C⁸), 63.1 (C⁶), 61.6 (C¹⁷), 42.5 (C¹⁶), 41.8 (C⁵), 40.1 (C³), 34.5 (C⁴), 14.8 (C¹⁴), 12.1 (C¹³) ppm

M.S. (C.I./CH₄-N₂O) : 379 ([M (³⁷Cl)+H]⁺, 4 %), 377 ([M (³⁵Cl)+H]⁺, 3 %), 296 ([M (³⁷Cl)-C₃H₄NO₂]⁺, 50 %), 294 ([M (³⁵Cl)-C₃H₄NO₂]⁺, 100 %)

E.A. :

Element	% calculated	% found	Δ
C	60.55	60.19	0.368
H	5.62	5.89	0.274
Cl	9.41	9.72	0.313
N	7.43	7.05	0.383

6 Synthesis of 2-piperidones *via* catalytic asymmetric [4+2] cycloadditions

General procedure

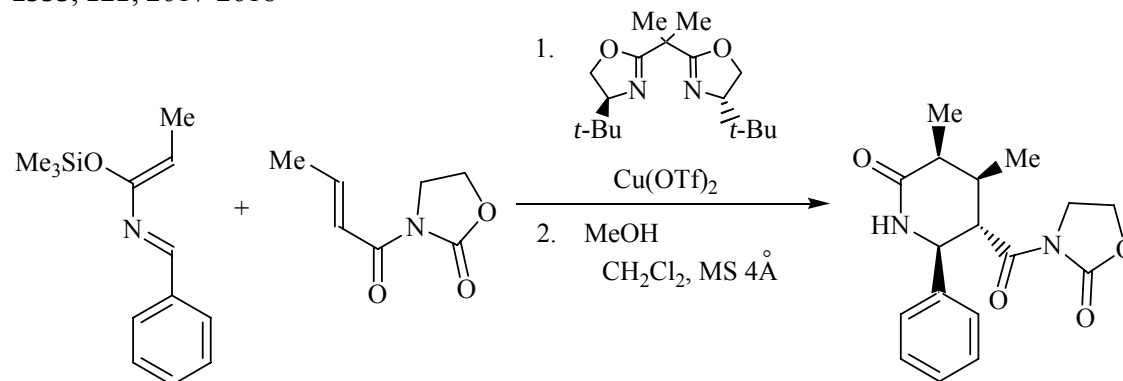
An oven-dried 25 mL round bottom flask containing a magnetic stirring bar and under an inert atmosphere was charged with molecular sieves 4Å in powder, (*S, S*)-*tert*-butylbis(oxazoline) and Cu(OTf)₂. Dry dichloromethane was added *via* syringe and the mixture was stirred for two hours to give a clear green solution.

The green solution was then cooled to -78 °C, and the dienophile in solution in 0.5 mL of dichloromethane was added in one portion *via* syringe. The 2-azadiene was then added *via* syringe through the rubber septum. The solution was stirred at the appropriate temperature during the time required. The reaction mixture was then treated by 2 mL MeOH. After filtration through celite and evaporation of the solvent under reduced pressure, the crude product was purified by flash column chromatography or recrystallization.

6.1 Synthesis of the (+)-(3*S*,4*R*,5*S*,6*S*)-3,4-dimethyl-5-[(2-oxo-1,3-oxazolidin-3-yl)carbonyl]-6-phenyltetrahydropyridin-2(1*H*)-one

104

Reference: Jnoff, E. *Dissertation, UCL-ORSY, 1999*, Jnoff, E.; Ghosez, L. *J. Am. Chem. Soc.* **1999**, *121*, 2617-2618



Prepared according to general procedure with Cu(OTf)₂ (0.016 g, 0.045 mmol, 0.1 eq.), (*S, S*)-*tert*-Bu-box (0.016 g, 0.054 mmol, 0.12 eq.) in 1 mL CH₂Cl₂. Followed by dienophile **88** (0.07 g, 0.451 mmol, 1 eq.) in 0.4 mL CH₂Cl₂ and azadiene **33b** (0.211 g, 0.902 mmol, 2 eq.), room temperature, 1 h 30. This reaction provided the *exo* adduct exclusively.

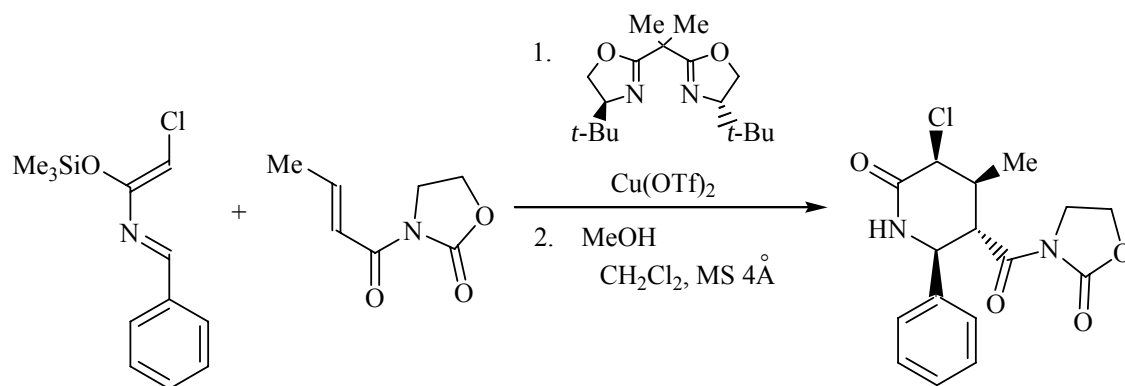
Purification: flash chromatography (AcOEt)

R.N.: [222638-06-4]

Yield: 0.131 g (92 %) (lit.: 96 %)

e.e.: 94 % (Chiralcel AD, *i*-PrOH/hexane (30/70), 1 mL/min, λ = 210 nm, $t_{r(\text{min})}$ = 9.42 min. and $t_{r(\text{maj})}$ = 14.86 min.)

6.2 Synthesis of the (+)-(3*S*,4*S*,5*S*,6*S*)-3-chloro-4-methyl-5-[(2-oxo-1,3-oxazolidin-3-yl)carbonyl]-6-phenyltetrahydropyridin-2(1*H*)-one **105**



Prepared according to general procedure with $\text{Cu}(\text{OTf})_2$ (0.019 g, 0.052 mmol, 0.1 eq.), (*S,S*)-*tert*-Bu-box (0.018 g, 0.062 mmol, 0.12 eq.) in 1 mL CH_2Cl_2 . Followed by dienophile **88** (0.08 g, 0.516 mmol, 1 equiv.) in 0.4 mL CH_2Cl_2 and azadiene **33e** (0.262 g, 1.031 mmol, 2 eq.), room temperature, 3 h 30. This reaction provided the *exo* adduct exclusively.

Purification: flash chromatography (AcOEt), then recrystallized in AcOEt (cold room)

Rf: 0.46 (AcOEt)

Physical aspect: white solid

Yield: 0.138 g (79 %)

F.B.: $\text{C}_{16}\text{H}_{17}\text{ClN}_2\text{O}_4$

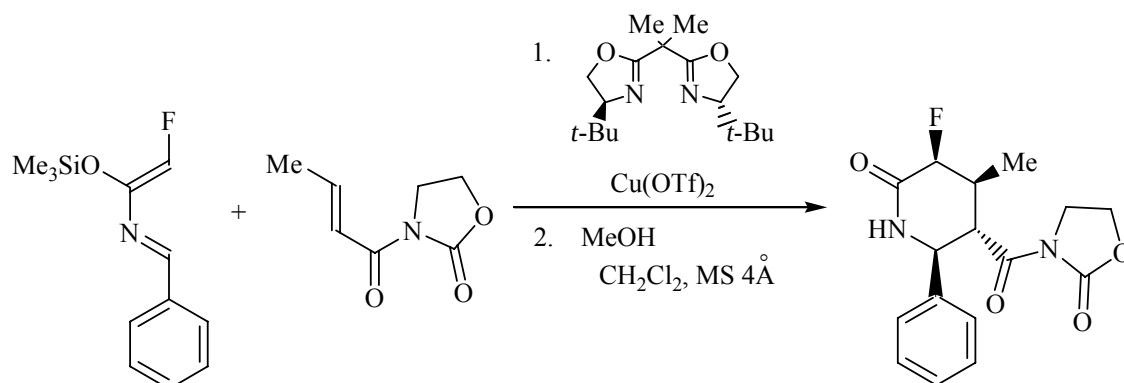
M.W.: 336.77

e.e.: 97.5 % (Chiralcel AD, *i*-PrOH/hexane (15/85), 2 mL/min, λ = 220 nm, $t_{r(\text{min})}$ = 17.07 min. and $t_{r(\text{maj})}$ = 27.84 min.)

$[\alpha]_{\text{D}}$ = + 78.3 ° (c = 0.87, CHCl_3)

The spectroscopic and spectrometric data are described for the thermal reaction.

6.3 Synthesis of the (+)-(3*S*,4*S*,5*S*,6*S*)-3-fluoro-4-methyl-5-[(2-oxo-1,3-oxazolidin-3-yl)carbonyl]-6-phenyltetrahydropyridin-2(1*H*)-one **106**



Prepared according to general procedure with $\text{Cu}(\text{OTf})_2$ (0.038 g, 0.104 mmol, 0.1 eq.), (*S,S*)-*tert*-Bu-box (0.037 g, 0.125 mmol, 0.12 eq.) in 1.5 mL CH_2Cl_2 . Followed by dienophile **88** (0.162 g, 1.043 mmol, 1 equiv.) in 0.4 mL CH_2Cl_2 and azadiene **33f** (0.495 g, 2.087 mmol, 2 eq.), room temperature, 3 days. This reaction provided the *exo* adduct exclusively.

Purification: flash chromatography (AcOEt), then recrystallized in AcOEt/hexane

Rf: 0.53 (AcOEt)

Physical aspect: white solid

M.P.: 190-191 °C

Yield: 0.194 g (58 %)

F.B.: $\text{C}_{16}\text{H}_{17}\text{FN}_2\text{O}_4$

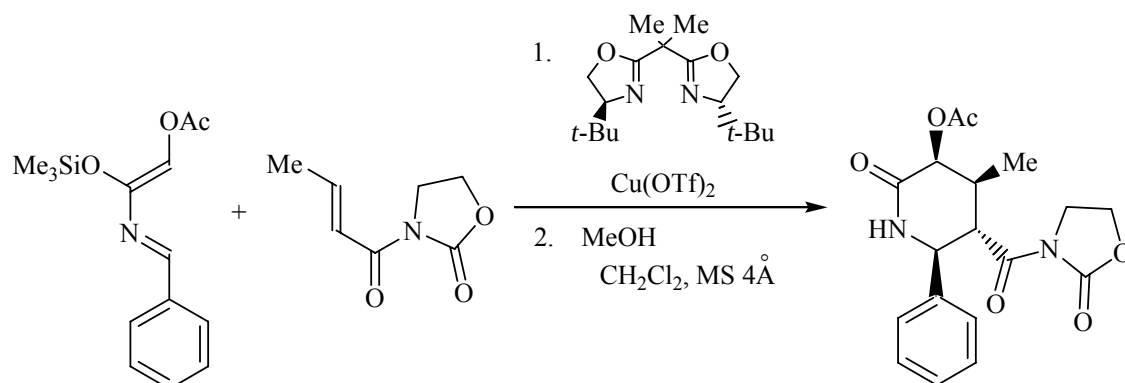
M.W.: 320.32

e.e.: 92 % (Chiralcel AD, *i*-PrOH/hexane (20/80), 2 mL/min, $\lambda = 220$ nm, $t_{\text{r (min)}} = 12.4$ min. and $t_{\text{r (maj)}} = 19.9$ min.)

$[\alpha]_{\text{D}}$ = + 107.1 ° ($c = 0.03$, CHCl_3)

The spectroscopic and spectrometric data are described for the thermal reaction.

6.4 Synthesis of the (+)-(3*S*,4*S*,5*S*,6*S*)-3-acetoxy-4-methyl-5-[(2-oxo-1,3-oxazolidin-3-yl)carbonyl]-6-phenyltetrahydropyridin-2(1*H*)-one **107**



Prepared according to general procedure with Cu(OTf)₂ (0.047 g, 0.129 mmol, 0.1 eq.), (*S,S*)-*tert*-Bu-box (0.046 g, 0.155 mmol, 0.12 eq.) in 1.5 mL CH₂Cl₂. Followed by dienophile **88** (0.2 g, 1.289 mmol, 1 equiv.) in 0.4 mL CH₂Cl₂ and azadiene **33h** (0.715 g, 2.578 mmol, 2 eq.), room temperature, 1 night. This reaction provided the *exo* adduct exclusively.

Purification: flash chromatography (AcOEt/cyclohexane (2/1), AcOEt)

Rf: 0.48 (AcOEt)

Physical aspect: white solid

M.P.: 197-199 °C

Yield: 0.178 g (38 %)

F.B.: C₁₈H₂₀N₂O₆

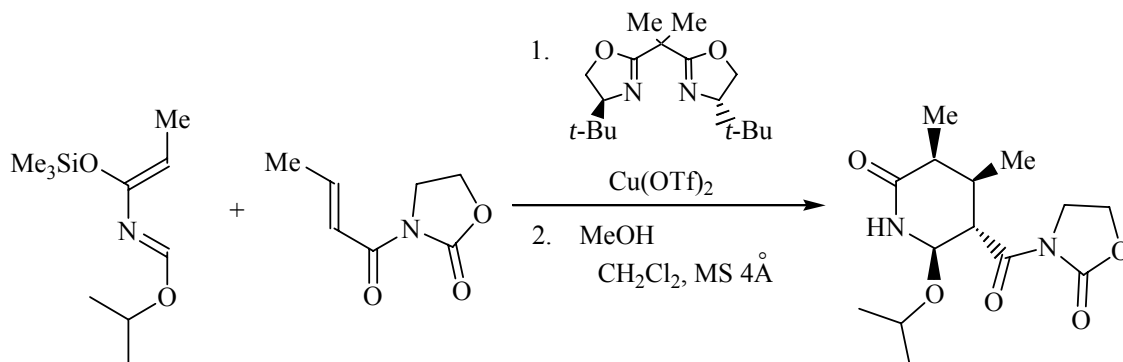
M.W.: 360.36

e.e.: 99 % (Chiralcel AD, *i*-PrOH/hexane (20/80), 2 mL/min, λ = 220 nm, t_r (min) = 9.8 min. and t_r (maj) = 17.8 min.)

[α]_D = + 2.20 ° (c = 0.64, CHCl₃)

The spectroscopic and spectrometric data are described for the thermal reaction.

6.5 Synthesis of the (+)-(3*S*,4*R*,5*S*,6*R*)-6-isopropoxy-3,4-dimethyl-5-[(2-oxo-1,3-oxazolidin-3-yl)carbonyl]tetrahydropyridin-2(1*H*)-one **108**



Prepared according to general procedure with Cu(OTf)₂ (0.019 g, 0.05 mmol, 0.1 eq.), (S, S)-*tert*-Bu-box (0.018 g, 0.06 mmol, 0.12 eq.) in 1 mL CH₂Cl₂. Followed by 3-crotonoyl-1,3-oxazolidin-2-one **88** (0.08 g, 0.52 mmol, 1 eq.) in 0.6 mL CH₂Cl₂ and 2-azadiene **29a** (0.27 g, 1.03 mmol, 2 eq.), room temperature, 6 hours. After the addition of MeOH, the solution was stirred for 1 night. This reaction provided only the *exo* adduct.

Purification: flash chromatography (AcOEt/cyclohexane: 2/1, AcOEt, AcOEt + 10 % *i*-PrOH)

Rf: 0.31 (AcOEt)

Physical aspect: white solid

M.P.: 50-52 °C

F.B.: C₁₄H₂₂N₂O₅

M.W.: 298.33

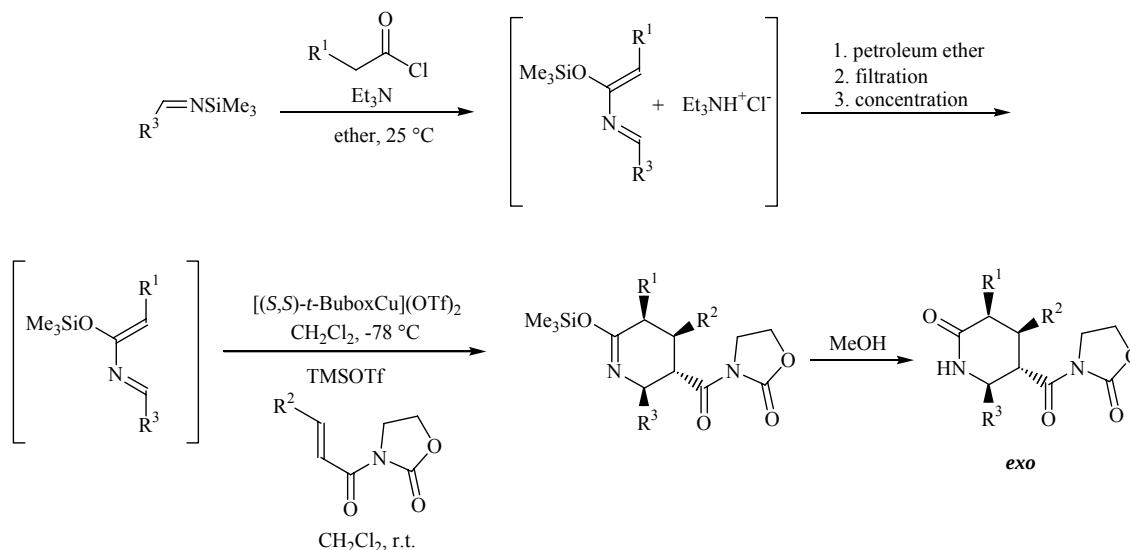
Yield: 0.11 g (67 %)

e.e.: 93 % (Chiralcel AD, EtOH/hexane (40/60), 1 mL/min, λ = 220 nm, t_r (min) = 7.0 min. and t_r (maj) = 9.5 min.)

[α]_D = + 57.79 ° (c = 0.87, CHCl₃)

The spectroscopic and spectrometric data are described for the thermal reaction.

7 Synthesis of 2-piperidones *via* an asymmetric catalytic three-components process



General procedure

In a 25 mL flask, equipped with a magnetic stirrer, dried under vacuum, the silylated imine, triethylamine and dry ether were introduced. The acid chloride in solution in ether was added dropwise and the mixture was maintained at room temperature under strong agitation during two hours. The mixture was filtered through celite. The filtrate was concentrated under vacuum and the residue was washed, filtered and concentrated several times with petroleum ether. Finally the solvent was evaporated under vacuum in order to remove the excess of triethylamine.

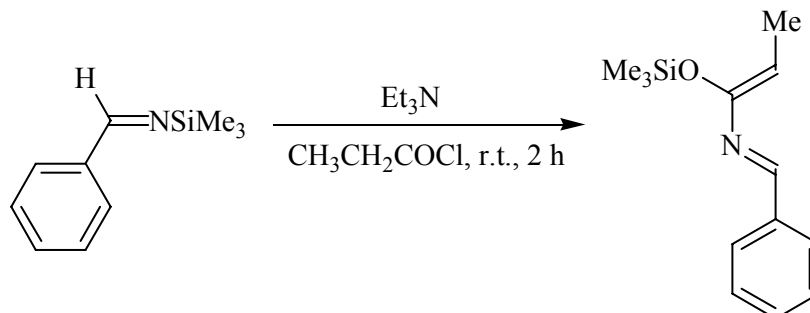
A schlenk equipped with a magnetic stirring bar and a septum, previously oven dried and placed under argon atmosphere, was charged with (*S,S*)-*tert*-butylbis(oxazoline) and $Cu(OTf)_2$. Dry dichloromethane was added *via* syringe and the mixture was stirred for two hours to give a clear green solution.

The solution was cooled to $-78\text{ }^\circ\text{C}$ and trimethylsilyltriflate (TMSOTf) was added, followed directly by the dienophile diluted in CH_2Cl_2 . Then, the azadiene was added in one portion. The reacting mixture was allowed to warm at room temperature and stirred at that temperature for the time required. The mixture was then treated with an excess methanol and stirred for one hour. The solvents were evaporated and passed through a flash column chromatography. A second flash chromatography or recrystallization was necessary to obtain the pure cycloadduct.

Rem.: The purity of the crude 2-azadienes was evaluated by ^1H NMR using hexamethylbenzene (HMB) or dimethylsulfoxide ($DMSO_2$) as standard

7.1 Synthesis of the (+)-(3*S*,4*R*,5*S*,6*S*)-3,4-dimethyl-5-[(2-oxo-1,3-oxazolidin-3-yl)carbonyl]-6-phenyltetrahydropyridin-2(1*H*)-one **104**

7.1.1 Synthesis of crude 1-phenyl-3-trimethylsilyloxy-2-aza-1,3-pentadiene **33b**



Prepared according to the general procedure with the following quantities and conditions:

- *N*-silylated imine **94**: 1.0 g (5.64 mmol, 1 eq.) in 13 mL ether
- Triethylamine: 7.84 mL (56.39 mmol, 10 eq.)
- Propionyl chloride: 0.54 mL (6.20 mmol, 1.1 eq.) in 2 mL ether
- the residue was washed, filtered and concentrated 3 times with petroleum ether

Reference of the product: Ghosez, L.; Bayard, Ph.; Nshimyumukiza, P.; Gouverneur, V. ; Sainte, F. ; Beaudegnies, R. ; Rivera, M. ; Frisque-Hesbain, A.-M. and Wynants, C. *Tet.* **1995**, *51*, 11021-11042

Physical aspect: yellow oil

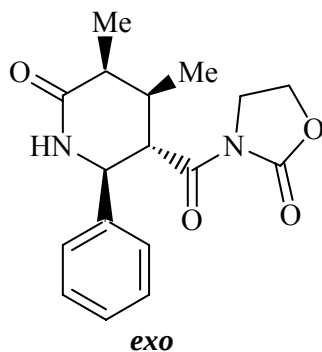
F.B.: $\text{C}_{13}\text{H}_{19}\text{NOSi}$

M.W.: 233.38

Yield: 1.03 g (78 %)

Purity: 80-85 % (HMB)

7.1.2 Synthesis of the (+)-(3*S*,4*R*,5*S*,6*S*)-3,4-dimethyl-5-[(2-oxo-1,3-oxazolidin-3-yl)carbonyl]-6-phenyltetrahydropyridin-2(1*H*)-one **104**



Prepared according to the general procedure with the following quantities and conditions:

- $\text{Cu}(\text{OTf})_2$: 0.016 g (0.045 mmol, 0.1 eq.)
- (*S,S*)-*tert*-butylbis(oxazoline): 0.016 (0.054 mmol, 0.12 eq.) in 0.8 mL CH_2Cl_2
- TMSOTf : 0.033 mL (0.18 mmol, 0.4 eq.)
- *N*-crotonyl-2-oxazolidinone **88**: 0.07 g (0.45 mmol, 1 eq.) in 0.5 mL CH_2Cl_2
- crude azadiene **33b**: 0.211 g (0.90 mmol, 2 eq., 80-85 % purity) in 0.5 mL CH_2Cl_2
- reaction time: 3 h 30 at room temperature
- methanol: 2 mL
- composition of the crude mixture: only the *exo* isomer was detected
- flash chromatography (AcOEt/cyclohexane: 3/1, AcOEt)

Reference of the product: Jnoff, E. *Dissertation, UCL-ORSY, 1999*, Jnoff, E.; Ghosez, L. *J. Am. Chem. Soc.* **1999**, *121*, 2617-2618

Physical aspect: white powder

R.N.: [222638-06-4]

F.B.: $\text{C}_{17}\text{H}_{20}\text{N}_2\text{O}_4$

M.W.: 316.36

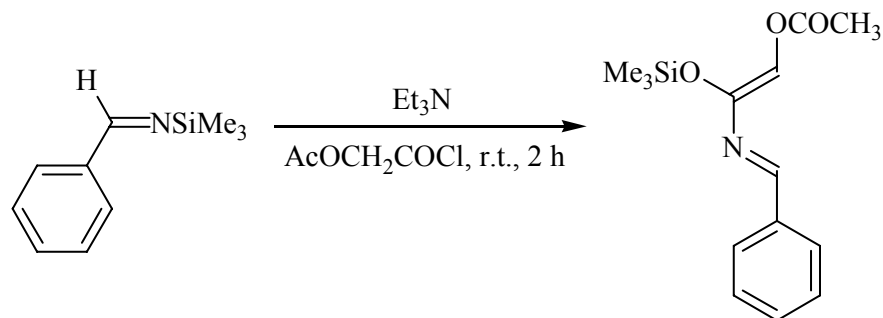
Yield: 0.12 g (81 %)

e.e.: 96 % (Chiralcel AD, *i*-PrOH/hexane (30/70), 1 mL/min, $\lambda = 210$ nm, $t_{\text{r (min)}} = 9.6$ min. and $t_{\text{r (maj)}} = 14.5$ min.)

The spectroscopic and spectrometric data are described for the thermal reaction.

7.2 Synthesis of the (+)-(3*S*,4*S*,5*S*,6*S*)-3-acetoxy-4-methyl-5-[(2-oxo-1,3-oxazolidin-3-yl)carbonyl]-6-phenyltetrahydropyridin-2(1*H*)-one **107**

7.2.1 Synthesis of crude 4-acetoxy-1-phenyl-3-trimethylsilyloxy-2-aza-1,3-butadiene **33h**



Prepared according to the general procedure with the following quantities and conditions:

- *N*-silylated imine **94**: 1.0 g (5.64 mmol, 1 eq.) in 10 mL ether

- Triethylamine: 7.84 mL (56.39 mmol, 10 eq.)
- Acetoxyacetyl chloride: 0.63 mL (5.64 mmol, 1 eq.) in 5 mL ether
- the residue was washed, filtered and concentrated 3 times with petroleum ether

Physical aspect: yellow oil

F.B.: C₁₄H₁₉NO₃Si

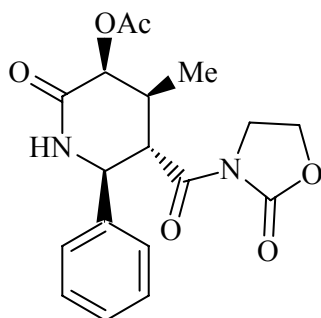
M.W.: 277.39

Yield: quant.

Purity: 78 % (DMSO₂)

¹H NMR (200 MHz, CDCl₃, T = 25 °C) δ 8.41 (s, 1H, H³), 7.83-7.78 (mult, 2H, H⁵), 7.44-7.41 (m, 4H, H⁶+H⁷+H¹), 2.23 (s, 3H, H¹⁰), 0.29 (s, 9H, H⁸) ppm

7.2.2 Synthesis of the (+)-(3*S*,4*S*,5*S*,6*S*)-3-acetoxy-4-methyl-5-[(2-oxo-1,3-oxazolidin-3-yl)carbonyl]-6-phenyltetrahydropyridin-2(1*H*)-one **107**



Prepared according to the general procedure with the following quantities and conditions:

- Cu(OTf)₂: 0.016 g (0.045 mmol, 0.1 eq.)
- (*S,S*)-*tert*-butylbis(oxazoline): 0.016 (0.054 mmol, 0.12 eq.) in 1 mL CH₂Cl₂
- TMSOTf: 0.049 mL (0.27 mmol, 0.6 eq.)
- *N*-crotonyl-2-oxazolidinone **88**: 0.07 g (0.45 mmol, 1 eq.) in 0.5 mL CH₂Cl₂
- crude azadiene **33h**: 0.250 g (0.90 mmol, 2 eq., 70 % purity) in 0.5 mL CH₂Cl₂
- reaction time: 3 h 30 at room temperature
- methanol: 2 mL
- composition of the crude mixture: only the *exo* isomer was detected
- flash chromatography (AcOEt/cyclohexane: 3/1, AcOEt)

Physical aspect: white solid

F.B.: C₁₈H₂₀N₂O₆

M.W.: 360.36

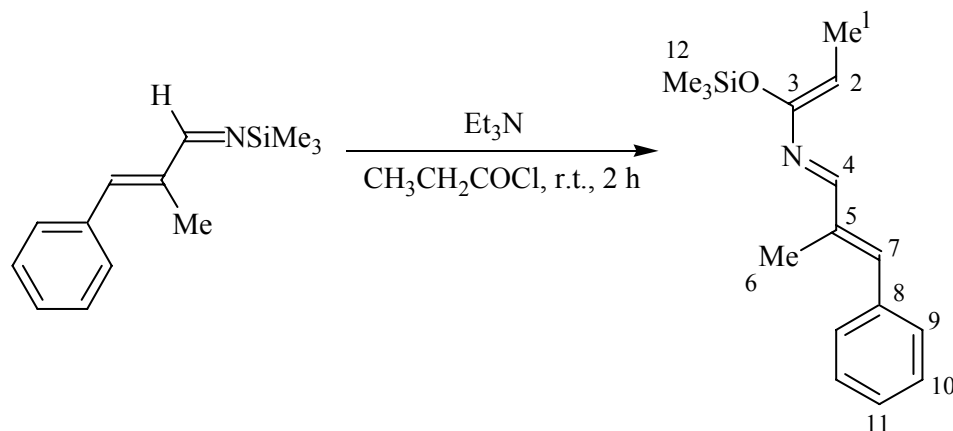
Yield: 0.145 g (89 %)

e.e.: 99 % (Chiralcel AD, *i*-PrOH/hexane (20/80), 2 mL/min, λ = 212 nm, t_r (min) = 11.0 min. and t_r (maj) = 20.3 min.)

The spectroscopic and spectrometric data are described for the thermal reaction.

7.3 Synthesis of the (+)-(3*S*,4*R*,5*S*,6*S*)-3,4-dimethyl-6-[(*E*)- α -methylstyryl]-5-[(2-oxo-1,3-oxazolidin-3-yl)carbonyl]tetrahydropyridin-2(1*H*)-one **111**

7.3.1 Synthesis of the crude (*Z*)-*N*-[(*E*,2*E*)-2-methyl-3-phenyl-2-propenylidene]-1-[(trimethylsilyl)oxy]-1-propen-1-amine **96**



Prepared according to the general procedure with the following quantities and conditions:

- *N*-silylated imine **110**: 1.75 g (8.05 mmol, 1 eq.) in 10 mL ether
- Triethylamine: 11.19 mL (80.50 mmol, 10 eq.)
- Propionyl chloride: 0.70 mL (8.05 mmol, 1 eq.) in 4 mL ether
- 10 mL hexane were added at the mixture and the triethylamine hydrochloride was filtered over celite. The filtrate was concentrated and the residue dried under vacuum.

Reference of the product: Jnoff, E. *Dissertation UCL-ORSY 1999*

R.N.: [222638-04-2]

Physical aspect: yellow oil

F.B.: C₁₃H₁₉NOSi

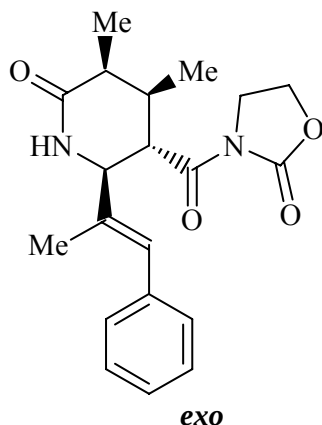
M.W.: 233.38

Yield: 2.11 g (96 %)

Purity: 61 % (DMSO₂)

¹H NMR (200 MHz, CDCl₃, T = 25 °C) δ 8.68 (s, 1H, CH=N), 7.50-7.25 (mult, 5H, Har), 6.93 (s, 1H, PhCH=CCH₃), 2.13 (s, 3H, PhCH=CCH₃), 0.25 (s, 9H, Me₃Si) ppm

7.3.2 Synthesis of the (+)-(3*S*,4*R*,5*S*,6*S*)-3,4-dimethyl-6-[(*E*)- α -methylstyryl]-5-[(2-oxo-1,3-oxazolidin-3-yl)carbonyl]tetrahydropyridin-2(1*H*)-one **111**



Prepared according to the general procedure with the following quantities and conditions:

- Cu(OTf)₂: 0.016 g (0.045 mmol, 0.1 eq.)
- (*S,S*)-*tert*-butylbis(oxazoline): 0.016 (0.054 mmol, 0.12 eq.) in 1 mL CH₂Cl₂
- TMSOTf: 0.066 mL (0.36 mmol, 0.8 eq.)
- *N*-crotonyl-2-oxazolidinone **88**: 0.07 g (0.45 mmol, 1 eq.) in 0.5 mL CH₂Cl₂
- crude azadiene **96**: 0.247 g (0.90 mmol, 2 eq., 70 % purity) in 0.5 mL CH₂Cl₂
- reaction time: 3 h 30 at room temperature
- methanol: 2 mL
- composition of the crude mixture: only the *exo* isomer was detected
- flash chromatography (AcOEt/cyclohexane: 3/1, AcOEt)

Reference of the product: Jnoff, E. *Dissertation, UCL-ORSY*, **1999**, Jnoff, E.; Ghosez, L. *J. Am. Chem. Soc.* **1999**, *121*, 2617-2618

R.N.: [222638-11-1]

Physical aspect: white powder

F.B.: C₂₀H₂₄N₂O₄

M.W.: 356.42

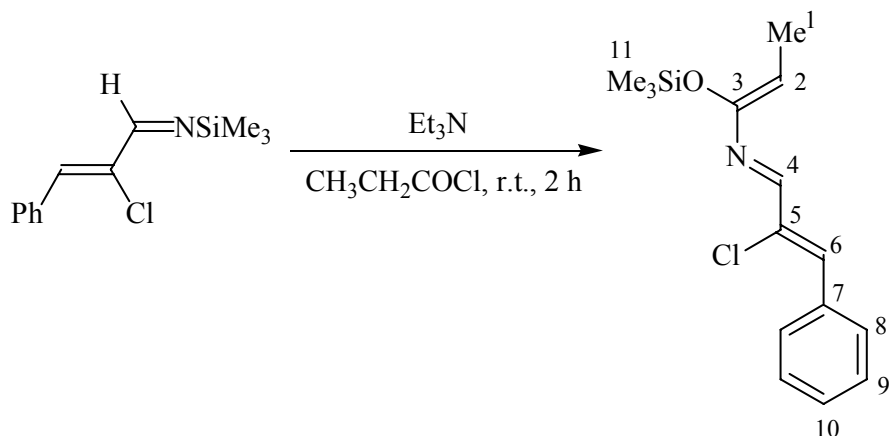
Yield: 0.113 g (70 %)

e.e.: > 92 % (Chiralcel AD, EtOH/hexane (40/60), 0.5 mL/min, λ = 254 nm, $t_{r\text{ (maj)}}$ = 13.8 min. and $t_{r\text{ (min)}}$ = 17.0 min.)

The spectroscopic and spectrometric data are described for the thermal reaction.

7.4 Synthesis of the (+)-(3*S*,4*R*,5*S*,6*S*)-6-[(*E*)- α -chlorostyryl]-4-methoxycarbonyl-3-methyl-5-[(2-oxo-1,3-oxazolidin-3-yl)carbonyl]tetrahydropyridin-2(1*H*)-one **114**

7.4.1 Synthesis of the crude (*Z*)-*N*-[(*E*,2*Z*)-2-chlor-3-phenyl-2-propenylidene]-1-[(trimethylsilyl)oxy]-1-propen-1-amine **99**



Prepared according to the general procedure with the following quantities and conditions:

- *N*-silylated imine **112**: 2.0 g (8.41 mmol, 1 eq.) in 20 mL ether
- Triethylamine: 5.85 mL (42.05 mmol, 5 eq.)
- Propionyl chloride: 0.73 mL (8.41 mmol, 1 eq.) in 6 mL ether
- the residue was washed, filtered and concentrated twice with petroleum ether

Physical aspect: viscous yellow oil

F.B.: C₁₅H₂₀ClNOSi

M.W.: 293.86

Yield: 1.99 g (80.5 %)

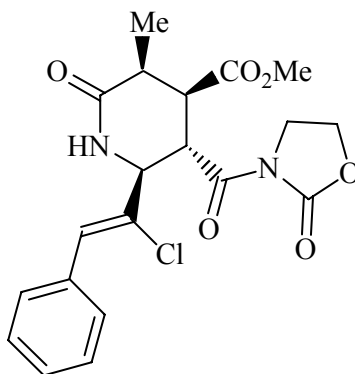
Purity: 55 % (HMB)

I.R. (film, cm⁻¹): 3058 (CH arom.), 2961 (CH aliph.), 1762 (C=N), 1620 (C=C), 1494, 1448, 1027, 837

¹H NMR (200 MHz, CDCl₃, T = 25 °C) δ 8.03 (s, 1H, CH=N), 7.88-7.28 (m, 5H, Har), 7.09 (s, 1H, CH=CCl), 5.37 (q, 1H, ³J = 7.5 Hz, CHCH₃), 1.77 (d, 3H, ³J = 7.4 Hz, CHCH₃), 0.27 (s, 9H, Me₃Si) ppm

M.S. (C.I./CH₄-N₂O) : 295 (M⁺ (³⁷Cl), 13%), 293 (M⁺ (³⁵Cl), 27%), 255 (15%), 253 (28%), 149 (68%), 147 (33%), 130 ([PhCHC³⁷Cl + H]⁺, 100%), 128 ([PhCHC³⁵Cl + H]⁺, 39%), 91 (Me₃SiOH + H]⁺, 19%)

7.4.2 Synthesis of the (+)-(3*S*,4*R*,5*S*,6*S*)-6-[(*E*)- α -chlorostyryl]-4-methoxycarbonyl-3-methyl-5-[(2-oxo-1,3-oxazolidin-3-yl)carbonyl]tetrahydropyridin-2(1*H*)-one **114**



Prepared according to the general procedure with the following quantities and conditions:

- Cu(OTf)₂: 0.018 g (0.050 mmol, 0.1 eq.)
- (*S,S*)-*tert*-butylbis(oxazoline): 0.018 (0.060 mmol, 0.12 eq.) in 1 mL CH₂Cl₂
- TMSOTf: 0.073 mL (0.402 mmol, 0.8 eq.)
- *N*-fumaroyl-2-oxazolidinone **91**: 0.1 g (0.502 mmol, 1 eq.) in 0.5 mL CH₂Cl₂
- crude azadiene **99**: 0.295 g (1.004 mmol, 2 eq., 60 % purity)
- reaction time: 18 hours at room temperature
- methanol: 2 mL
- composition of the crude mixture: only the *exo* isomer was detected
- flash chromatography (AcOEt/cyclohexane: 3/1, AcOEt)

Rf: 0.50 (AcOEt)

Physical aspect: beige solid

M.P.: 160-161 °C

F.B.: C₂₀H₂₁ClN₂O₆

M.W.: 420.84

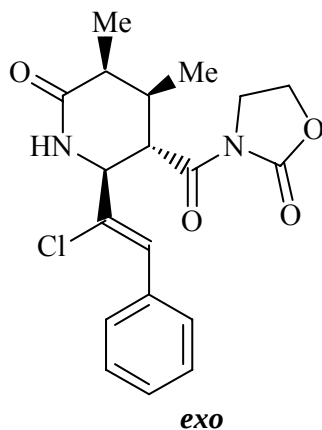
Yield: 0.043 g (20 %)

e.e.: 93 % (Chiralcel AD, *i*-PrOH/hexane (60/40), 0.2 mL/min, λ = 254 nm, $t_{r \text{ (min)}}$ = 35.2 min. and $t_{r \text{ (maj)}}$ = 37.7 min.)

[α]_D = + 27.38 ° (c = 1.3, EtOH)

The spectroscopic and spectrometric data are described for the thermal reaction.

7.5 Synthesis of the (+)-(3*S*,4*R*,5*S*,6*S*)-6-[(*Z*)-1-chloro-2-phenylethenyl]-3,4-dimethyl-5-[(2-oxo-1,3-oxazolidin-3-yl)carbonyl]-2-piperidinone **113**



Prepared according to the general procedure with the following quantities and conditions:

- Cu(OTf)₂: 0.016 g (0.045 mmol, 0.1 eq.)
- (*S,S*)-*tert*-butylbis(oxazoline): 0.016 (0.054 mmol, 0.12 eq.) in 1 mL CH₂Cl₂
- TMSOTf: 0.073 mL (0.41 mmol, 0.9 eq.)
- *N*-crotonyl-2-oxazolidinone **88**: 0.07 g (0.45 mmol, 1 eq.) in 0.5 mL CH₂Cl₂
- crude azadiene **99**: 0.265 g (0.90 mmol, 2 eq., 55 % purity)
- reaction time: 18 hours at room temperature
- methanol: 2 mL
- composition of the crude mixture: only the *exo* isomer was detected
- flash chromatography (AcOEt/cyclohexane: 3/1, AcOEt)
- purification by recrystallization in AcOEt/hexane

Rf: 0.5 (AcOEt)

Physical aspect: beige solid

M.P.: 177-178 °C

F.B.: C₁₉H₂₁ClN₂O₄

M.W.: 376.83

Yield: 0.11 g (65 %)

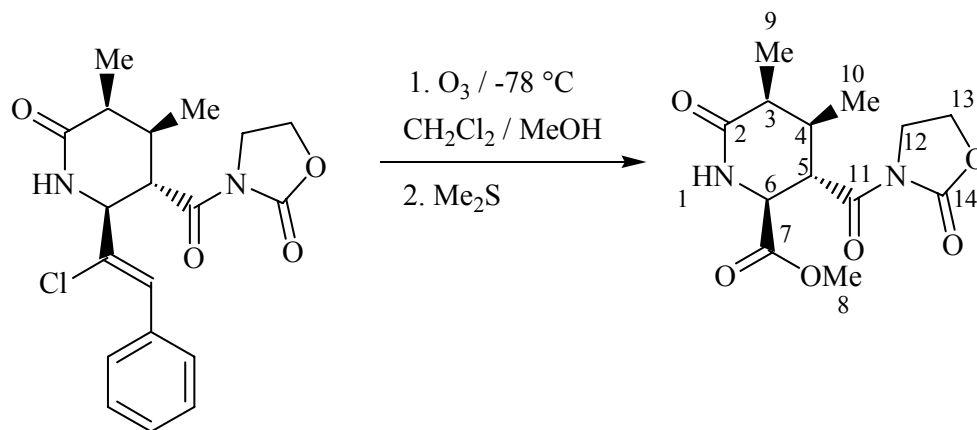
e.e.: not measured

[α]_D = + 92.1 ° (c = 0.076, CHCl₃)

The spectroscopic and spectrometric data are described for the thermal reaction.

8 Ozonolysis of compound **113**

8.1 Ozonolysis of compound (*rac*)-**113**: Synthesis of (*rac*)-methyl-4,5-dimethyl-6-oxo-3-[(2-oxo-1,3-oxazolidin-3-yl)carbonyl]-2-piperidinecarboxylate **127** *exo*



In a three-necked round bottom flask, equipped with a magnetic stirring bar, a septum, and a silicagel tube connected to a trap, oven dried and placed under an argon atmosphere, cycloadduct (*rac*)-**113** (0.12 g, 0.32 mmol, 1 eq.) was introduced and dichloromethane (30 mL) was added. After cooling the solution at $-78\text{ }^{\circ}\text{C}$, the reacting mixture was saturated by an ozon stream for 30 minutes. The excess of ozon was eliminated by an argon stream. The reacting mixture is then treated with methanol (0.40 mL, 9.95 mmol, 31 eq.) followed by the addition of methyl sulfide (0.24 mL, 3.21 mmol, 10 eq.) *via* a syringe through the septum. The cold bath was removed and the stirring maintained for 2 hours at room temperature. The solvent was evaporated under reduced pressure, and the residue was washed with water and the product extracted with 3 X 20 mL of dichloromethane. The organic layers were combined and dried over MgSO_4 . After evaporation of the solvent, a white solid was isolated.

Purification: flash chromatography (AcOEt)

Rf: 0.32 (AcOEt)

Physical aspect: white solid

M.P.: $135\text{--}137\text{ }^{\circ}\text{C}$

F.B.: $\text{C}_{13}\text{H}_{18}\text{N}_2\text{O}_6$

M.W.: 298.29

Yield: 0.10 g (98 %)

HPLC: Chiralcel AD, EtOH/hexane (18/82), 2 mL/min, $\lambda = 204\text{ nm}$, $t_r = 18.7\text{ min.}$ and $t_r = 24.8\text{ min.}$

I.R.: (KBr , cm^{-1}): 3210, 3091, 2980, 1774 (CO oxazolidinone), 1700 (CO imide), 1663 (CO lactam), 1393

¹H NMR (500 MHz, CDCl₃, T = 25 °C)

Proton	δ (ppm)	Mult.	Integ.	J (Hz)
1	6.12	d	1	³ J ₁₋₆ = 0.7
6	4.60	d	1	³ J ₆₋₅ = 9.6
5	4.48	mult	1	³ J ₅₋₆ = 9.6, ³ J ₅₋₄ = 8.4
13	4.46	mult	2	/
12	4.10	mult	2	/
8	3.75	s	3	/
3	2.52	q	1	³ J ₃₋₉ = 7.0
4	2.33	mult	1	³ J ₄₋₁₀ = 7.0, ³ J ₄₋₅ = 8.4, ³ J ₄₋₃ = 4.6
9	1.20	d	3	³ J ₉₋₃ = 7.0
10	1.00	d	3	³ J ₁₀₋₄ = 7.0

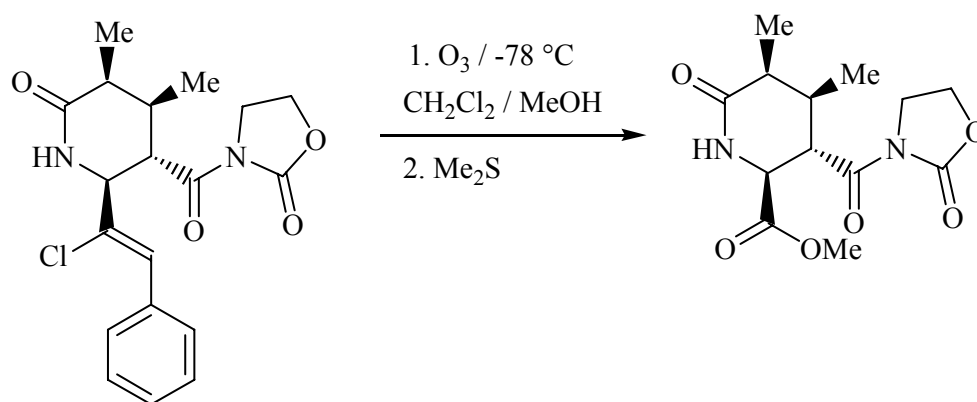
¹³C NMR (125 MHz, CDCl₃, T = 25 °C) δ 173.9 (C²), 173.4 (C¹¹), 169.6 (C⁷), 153.2 (C¹⁴), 61.8 (C¹³), 55.8 (C⁶), 53.0 (C⁸), 42.7 (C¹²), 41.5 (C⁵), 39.3 (C³), 35.3 (C⁴), 14.8 (C¹⁰), 12.1 (C⁹) ppm

M.S. (C.I./CH₄-N₂O) : 327 ([M+C₂H₅]⁺, 4 %), 299 ([M+H]⁺, 24 %), 267 ([M-CH₃O]⁺, 13 %), 241 (M+2H-CO₂Me)⁺, 100 %)

E.A. :

Element	% calculated	% found	Δ
C	52.34	52.28	0.06
H	6.08	6.13	0.05
N	9.39	9.12	0.27

8.2 Ozonolysis of compound (+)-**113**: Synthesis of (+)-(3*S*,4*R*,5*S*,6*S*)-3,4-dimethyl-6-methoxycarbonyl-5-[(2-oxo-1,3-oxazolidin-3-yl)carbonyl]tetrahydropyridin-2(1*H*)-one **127**



In a three-necked round bottom flask, equipped with a magnetic stirring bar, a septum, and a silicagel tube connected to a trap, oven dried and placed under an argon atmosphere, cycloadduct (+)-**113** (0.082 g, 0.22 mmol, 1 equiv.) was introduced and dichloromethane (20 mL) was added. After cooling the solution at -78 °C, the reacting mixture was saturated by an ozon stream for 30 minutes. The excess of ozon was eliminated by an argon stream. The reacting mixture is then treated with methanol (0.27 mL, 6.75 mmol, 31 eq.) followed by

the addition of methyl sulfide (0.16 mL, 2.18 mmol, 10 eq.) *via* a syringe through the septum. The cold bath was removed and the stirring maintained for 2 hours at room temperature. The solvent was evaporated under reduced pressure, and the residue was washed with water and the product extracted with 3 X 15 mL of dichloromethane. The organic layers were combined and dried over MgSO₄. After evaporation of the solvent, the white solid was isolated.

Purification: flash chromatography (AcOEt)

Rf: 0.32 (AcOEt)

Physical aspect: white solid

M.P.: 135-137 °C

F.B.: C₁₃H₁₈N₂O₆

M.W.: 298.29

Yield: 0.064 g (99 %)

e.e.: 91 % (Chiralcel AD, EtOH/hexane (18/82), 2 mL/min, λ = 204 nm, $t_{r \text{ (min)}}$ = 17.7 min. and $t_{r \text{ (maj)}}$ = 22.8 min.)

$[\alpha]_D$ = + 2.92 ° (c = 1.3, CHCl₃)

9 Synthesis of the azo dienophiles

9.1 Synthesis of the hydrazides

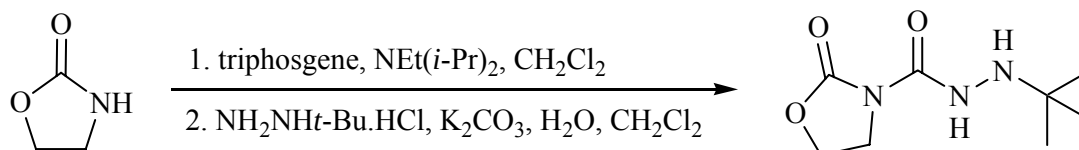
9.1.1 One-pot synthesis of the hydrazides

General procedure

In a 250 mL round bottom flask, equipped with a magnetic stirring bar and a condenser, 2-oxazolidinone (1 eq.) was dissolved in dichloromethane and diisopropylethylamine (3 eq.) was added. The mixture was cooled to 0 °C, then triphosgene (1 eq.) was added. After 15 min. stirring at 0 °C, the cold bath was removed and the stirring maintained during one night. The substituted hydrazine hydrochloride (5 eq.) was then added and an aqueous solution of potassium carbonate was added under strong agitation. An oil trap connected at the reaction flask allowed the observation of a strong carbone dioxide emission. After 24 hours at room temperature, the reaction mixture was diluted with water and the layers were separated. The aqueous phase was extracted with dichloromethane and the organic layers were combined and washed with water, dried over MgSO₄ and concentrated under reduced pressure.

The product was purified by flash chromatography.

9.1.1.1 Synthesis of 2-Oxo-oxazolidine-3-carboxylic acid *N'*-tert-butyl-hydrazide **169c**



Prepared according to the general procedure with 2-oxazolidinone (3.0 g, 33.8 mmol, 1 eq.), CH₂Cl₂ (105 mL), diisopropylethylamine (18 mL, 101.3 mmol, 3 eq.), triphosgene (10.22 g, 33.8 mmol, 1 eq.), *tert*-butylhydrazine hydrochloride (21.47 g, 168.81 mmol, 5 eq.), K₂CO₃ (14.14 g, 101.3 mmol, 3 eq.) in H₂O (45 mL). A yellowish oil was obtained.

Purification: flash chromatography (AcOEt/cyclohexane: 1/3, 3/1 and AcOEt)

Rf: 0.32 (AcOEt/cyclohexane: 4/1)

Physical aspect: yellowish oil

M.F.: C₈H₁₅N₃O₃

M.W.: 201.22

Yield: 5.41 g (80 %)

I.R.: (film, cm⁻¹): 3369 (NH), 3269 (NH), 2974 (st CH), 1760 (CO oxazolidinone), 1687 (CO imide), 1403, 1235

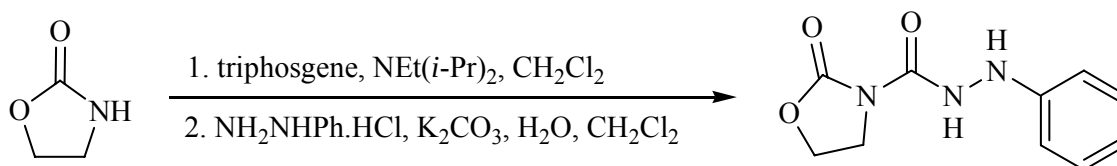
¹H NMR (200 MHz, CDCl₃, T = 25 °C) δ 8.88 (br s, 1H, NH), 4.48 (t, 2H, ³J = 7.9 Hz, CH₂O), 4.08 (t, 2H, ³J = 7.9 Hz, CH₂N), 1.12 (s, 9H, *t*-Bu) ppm

¹³C NMR (50 MHz, CDCl₃, T = 25 °C) δ 155.4 (NCONH), 152.3 (OCON), 62.8 (CH₂O), 55.1 (C(CH₃)₃), 42.6 (CH₂N), 27.1 (C(CH₃)₃) ppm

M.S. (C.I./CH₄-N₂O): 230 ([M+C₂H₅]⁺, 5 %), 202 ([M+H]⁺, 52 %), 201 (M⁺, 24 %), 146 ([M-C₄H₉+2H]⁺, 100 %)

HRMS (C.I.): Calculated for C₈H₁₅N₃O₃: 201.110644
Found: 201.111342

9.1.1.2 Synthesis of 2-Oxo-oxazolidine-3-carboxylic acid *N*'-phenyl-hydrazide **169a**



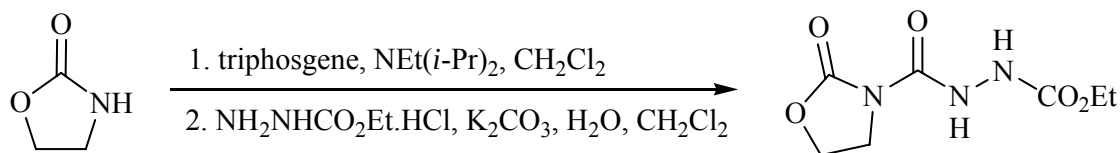
Prepared according to the general procedure with 2-oxazolidinone (1.0 g, 11.3 mmol, 1 eq.), CH₂Cl₂ (80 mL), diisopropylethylamine (6.0 mL, 33.8 mmol, 3 eq.), triphosgene (3.41 g, 11.3 mmol, 1 eq.), phenylhydrazine hydrochloride (8.22 g, 56.3 mmol, 5 eq.), K₂CO₃ (4.71 g, 33.8 mmol, 3 eq.) in H₂O (15 mL). A beige solid was obtained.

Purification: flash chromatography (AcOEt/cyclohexane: 1/3 to 3/1)

Yield: 0.9 g (36 %)

The spectroscopic and spectrometric data are described at point 9.1.2.2.

9.1.1.3 Synthesis of *N'*-(2-Oxo-oxazolidine-3-carbonyl)-hydrazinecarboxylic acid ethyl ester **169d**



Prepared according to the general procedure with 2-oxazolidinone (1.0 g, 11.3 mmol, 1 eq.), CH₂Cl₂ (35 mL), diisopropylethylamine (6.0 mL, 33.8 mmol, 3 eq.), triphosgene (3.41 g, 11.3 mmol, 1 eq.), ethyl carbazate hydrochloride (8.07 g, 56.3 mmol, 5 eq.), K₂CO₃ (4.71 g, 33.8 mmol, 3 eq.) in H₂O (15 mL). A white solid was obtained.

Purification: flash chromatography (AcOEt/cyclohexane gradient)

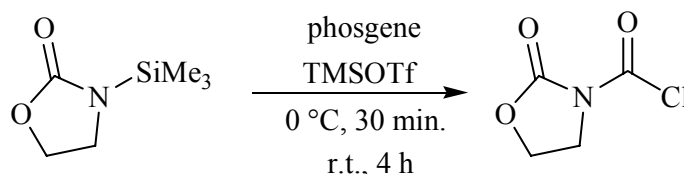
Yield: 2.0 g (82 %)

The spectroscopic and spectrometric data are described at point 9.1.2.4.

9.1.2 Second synthesis of the hydrazides

9.1.2.1 Synthesis of 2-Oxo-1,3-oxazolidine-3-carbonyl chloride **171b**

Reference: Johnson, D. S. and Evans, D. A. *Org. Lett.* **1999**, *1*, 595-598



3-(trimethylsilyl)-2-oxazolidinone (48 mL, 310.31 mmol, 1 eq.) was added to a solution of phosgene (20 % in toluene) (344.71 mL, 651.66 mmol, 2.1 eq.) at 0 °C. Trimethylsilyl trifluoromethanesulfonate (0.228 mL, 1.18 mmol, 0.0038 eq.) was added and the reaction was stirred at 0 °C for 30 min., warmed to room temperature, and stirred an additional 4 hours. The solution was concentrated under reduced pressure to give a brown oil which crystallized upon cooling. The product was recrystallized from CH₂Cl₂/hexanes to afford light brown needles.

R.N.: [6313-48-2]

Physical aspect: brown needles

F.B.: C₄H₄NO₃Cl

M.W.: 149.53

Yield: 42.17 g (91 %) (lit.: 98 %)

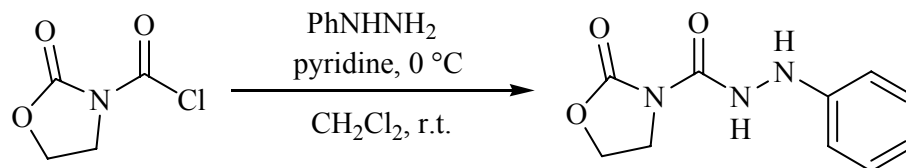
¹H NMR (200 MHz, CDCl₃, T = 25 °C) δ 4.48 (t, 2H, CH₂O, ³J = 7.9 Hz), 4.22 (t, 2H, CH₂N, ³J = 7.9 Hz)

^{13}C NMR (50 MHz, CDCl_3 , $T = 25\text{ }^\circ\text{C}$) δ 150.0, 144.9, 61.4, 45.6 ppm

General procedure

To a solution of hydrazine (1.05 eq.) in CH_2Cl_2 cooled to $0\text{ }^\circ\text{C}$ was added pyridine (1.05 eq.). 2-Oxo-1,3-oxazolidine-3-carbonyl chloride (1.0 eq.) was added as a solution in CH_2Cl_2 via a cannula. The reaction was allowed to warm to room temperature and stirred for 16 hours. The mixture was diluted with CH_2Cl_2 and poured into H_2O . The layers were separated and the aqueous layer was extracted with CH_2Cl_2 . The combined organic layers were washed with 5 % aqueous HCl, H_2O and brine, dried over MgSO_4 , and concentrated to give the hydrazide.

9.1.2.2 Synthesis of 2-Oxo-oxazolidine-3-carboxylic acid *N'*-phenyl-hydrazide **169a**



Prepared according to the general procedure with phenylhydrazine (3.68 mL, 35.1 mmol, 1.05 eq.), pyridine (2.84 mL, 35.1 mmol, 1.05 eq.), CH_2Cl_2 (25 mL) and 2-oxo-1,3-oxazolidine-3-carbonyl chloride (5.0 g, 33.4 mmol, 1 eq.) in CH_2Cl_2 (25 mL). 16 hours at room temperature. A yellowish-orange solid was obtained.

Purification: recrystallization in AcOEt/hexane

Rf: 0.51 (AcOEt)

Physical aspect: beige crystals

M.P.: $139\text{--}140\text{ }^\circ\text{C}$

M.F.: $\text{C}_{10}\text{H}_{11}\text{N}_3\text{O}_3$

M.W.: 221.21

Yield: 6.3 g (85 %)

I.R.: (KBr, cm^{-1}): 3354 (NH), 3313 (NH), 3024-2921 (st. CH arom), 1766 (CO oxazolidinone), 1702 (CO imide), 1603, 761, 698

^1H NMR (200 MHz, CDCl_3 , $T = 25\text{ }^\circ\text{C}$) δ 9.4 (br s, 1H, NH), 7.23 (m, 2H, CHar), 6.88 (m, 3H, CHar), 6.00 (br s, 1H, NH), 4.45 (t, 2H, OCH₂, $^3J = 8\text{ Hz}$), 3.99 (t, 2H, NCH₂, $^3J = 8\text{ Hz}$) ppm

^{13}C NMR (50 MHz, CDCl_3 , $T = 25\text{ }^\circ\text{C}$) δ 155.6 (NCONH), 152.7 (OCON), 148.0 (NHCar), 129.4 (CHar-m), 121.6 (CHar-p), 113.7 (CHar-o), 63.2 (OCH₂), 42.6 (NCH₂) ppm

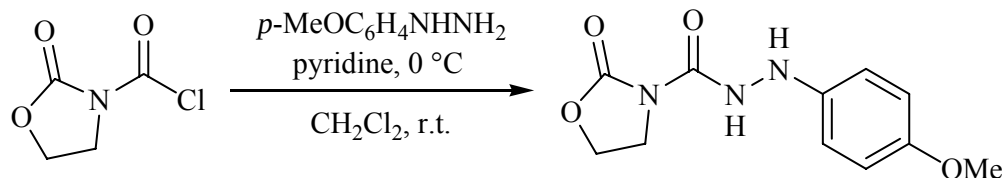
M.S. (C.I./ $\text{CH}_4\text{-N}_2\text{O}$): 222 ($[\text{M}+\text{H}]^+$, 65 %), 221 (M^{+} , 30 %), 205 (40 %), 131 (62 %), 135 ($[\text{M}-\text{C}_3\text{H}_4\text{NO}_2]^+$, 67 %), 94 (49 %), 92 (71 %), 88 ($[\text{C}_3\text{H}_5\text{NO}_2+\text{H}]^+$, 100 %)

HRMS (C.I.): Calculated for $C_{10}H_{11}N_3O_3$: 221.079490
Found: 221.080041

E.A. :

Element	% calculated	% found	Δ
C	54.29	54.16	0.13
H	5.01	4.94	0.07
N	18.99	18.82	0.17

9.1.2.3 Synthesis of 2-Oxo-oxazolidine-3-carboxylic acid *N'*-(4-methoxyphenyl)-hydrazide **169f**



Prepared according to the general procedure with *para*-methoxyphenylhydrazine (5.13 g, 37.1 mmol, 1.05 eq.), pyridine (4.29 mL, 53 mmol, 1.5 eq.), CH_2Cl_2 (35 mL) and 2-oxo-1,3-oxazolidine-3-carbonyl chloride (5.29 g, 35.4 mmol, 1 eq.) in 15 mL CH_2Cl_2 . 16 hours at room temperature.

Purification: recrystallization in AcOEt (-20 °C)

Rf: 0.63 (AcOEt)

Physical aspect: orange-red solid

M.P.: 125-127 °C

M.F.: $C_{11}H_{13}N_3O_4$

M.W.: 251.24

Yield: 6.31 g (71 %)

I.R.: (KBr, cm^{-1}): 3333 (NH), 3296 (NH), 2838 (CH in $-OCH_3$), 1764 (CO oxazolidinone), 1702 (CO imide), 1510, 1251 (C-O st. in aryl alkyl ether)

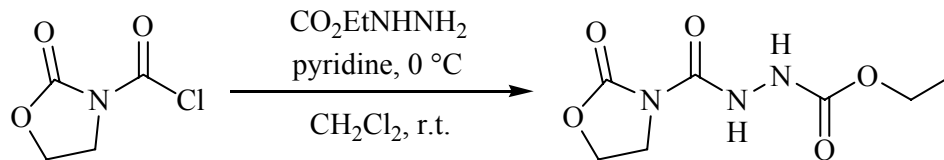
^1H NMR (200 MHz, $CDCl_3$, T = 25 °C) δ 9.35 (br d, 1H, NH , $^3J = 3.5$ Hz), 6.83 (s, 4H, CH_{ar}), 5.78 (br d, 1H, NH , $^3J = 3.5$ Hz), 4.48 (t, 2H, OCH_2 , $^3J = 9$ Hz), 4.06 (t, 2H, NCH_2 , $^3J = 9$ Hz), 3.75 (s, 3H, OCH_3) ppm

^{13}C NMR (50 MHz, $CDCl_3$, T = 25 °C) δ 156.0 ($NCONH$), 155.6 ($OCON$), 153.3 (C_{ar-p}), 142.2 (NH_{Car}), 116.3 (C_{ar-m}), 115.4 (C_{ar-o}), 63.7 (OCH_2), 56.3 (OCH_3), 43.1 (NCH_2) ppm

M.S. (C.I./ CH_4-N_2O): 280 ($[M+C_2H_5]^+$, 3 %), 252 ($[M+H]^+$, 13 %), 251 (M^{+} , 34 %), 123 ($[p-MeOC_6H_5N+H]^+$, 17 %), 122 ($[p-MeOC_6H_5N]^+$, 100 %), 88 ($[C_3H_5NO_2+H]^+$, 100 %)

HRMS (C.I.): Calculated for $C_{11}H_{13}N_3O_4$: 251.090738
Found: 251.090606

9.1.2.4 Synthesis of *N'*-(2-Oxo-oxazolidine-3-carbonyl)-hydrazinecarboxylic acid ethyl ester **169d**



Prepared according to the general procedure with ethyl carbazate (3.77 g, 35.1 mmol, 1.05 eq.), pyridine (2.84 mL, 35.1 mmol, 1.05 eq.), CH_2Cl_2 (30 mL) and 2-oxo-1,3-oxazolidine-3-carbonyl chloride (5 g, 33.4 mmol, 1 eq.) in 15 mL CH_2Cl_2 . 16 hours at room temperature. A white solid was obtained.

Purification: recrystallization in AcOEt

Rf: 0.51 (AcOEt)

Physical aspect: white crystals

M.P.: 104-105 °C

M.F.: $C_7H_{11}N_3O_5$

M.W.: 217.18

Yield: 4.13 g (57 %)

I.R. (KBr, cm^{-1}): 3321 (NH), 3263 (NH), 1772 (CO in CO_2Et), 1753 (CO oxazolidinone), 1702 (CO imide), 1542, 1413, 1218

^1H NMR (200 MHz, $CDCl_3$, T = 25 °C) δ 9.25 (br s, 1H, NH), 6.48 (br s, 1H, NH), 4.5 (t, 2H, OCH_2 , $^3J = 7.4$ Hz), 4.23 (q, 2H, $CO_2CH_2CH_3$, $^3J = 7.2$ Hz), 4.08 (t, 2H, NCH_2 , $^3J = 7.4$ Hz), 1.29 (t, 3H, $CO_2CH_2CH_3$, $^3J = 7.2$ Hz) ppm

^{13}C NMR (50 MHz, $CDCl_3$, T = 25 °C) δ 157.0 ($\underline{CO_2CH_2CH_3}$), 155.9 ($\underline{NCONH}$), 152.9 ($\underline{OCON}$), 63.8 ($\underline{OCH_2}$), 63.0 ($\underline{CO_2CH_2CH_3}$), 43.0 ($\underline{NCH_2}$), 15.0 ($\underline{CO_2CH_2CH_3}$) ppm

M.S. (C.I./ CH_4-N_2O): 246 ($[M+C_2H_5]^+$, 5 %), 218 ($[M+H]^+$, 100 %), 217 (M^+ , 15 %), 177 (44 %), 146 ($[C_4H_6N_3O_3+2H]^+$, 52 %), 105 ($[C_3H_7N_2O_2+2H]^+$, 40 %), 88 ($[C_3H_5NO_2+H]^+$, 100 %)

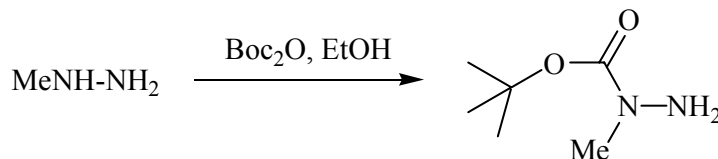
HRMS (C.I.): Calculated for $C_7H_{11}N_3O_5$: 217.070023
Found: 217.069871

E.A. :

Element	% calculated	% found	Δ
C	38.71	39.00	0.29
H	5.11	5.21	0.10
N	19.35	18.89	0.46

9.1.2.5 Synthesis of 2-Oxo-oxazolidine-3-carboxylic acid *N'*-methyl-hydrazide **169b**9.1.2.5.1 Synthesis of 1-Methylhydrazinecarboxylic acid 1,1-dimethylethyl ester **178**

Reference: Oliva, A.; Ellis, M.; Fiocchi, L.; Menta, E. and Krapcho, A. P. *J. Heterocycl. Chem.* **2000**, 37, 47-55



A solution of di-*tert*-butyl dicarbonate (8.3 g, 36.8 mmol, 1 eq.) in dry ethanol (20 mL) was added dropwise over 1.5 hours to a solution of methylhydrazine (2.0 mL, 36.8 mmol, 1 eq.) in dry ethanol (20 mL) which was being cooled in an ice bath. After completion of the addition, the solution was allowed to warm to room temperature and stirring was continued for 15 hours. The solvent was removed by rotary evaporation to yield hydrazide as a clear colorless liquid which was sufficiently pure.

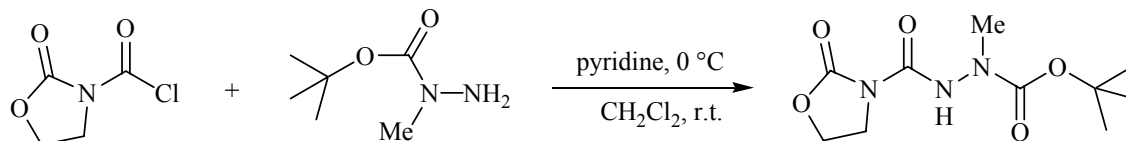
Physical aspect: clear colorless liquid

M.F.: C₆H₁₄N₂O₂

M.W.: 146.18

Yield: 5.2 g (96 %)

¹H NMR (200 MHz, CDCl₃, T = 25 °C) δ 4.05 (br s, 2H), 3.05 (s, 3H), 1.47 (s, 9H) ppm

9.1.2.5.2 Synthesis of *N*-Methyl-*N'*-(2-oxo-oxazolidine-3-carbonyl)-hydrazinecarboxylic acid *tert*-butyl ester **169e**

To a solution of hydrazide **178** (4.0 g, 27.4 mmol, 1.05 eq.) in CH₂Cl₂ (30 mL) cooled to 0 °C was added pyridine (2.21 mL, 27.4 mmol, 1.05 eq.). 2-Oxo-1,3-oxazolidine-3-carbonyl chloride (3.90 g, 26.05 mmol, 1.0 eq.) was added as a solution in CH₂Cl₂ (15 mL) *via* a cannula. The reaction was allowed to warm to room temperature and stirred for 48 hours. The mixture was diluted with CH₂Cl₂ and poured into H₂O. The layers were separated and the aqueous layer was extracted with CH₂Cl₂. The combined organic layers were washed with 5 % aqueous HCl, H₂O and brine, dried over MgSO₄, and concentrated to give the crude hydrazide **169e** as a white solid.

Rf: 0.67 (AcOEt)

Physical aspect: white solid

M.F.: C₁₀H₁₇N₃O₅

M.W.: 259.26

Yield: 6.72 g (quant.)

I.R.: (KBr, cm⁻¹): 3328 (st NH), 2981 and 2929 (st CH), 1773 (CO in Boc), 1750 (CO oxazolidinone), 1720 (CO imide)

¹H NMR (200 MHz, CDCl₃, T = 25 °C) δ 9.37 (br s, 1H, NH), 4.45 (t, 2H, ³J = 7.9 Hz, CH₂O), 4.09 (t, 2H, ³J = 7.9 Hz, CH₂N), 3.17 (s, 3H, CH₃), 1.47 (s, 9H, Boc) ppm

¹³C NMR (50 MHz, CDCl₃, T = 25 °C) δ 155.4 (NCONH), 155.2 (OCON), 151.5 (CO Boc), 81.7 (C(CH₃)₃), 63.2 (CH₂O), 42.4 (CH₂N), 28.2 (C(CH₃)₃) ppm

M.S. (C.I./CH₄-N₂O): 260 ([M+1]⁺, 11 %), 204 ([M-C₄H₉+2H]⁺, 67 %), 186 ([M-C₄H₉O]⁺, 12 %), 160 ([M-C₄H₉-CO₂+2H]⁺, 100 %), 159 ([M-C₄H₉-CO₂+H]⁺, 60 %)

HRMS (C.I.): Calculated for C₁₀H₁₈N₃O₅: 260.125169

Found: 260.124646

9.1.2.5.3 Synthesis of 2-Oxo-oxazolidine-3-carboxylic acid N'-methyl-hydrazide **169b**



In a round-bottom flask, dried and placed under argon atmosphere, hydrazide **169e** (4.03 g, 15.56 mmol, 1 eq.) was dissolved in CH₂Cl₂ (70 mL). Then, trifluoroacetic acid (36 mL, 30 eq.) was added and the mixture was stirred 1 h 30 at room temperature. The solvents were evaporated and the residue was dissolved in CH₂Cl₂. The organic layer was washed by an aqueous solution of NaHCO₃ (2X), a saturated aqueous solution of NaCl, and dried over MgSO₄. After filtration and concentration, methylhydrazide **169b** was obtained as a white solid.

Physical aspect: white solid

M.F.: C₅H₉N₃O₃

M.W.: 159.14

Yield: 2.0 g (81 %)

I.R.: (film, cm⁻¹): 3359 (st NH), 2985-2924 (CH aliph.), 1758 (CO oxazolidinone), 1697 (CO imide), 1532, 1479, 1401

^1H NMR (300 MHz, CDCl_3 , $T = 25\text{ }^\circ\text{C}$) δ 8.95 (br s, 1H, NH), 4.47 (t, 2H, $^3J = 7.9\text{ Hz}$, CH_2O), 4.21 (br s, 1H, NH), 4.07 (t, 2H, $^3J = 7.9\text{ Hz}$, CH_2N), 2.68 (s, 3H, CH_3) ppm

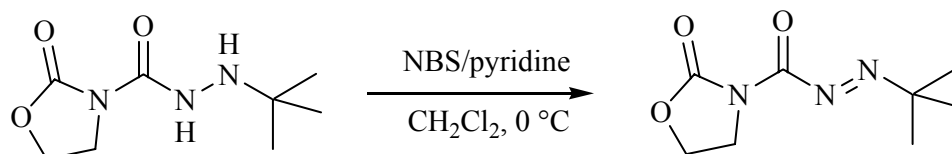
^{13}C NMR (50 MHz, CDCl_3 , $T = 25\text{ }^\circ\text{C}$) δ 155.4 (NCONH), 152.4 (OCON), 63.0 (CH_2O), 42.5 (CH_2N), 14.4 (CH_3) ppm

M.S. (C.I./ $\text{CH}_4\text{-N}_2\text{O}$): 160 ($[\text{M}+\text{H}]^+$, 17 %), 131 ($[\text{M}-\text{CH}_3\text{NH}+2\text{H}]^+$, 7 %), 86 ($\text{C}_3\text{H}_4\text{NO}_2^+$, 65 %)

HRMS (C.I.): Calculated for $\text{C}_5\text{H}_9\text{N}_3\text{O}_3$: 159.063842
Found: 159.064391

9.2 Oxidation of the hydrazides to azo compounds

9.2.1 Synthesis of 1- $\{[(E)\text{-}2\text{-(tert-butyl)diazenyl}]\text{carbonyl}\}$ -1,3-oxazolidin-2-one **168c**



In a 25 mL round bottom flask, dried and placed under argon atmosphere, *tert*-butylhydrazide **169c** (0.3 g, 1.49 mmol, 1 eq.) was dissolved in CH_2Cl_2 (10 mL). The mixture was cooled to $0\text{ }^\circ\text{C}$ and *N*-bromosuccinimide (0.536 g, 2.98 mmol, 2 eq.) was added. The solution became directly red. Three drops of pyridine were added and the mixture was allowed to react one hour at $0\text{ }^\circ\text{C}$. A red precipitate appeared. The filtrate was washed with an aqueous solution of Na_2SO_3 (1M), and water. The solution was dried over Na_2SO_4 , filtrated and concentrated. A yellow oil was isolated.

Rf: 0.79 (AcOEt/cyclohexane: 4/1)

Physical aspect: yellow oil

M.F.: $\text{C}_8\text{H}_{13}\text{N}_3\text{O}_3$

M.W.: 199.20

Yield: 0.28 g (94 %)

I.R.: (film, cm^{-1}): 2977 and 2933 (st CH), 1783 (CO oxazolidinone), 1722 (CO imide), 1479 (st $\text{N}=\text{N}$)

^1H NMR (200 MHz, CDCl_3 , $T = 25\text{ }^\circ\text{C}$) δ 4.53 (t, 2H, $^3J = 7.8\text{ Hz}$, CH_2O), 4.17 (t, 2H, $^3J = 7.8\text{ Hz}$, CH_2N), 1.36 (s, 9H, *t*-Bu) ppm

^{13}C NMR (50 MHz, CDCl_3 , $T = 25\text{ }^\circ\text{C}$) δ 163.5 (NCONH), 152.2 (OCON), 71.8 ($\text{C}(\text{CH}_3)_3$), 63.5 (CH_2O), 43.3 (CH_2N), 26.6 ($\text{C}(\text{CH}_3)_3$) ppm

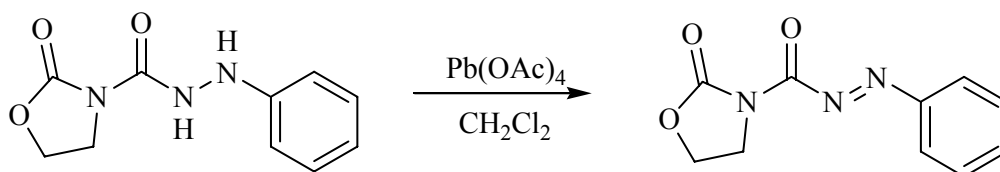
M.S. (E.I. +Q1MS) : 200 ($[\text{M}+\text{H}]^+$, 6 %), 116 (*t*-Bu $\text{N}_2\text{H}_2\text{CO}^+$, 14 %), 57 (C_4H_9^+ , 100 %)

E.A. :

Element	% calculated	% found	Δ
C	48.07	48.23	0.164
H	6.68	6.58	0.100
N	20.43	21.09	0.660

General procedure for the oxidation of the hydrazides **168a**, **168f**, **168d** and **168b**

A solution of lead tetraacetate (1.2 eq.) in CH_2Cl_2 is added *via* a cannula to a solution of hydrazide (1 eq.) in CH_2Cl_2 cooled to $-20\text{ }^\circ\text{C}$. The solution was stirred for 30 minutes at room temperature. Water was then added and the layers were separated. The organic layer was washed with water (5X), twice with sat. aqueous K_2CO_3 , water, dried over MgSO_4 , and concentrated to give the azo compound.

9.2.2 Synthesis of 1- $\{[(E)\text{-}2\text{-phenyldiazenyl}]\text{carbonyl}\}$ -1,3-oxazolidin-2-one **168a**

Prepared according to general procedure with phenylhydrazide **169a** (2.99 g, 13.5 mmol, 1 eq.) in 25 mL CH_2Cl_2 and lead tetraacetate (7.57 g, 16.2 mmol, 1.2 eq.) in 30 mL CH_2Cl_2 . 30 minutes at room temperature. An orange solid was obtained.

Purification: recrystallization in AcOEt/hexane ($-20\text{ }^\circ\text{C}$)

Rf: 0.76 (AcOEt/cyclohexane: 4/1)

Physical aspect: orange crystals

M.P.: $90\text{--}91\text{ }^\circ\text{C}$

M.F.: $\text{C}_{10}\text{H}_9\text{N}_3\text{O}_3$

M.W.: 219.19

Yield: 2.96 g (quant.)

I.R.: (KBr, cm^{-1}): 3065 (Aryl-H), 1801 (CO oxazolidinone), 1702 (CO imide), 1506, 1383, 1340, 1030

^1H NMR (200 MHz, CDCl_3 , $T = 25\text{ }^\circ\text{C}$) δ 7.94 (m, 2H, $\text{CH}_{\text{ar-m}}$), 7.55 (m, 3H, $\text{CH}_{\text{ar-o}}$ + $\text{CH}_{\text{ar-p}}$), 4.56 (t, 2H, $^3J = 7.9\text{ Hz}$, OCH_2), 4.25 (t, 2H, $^3J = 7.9\text{ Hz}$, NCH_2) ppm

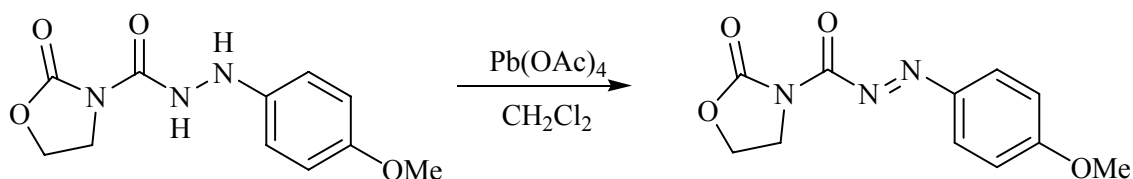
^{13}C NMR (50 MHz, CDCl_3 , $T = 25\text{ }^\circ\text{C}$) δ 162.2 (NCON), 152.3 (OCON), 151.8 (NCar), 133.8 ($\text{CH}_{\text{ar-m}}$), 129.5 ($\text{CH}_{\text{ar-p}}$), 123.9 ($\text{CH}_{\text{ar-o}}$), 63.2 (OCH_2), 43.0 (NCH_2) ppm

M.S. (C.I./CH₄-N₂O): 248 ([M+C₂H₅]⁺, 6 %), 221 ([M+2H]⁺, 16 %), 220 ([M+H]⁺, 100 %), 105 (C₆H₅N₂⁺, 93 %), 77 (C₆H₅⁺, 100 %)

E.A. :

Element	% calculated	% found	Δ
C	54.79	54.81	0.02
H	4.14	4.28	0.14
N	19.17	19.21	0.04

9.2.3 Synthesis of 1-[(*E*)-2-(4-methoxyphenyl)diazenyl]carbonyl]-1,3-oxazolidin-2-one **168f**



Prepared according to general procedure with *para*-methoxyphenylhydrazide **169f** (0.48 g, 1.9 mmol, 1 eq.) in 10 mL CH₂Cl₂ and lead tetraacetate (1.07 g, 2.3 mmol, 1.2 eq.) in 10 mL CH₂Cl₂. 30 minutes at room temperature. An orange solid was obtained.

Purification: recrystallization in AcOEt (-20 °C)

Rf: 0.77 (AcOEt)

Physical aspect: orange crystals

M.P.: 133-135 °C

M.F.: C₁₁H₁₁N₃O₄

M.W.: 249.22

Yield: 0.44 g (83 %)

I.R.: (KBr, cm⁻¹): 1788 (CO oxazolidinone), 1709 (CO imide), 1601 and 1504 (C=C st. in Ar), 1260 (C-O st. in aryl alkyl ether)

¹H NMR (200 MHz, CDCl₃, T = 25 °C) δ 7.95 (d, 2H, CH_{ar-m}, ³J = 8.4 Hz), 7.00 (d, 2H, CH_{ar-o}, ³J = 8.7 Hz), 4.56 (t, 2H, OCH₂, ³J = 8.1 Hz), 4.24 (t, 2H, NCH₂, ³J = 8.1 Hz), 3.91 (s, 3H, OCH₃) ppm

¹³C NMR (50 MHz, CDCl₃, T = 25 °C) δ 164.8 (NCONH), 162.1 (OCON), 151.9 (C_{ar-p}), 146.8 (N_{Car}), 126.6 (C_{ar-m}), 114.7 (C_{ar-o}), 63.0 (OCH₂), 55.9 (OCH₃), 43.07 (NCH₂) ppm

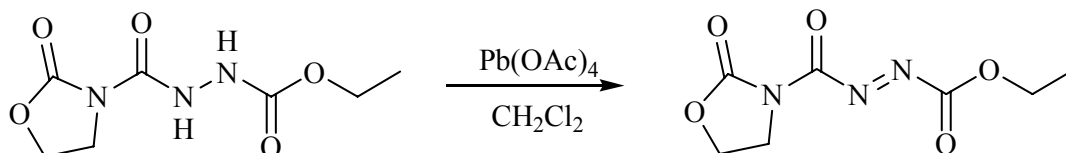
M.S. (C.I./CH₄-N₂O): 251 ([M+2H]⁺, 29 %), 250 ([M+H]⁺, 100 %), 249 (M⁺, 100 %), 163 (50 %), 135 (C₇H₇N₂O⁺, 32 %), 122 (43 %), 107 (C₇H₇O⁺, 100 %), 88 ([C₃H₅NO₂+H]⁺, 20 %)

HRMS (C.I.): Calculated for $C_{11}H_{12}N_3O_4$: 250.083383
Found: 250.082781

E.A. :

Element	% calculated	% found	Δ
C	53.01	52.44	0.57
H	4.45	4.37	0.08
N	16.86	16.28	0.58

9.2.4 Synthesis of ethyl{[(2-oxo-1,3-oxazolidin-3-yl)carbonyl]diazenyl} formate **168d**



Prepared according to general procedure with ethoxycarbonyl hydrazide **169d** (4 g, 18.4 mmol, 1 eq.) in 25 mL CH_2Cl_2 and lead tetraacetate (9.46 g, 20.3 mmol, 1.2eq.) in 30 mL CH_2Cl_2 . 30 minutes at room temperature. An orange oil was obtained.

Rf: 0.71 (AcOEt)

Physical aspect: orange oil

M.F.: $C_7H_9N_3O_5$

M.W.: 215.16

Yield: 3.4 g (86 %)

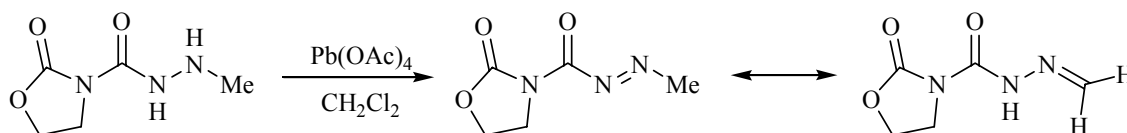
I.R.: (film, cm^{-1}): 2990 and 2930 (st CH), 1800 (CO ester), 1785 (CO oxazolidinone), 1732 (CO imide), 1477 (st $N=N$), 1255, 1034, 1017

^1H NMR (200 MHz, $CDCl_3$, T = 25 °C) δ 4.61 (t, 2H, OCH_2 , $^3J = 8$ Hz), 4.53 (q, 2H, $CO_2CH_2CH_3$, $^3J = 7.2$ Hz), 4.2 (t, 2H, NCH_2 , $^3J = 8$ Hz), 1.46 (t, 3H, $CO_2CH_2CH_3$, $^3J = 7.2$ Hz) ppm

^{13}C NMR (50 MHz, $CDCl_3$, T = 25 °C) δ 160.0 ($CO_2CH_2CH_3$), 159.8 ($NCONH$), 151.6 ($OCON$), 65.8 (OCH_2), 63.7 ($CO_2CH_2CH_3$), 42.6 (NCH_2), 14.2 ($CO_2CH_2CH_3$) ppm

M.S. (C.I./ CH_4-N_2O): 216 ($[M+H]^+$, 4 %), 175, 144 ($[M-C_3H_5O_2+2H]^+$, 8 %), 103 ($CO_2EtN_2H_2^+$, 100 %), 75 ($C_2H_5CO_2H_2^+$, 21 %)

9.2.5 Synthesis of 1-{[(*E*)-2-methyldiazenyl]carbonyl}-1,3-oxazolidin-2-one **168b**



Prepared according to general procedure with methylhydrazide **169b** (1.0 g, 6.28 mmol, 1 eq.) in CH₂Cl₂ (25 mL) and lead tetraacetate (3.52 g, 7.54 mmol, 1.2 eq.) in CH₂Cl₂ (20 mL). 30 minutes at room temperature. A beige-yellowish solid was obtained.

Physical aspect: beige-yellowish solid

M.F.: C₅H₇N₃O₃

M.W.: 157.12

Yield: 0.60 g (61 %)

I.R.: (KBr, cm⁻¹): 3294 (st NH), 2926 (st CH), 1761 (CO oxazolidinone), 1702 (CO imide), 1523 (st N=N), 1481 (st C=N), 1402

¹H NMR (200 MHz, CDCl₃, T = 25 °C) δ 10.91 (br s, 1H, NH), 7.08 (d, 1H, ²J = 11.2 Hz, N=CH₂), 6.67 (d, 1H, ²J = 11.2 Hz, N=CH₂), 4.61 (t, 2H, ³J = 8.0 Hz, CH₂O), 4.17 (t, 2H, ³J = 8.0 Hz, CH₂N), 1.22 (s, 3H, CH₃) ppm

¹³C NMR (50 MHz, CDCl₃, T = 25 °C) δ 155.6 (NCONH), 151.1 (OCON), 137.5 (N=CH₂), 74.0 (OCH₂ hydrazone), 63.2 (OCH₂ azo), 42.5 (NCH₂), 0.1 (CH₃) ppm

M.S. (C.I./CH₄-N₂O): 158 ([M+H]⁺, 55 %), 111 (C₄H₄NO₃⁺, 5 %), 73 (CH₃N₂H₂CO⁺, 7 %), 59 (100 %)

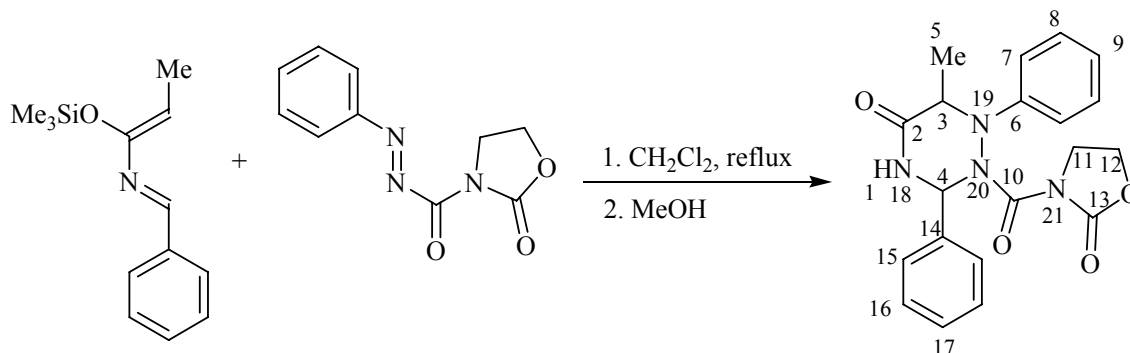
HRMS (C.I.): Calculated for C₅H₈N₃O₃: 158.057235
Found: 158.056566

10 Thermal [4+2] cycloadditions with azo dienophiles

General procedure

In a two-necked flask of 25 mL, equipped with a magnetic stirrer and a condenser; is dried under vacuum. In the flask, are introduced the dienophile and the diene in solution. The reaction is carried out at the temperature and the time required. Then, a large excess of MeOH is added on the mixture and is shaken for minimum 30 minutes. After evaporation of the solvents under reduced pressure, the cycladduct is purified by a flash chromatography and/or recrystallized.

10.1 Synthesis of 6-methyl-2-[(2-oxo-1,3-oxazolidin-3-yl)carbonyl]-1,3-diphenyl-1,2,4-triazinan-5-one **181**



Prepared according to the general procedure with azo compound **168a** (0.3 g, 1.369 mmol, 1 eq.) in 3 mL CH₂Cl₂ and azadiene **33b** (0.946 g, 4.106 mmol, 3 eq.), reflux, 2 h.

Purification: flash chromatography (AcOEt)

Rf: 0.4 (AcOEt/cyclohexane: 80/20)

Physical aspect: white crystals

M.P.: 177-178 °C

M.F.: C₂₀H₂₀N₄O₄

M.W.: 380.4

Yield: 0.520 g (99.8 %)

HPLC: Chiralcel AD, EtOH/hexane (13/87), 2 mL/min, λ = 254 nm, t_r = 13.9 min. and t_r = 19.5 min.

I.R.: (KBr, cm⁻¹): 3326 (NH), 2972 (Aryl-H), 1785 (CO oxazolidinone), 1702 (CO imide), 1676 (CO lactam), 1600 (C=C st. in Ar), 1496

¹H NMR (500 MHz, CDCl₃, T = 25 °C)

Proton	δ (ppm)	Mult.	Integ.	J (Hz)
1	8.16	br s	1	³ J ₁₋₄ = 4.0
15	7.82	d	2	/
16	7.41	dd	2	/
17	7.35	dd	1	/
8	7.19	t	2	/
7	6.91	mult	2	/
9	6.90	mult	1	/
4	6.40	d	1	³ J ₄₋₁ = 4.0
3	4.89	q	1	/
12	4.33	mult	1	/
12'	4.28	mult	1	/

Proton	δ (ppm)	Mult.	Integ.	J (Hz)
11	4.02	mult	1	/
11'	3.75	mult	1	/
5	1.42	d	3	/

^{13}C NMR (125 MHz, CDCl_3 , T = 25 °C) δ 171.6 (C^2), 155.0 (C^{10}), 152.6 (C^{13}), 145.1 (C^6), 128.7 (C^{17}), 128.6 (C^{14}), 128.3 (C^{15}), 127.2 (C^8), 127.2 (C^{16}), 122.0 (C^9), 117.7 (C^7), 70.2 (C^4), 62.5 ($\text{C}^{12} + \text{C}^{12'}$), 57.1 (C^3), 44.2 ($\text{C}^{11} + \text{C}^{11'}$), 17.5 (C^5) ppm

^{15}N NMR (50 MHz, solvent: CDCl_3 , calibration with CH_3NO_2 (δ = 375 ppm) as external reference, T = 25 °C) δ 119.19 (N^{21}), 117.39 (N^{18} , $^1\text{J}_{\text{N}^{18}-\text{H}^1}$), 113.95 (N^{20}), 95.00 (N^{19} , $^3\text{J}_{\text{N}^{19}-\text{H}^4}$ and $^3\text{J}_{\text{N}^{19}-\text{H}^5}$) ppm

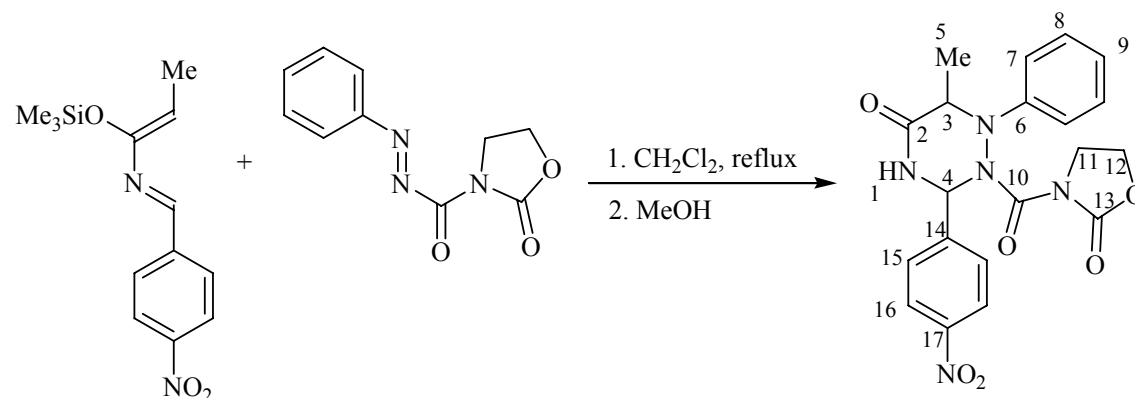
M.S. (E.I. +Q1MS) : 380 (M^{+} , 6 %), 248 (100 %), 161 (43 %)

HRMS: Calculated for $\text{C}_{20}\text{H}_{20}\text{N}_4\text{O}_4$: 380.147735
Found: 380.148455

E.A.:

Element	% calculated	% found	Δ
C	63.15	63.02	0.13
H	5.30	5.45	0.15
N	14.73	14.60	0.13

10.2 Synthesis of 6-methyl-3-(4-nitrophenyl)-2-[(2-oxo-1,3-oxazolan-3-yl)carbonyl]-1-phenyl-1,2,4-triazinan-5-one **183**



Prepared according to the general procedure with azo compound **168a** (0.220 g, 1.006 mmol, 1 eq.) in 3 mL CH_2Cl_2 and azadiene **33c** (0.7 g, 2.515 mmol, 2.5 eq.), reflux, 3 h.

Purification: flash chromatography (AcOEt)

Rf: 0.2 (AcOEt)

Physical aspect: beige crystals

M.P.: 130 °C

M.F.: C₂₀H₁₉N₅O₆

M.W.: 425.4

Yield: 0.4 g (93 %)

HPLC: Chiralcel AD, *i*-PrOH/hexane (30/70), 1 mL/min, λ = 254 nm, t_r = 9.5 min. and t_r = 12.5 min.

I.R.: (KBr, cm⁻¹): 3210 (NH), 3113-2923 (Aryl-H), 1781 (CO oxazolidinone), 1704 (CO imide), 1677 (CO lactam), 1598 (C=C st. in Ar), 1522 (st. as. NO₂), 1350 and 1309 (st. sym. NO₂)

¹H NMR (500 MHz, CDCl₃, T = 47 °C)

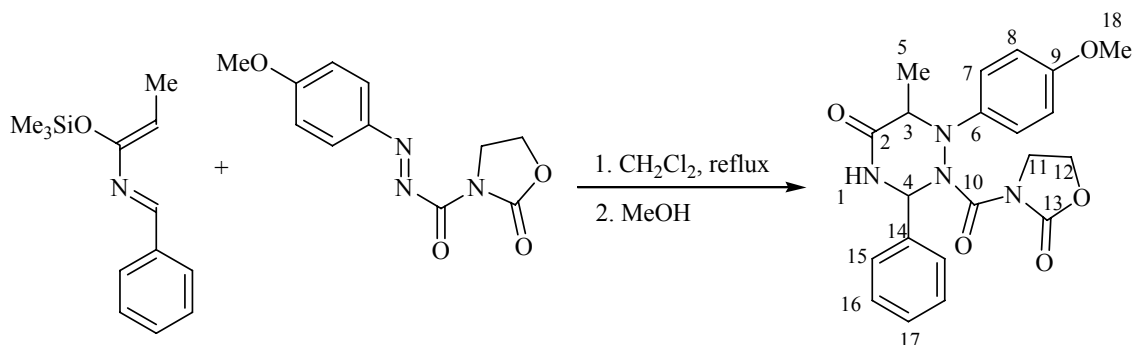
Proton	δ (ppm)	Mult.	Integ.	J (Hz)
16	8.29	d	2	³ J ₁₆₋₁₅ = 8.8
15	8.09	d	2	³ J ₁₅₋₁₆ = 8.8
8	7.20	t	2	³ J ₈₋₇ = 8.5
9	6.95	t	1	/
7	6.87	d	2	³ J ₇₋₈ = 8.5
1	6.71	br s	1	³ J ₁₋₄ = 4.9
4	6.47	d	1	³ J ₄₋₁ = 4.9
3	5.04	q	1	³ J ₃₋₅ = 6.7
12	4.46	ddd	1	² J _{12-12'} = 8.8, ³ J ₁₂₋₁₁ = 9.1, ³ J _{12-11'} = 4.0
12'	4.37	mult	1	² J _{12'-12} = 8.8, ³ J _{12'-11} = 9.1, ³ J _{12'-11'} = 8.5
11	4.16	mult	1	² J _{11-11'} = 10.4, ³ J ₁₁₋₁₂ = 9.1, ³ J _{11-12'} = 9.1
11'	3.82	ddd	1	² J _{11'-11} = 10.4, ³ J _{11'-12} = 4.0, ³ J _{11'-12'} = 8.5
5	1.46	d	3	³ J ₅₋₃ = 6.7

¹³C NMR (125 MHz, CDCl₃, T = 47 °C) δ 128.8 (C⁸ + C^{8'}), 128.5 (C¹⁵ + C^{15'}), 123.6 (C¹⁶ + C^{16'}), 122.8 (C⁹), 118.4 (C⁷ + C^{7'}), 69.9 (C⁴), 62.7 (C¹² + C^{12'}), 57.7 (C³), 44.3 (C¹¹ + C^{11'}), 17.5 (C⁵) ppm (C², C¹⁰, C¹³, C¹⁷ and C⁶ not seen)

¹³C NMR (125 MHz, CDCl₃, T = 25 °C) δ 171.0 (C²), 154.7 (C¹⁰), 152.7 (C¹³), 148.1 (C¹⁷), 144.2 (C⁶), 128.8 (C⁸ + C^{8'}), 128.4 (C¹⁵ + C^{15'}), 123.6 (C¹⁶ + C^{16'}), 122.7 (C⁹), 118.0 (C⁷ + C^{7'}), 69.7 (C⁴), 62.7 (C¹² + C^{12'}), 57.3 (C³), 44.3 (C¹¹ + C^{11'}), 17.6 (C⁵) ppm

M.S. (C.I./CH₄-N₂O) : 426 ([M+H]⁺, 25 %), 293 (40 %), 248 (100 %), 243 (52 %), 161 (19 %), 131 (85 %), 88 ([C₃H₅NO₂+H]⁺, 100 %)

10.3 Synthesis of 1-(4-methoxyphenyl)-6-methyl-2-[(2-oxo-1,3-oxazolan-3-yl)carbonyl]-3-phenyl-1,2,4-triazinan-5-one **182**



Prepared according to the general procedure with azo compound **168f** (0.65 g, 2.040 mmol, 1 eq.) in 9 mL CH₂Cl₂ and azadiene **33b** (1.428 g, 6.119 mmol, 3 eq.), reflux, 1 night.

Purification: Recrystallized in CH₂Cl₂

Rf: 0.56 (AcOEt)

Physical aspect: white solid

M.P.: 118-120 °C

M.F.: C₂₁H₂₂N₄O₅

M.W.: 410.42

Yield: 0.825 g (98.5 %)

HPLC: Chiralcel AD, *i*-PrOH/hexane (30/70), 1 mL/min, λ = 254 nm, t_r = 12.7 min. and t_r = 16.7 min.

I.R.: (KBr, cm⁻¹): 3302 (NH), 3007 (st. Aryl-H), 2836 (CH in -OCH₃), 1783 (CO oxazolidinone), 1700 (CO imide), 1673 (CO lactam), 1510 (C=C st. in Arom.), 1245 (C-O st. in aryl alkyl ether)

¹H NMR (200 MHz, CDCl₃, T = 25 °C)

Proton	δ (ppm)	Mult.	Integ.	J (Hz)
16	7.83	d	2	/
15, 17	7.43	m	3	/
1	7.04	br d	1	³ J ₁₋₄ = 4.0
7, 8	6.78	m	4	/
4	6.36	d	1	³ J ₄₋₁ = 4.0
3	4.97	q	1	³ J ₃₋₅ = 6.7
12	4.36	mult	2	/
11	4.12	mult	1	/
11'	3.81	mult	1	/
18	3.71	s	3	/
5	1.44	d	3	³ J ₅₋₃ = 6.7

^{13}C NMR (50 MHz, CDCl_3 , $T = 25\text{ }^\circ\text{C}$) δ 172.3 (C^2), 156.3 (C^{10}), 155.6 (C^{13}), 153.5 (C^9), 138.8 (C^{14}), 138.3 (C^6), 129.5 ($\text{C}^{16} + \text{C}^{16'}$), 129.1 ($\text{C}^{15} + \text{C}^{15'}$), 128.2 (C^{17}), 121.9 ($\text{C}^8 + \text{C}^{8'}$), 114.7 ($\text{C}^7 + \text{C}^{7'}$), 71.2 (C^4), 63.3 (C^{12}), 58.0 (C^3), 56.0 (C^{18}), 45.1 (C^{11}), 18.0 (C^5) ppm

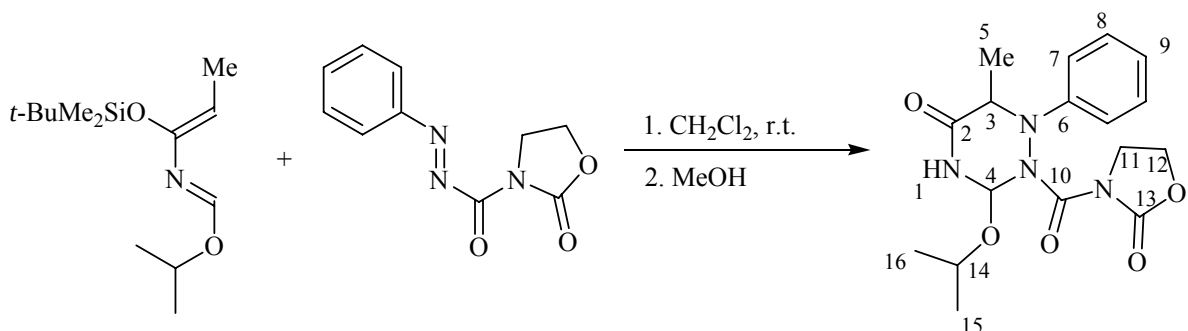
M.S. (C.I./ $\text{CH}_4\text{-N}_2\text{O}$) : 411 ($[\text{M}+\text{H}]^+$, 1 %), 327 ($[\text{M}-\text{C}_3\text{H}_4\text{NO}_2+\text{H}]^+$, 100 %), 191 (37 %), 149 (37 %)

M.S. (EI +Q1MS): 285 (100 %), 268 (55 %), 257 ($[\text{M}-\text{C}_6\text{H}_5-\text{C}_3\text{H}_4\text{NO}_2+\text{H}]^+$, 35 %), 240.5 (17 %), 239 (20 %), 229 ($[\text{M}-\text{C}_6\text{H}_5-\text{C}_4\text{H}_4\text{NO}_3+\text{H}]^+$, 45 %), 226 ($[\text{M}-p\text{-MeOC}_6\text{H}_4-\text{C}_6\text{H}_5]^+$, 7 %)

E.A.:

Element	% calculated	% found	Δ
C	61.45	60.61	0.84
H	5.40	5.16	0.24
N	13.65	13.48	0.17

10.4 Synthesis of 3-isopropoxy-6-methyl-2-[(2-oxo-1,3-oxazolan-3-yl)carbonyl]-1-phenyl-1,2,4-triazinan-5-one **179**



Prepared according to the general procedure with azo compound **168a** (0.1 g, 0.370 mmol, 1 eq.) in 3 mL CH_2Cl_2 and azadiene **29a** (0.190 g, 0.739 mmol, 2 eq.), room temperature, 2 h.

Purification: flash chromatography (AcOEt/cyclohexane: 2/1, then AcOEt)

Rf: 0.53 (AcOEt)

Physical aspect: white solid

M.F.: $\text{C}_{17}\text{H}_{22}\text{N}_4\text{O}_5$

M.W.: 362.38

Yield: 0.13 g (97 %)

HPLC: Chiralcel AD, *i*-PrOH/hexane (20/80), 2 mL/min, $\lambda = 254\text{ nm}$, $t_r = 8.4\text{ min.}$ and $t_r = 13.0\text{ min.}$

I.R.: (film, cm^{-1}): 3297 (NH), 2976 (Aryl-H), 1821 (CO oxazolidinone), 1791 (CO imide), 1699 (CO lactam)

¹H NMR (500 MHz, CDCl₃, T = 50 °C)

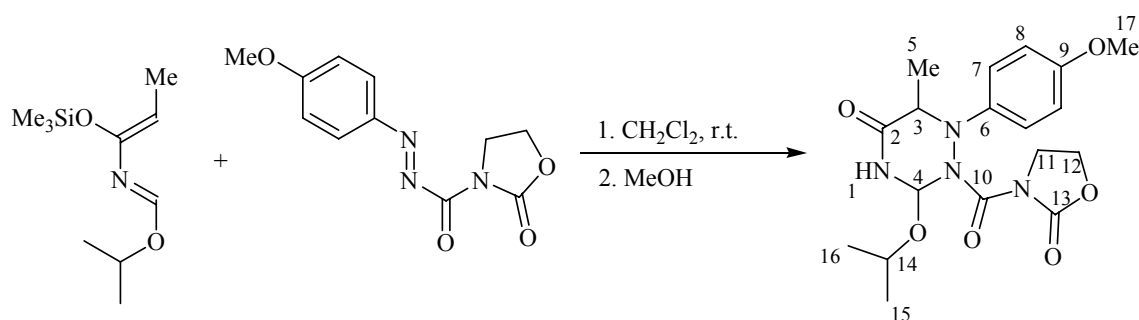
Proton	δ (ppm)	Mult.	Integ.	J (Hz)
8	7.25	mult	2	³ J ₈₋₉ = 7.3
7	7.04	mult	2	⁴ J ₇₋₉ = 1.2
9	6.99	mult	1	³ J ₉₋₈ = 7.3, ⁴ J ₉₋₇ = 1.2
1	6.56	br d	1	³ J ₁₋₄ = 3.1
4	6.44	d	1	³ J ₄₋₁ = 3.1
3	4.65	q	1	³ J ₃₋₅ = 6.7
12	4.31	t	2	³ J ₁₂₋₁₁ = 7.9
14	4.10	m	1	³ J ₁₄₋₁₅ = ³ J ₁₄₋₁₆ = 6.4
11	3.95	t	2	³ J ₁₁₋₁₂ = 7.9
5	1.65	d	3	³ J ₅₋₃ = 6.7
16	1.19	d	3	³ J ₁₆₋₁₄ = 6.4
15	1.07	d	3	³ J ₁₅₋₁₄ = 6.4

¹³C NMR (125 MHz, CDCl₃, T = 50 °C) δ 171.5 (C²), 153.1 (C¹³), 152.8 (C¹⁰), 147.2 (C⁶), 129.1 (C⁸ + C^{8'}), 123.2 (C⁹), 118.7 (C⁷ + C^{7'}), 87.8 (C⁴), 70.1 (C¹⁴), 62.6 (C¹²), 60.5 (C³), 44.6 (C¹¹), 22.6 (C¹⁶), 22.1 (C¹⁵), 14.9 (C⁵) ppm

M.S. (C.I./CH₄-N₂O): 363 ([M+H]⁺, 2 %), 248 ([M-C₄H₄NO₃]⁺, 25 %), 161 (100 %)

HRMS (C.I.): Calculated for C₁₇H₂₃N₄O₅: 363.167718
Found: 363.166845

10.5 Synthesis of 3-isopropoxy-1-(4-methoxyphenyl)-6-methyl-2-[(2-oxo-1,3-oxazolan-3-yl)carbonyl]-1,2,4-triazinan-5-one **180**



Prepared according to the general procedure with azo compound **168f** (0.35 g, 1.404 mmol, 1 eq.) in 4 mL CH₂Cl₂ and azadiene **29a** (0.723 g, 2.808 mmol, 2 eq.), room temperature, 20 h.

Purification: flash chromatography (AcOEt/cyclohexane: 2/1)

R_f: 0.54 (AcOEt)

Physical aspect: white solid

M.P.: 62-64 °C

M.F.: C₁₈H₂₄N₄O₆

M.W.: 392.41

Yield: 0.516 g (94 %)

I.R.: (KBr, cm⁻¹): 3276 (st NH), 2976 (Aryl-H), 2838 (CH in -OCH₃), 1788 (CO oxazolidinone), 1693 (CO lactam), 1510 (st C=C in Arom.), 1034 (st C-O in aryl alkyl ether)

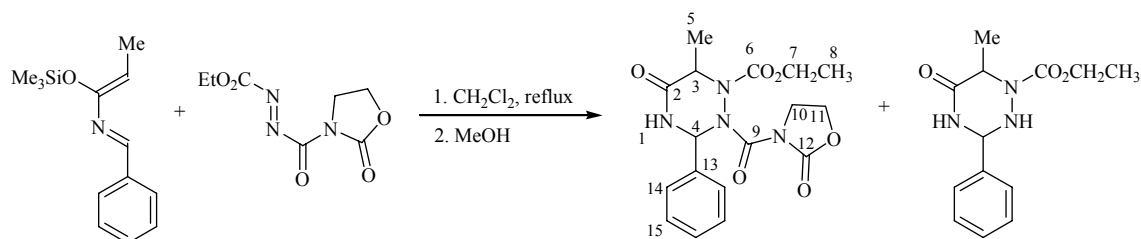
¹H NMR (200 MHz, CDCl₃, T = 25 °C)

Proton	δ (ppm)	Mult.	Integ.	J (Hz)
8	7.04	mult	2	/
7	6.80	mult	2	/
1	6.67	br s	1	/
4	6.43	d	1	³ J ₄₋₁ = 2.8
3	4.59	q	1	³ J ₃₋₅ = 7.1
12	4.39	t	2	³ J ₁₂₋₁₁ = 7.9
11, 14	4.16-3.93	m	3	/
17	3.77	s	3	/
5	1.52	d	3	³ J ₅₋₃ = 7.1
16	1.18	d	3	³ J ₁₆₋₁₄ = 6.1
15	1.00	d	3	³ J ₁₅₋₁₄ = 5.8

¹³C NMR (50 MHz, CDCl₃, T = 25 °C) δ 175.2 (C²), 164.0 (C¹⁰), 163.5 (C¹³), 155.6 (C⁹), 140.5 (C⁶), 116.2 (C⁸), 115.4 (C⁷), 64.0 (C³, C¹⁴), 63.6 (C¹²), 55.9 (C¹⁷), 42.8 (C¹¹), 25.6 (C¹⁵, C¹⁶), 13.5 (C⁵) ppm

M.S. (E.I. +Q1MS) : 277 ([M-C₄H₄NO₃]⁺, 27 %), 199 ([M-*p*-MeOC₆H₄-C₃H₄NO₂]⁺, 100 %), 149 (49 %), 112 ([M-C₃H₇O-C₄H₄NO₃-*p*-MeOC₆H₄]⁺, 8 %)

10.6 Synthesis of ethyl 6-methyl-5-oxo-2-[(2-oxo-1,3-oxazolan-3-yl)carbonyl]-3-phenyl-1,2,4-triazinone-1-carboxylate **184**



Prepared according to the general procedure with azo compound **168d** (0.217 g, 0.958 mmol, 1 eq.) in 4 mL CH₂Cl₂ and azadiene **33b** (0.671 g, 2.874 mmol, 3 eq.), reflux, 1 h.

Purification: Recrystallization in CH₂Cl₂/MeOH at -20 °C and trituration of the filtrate in Et₂O followed by evaporation provided a white solid which is a mixture of **184** and the cycloadduct without the acyl oxazolidinone group **185**.

Yield for 184: 0.164 g (45 %)
for 185: 0.096 g (38 %)

Compound 184:

Rf: 0.54 (AcOEt)

Physical aspect: white solid

M.F.: C₁₇H₂₀N₄O₆

M.W.: 376.36

HPLC: Chiralcel AD, *i*-PrOH/hexane (20/80), 1 mL/min, λ = 220 nm, t_r = 18.3 min. and t_r = 22.1 min.

I.R.: (KBr, cm⁻¹): 3175 (NH), 2983 (Aryl-H), 1791 (CO oxazolidinone), 1730 (CO in CO₂Et), 1709 (CO imide), 1670 (CO lactam), 1464

¹H NMR (500 MHz, CDCl₃, T = 25 °C)

Proton	δ (ppm)	Mult.	Integ.	J (Hz)
15	7.65	d	2	/
1	7.59	br d	1	³ J ₁₋₄ = 4.4
16	7.39	mult	2	/
17	7.37	mult	1	/
4	6.45	d	1	³ J ₄₋₁ = 4.4
3	4.68	q	1	³ J ₃₋₅ = 6.8
12	4.53	dt	1	² J _{12-12'} = ³ J ₁₂₋₁₁ = 8.8, ³ J _{12-11'} = 3.2
12'	4.41	mult	1	² J _{12'-12} = ³ J _{12'-11'} = 8.8, ³ J _{12'-11} = 10.6
11	4.30	mult	1	² J _{11-11'} = ³ J ₁₁₋₁₂ = 8.8, ³ J _{11-12'} = 10.6
19	4.05	q	2	/
11'	3.88	mult	1	² J _{11'-11} = ³ J _{11'-12'} = 8.8, ³ J _{11'-12} = 3.2
5	1.43	d	3	³ J ₅₋₃ = 6.8
20	1.16	t	3	/

¹³C NMR (125 MHz, CDCl₃, T = 25 °C) δ 170.4 (C²), 154.4 (C¹⁰), 152.5 (C¹³), 136.1 (C¹⁴), 128.3 (C¹⁶ + C^{16'}), 127.0 (C¹⁵ + C^{15'}), 69.0 (C⁴), 62.7 (C¹²), 62.3 (C¹⁹), 58.0 (C³), 44.5 (C¹¹), 18.1 (C⁵), 14.2 (C²⁰) ppm, C¹⁸ not seen

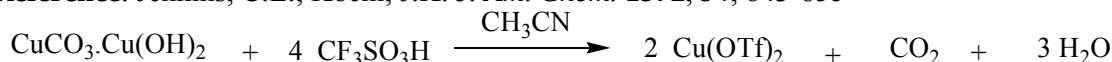
M.S. (E.I. +Q1MS): 246 (60 %), 204 (89 %), 189 ([M-C₃H₅O₂-C₄H₄NO₃]⁺, 100 %), 186 ([M+H-C₄H₄NO₃-C₆H₅]⁺, 56 %)

11 Catalytic asymmetric [4+2] cycloadditions with azo dienophiles

11.1 Synthesis of the chiral catalyst

11.1.1 Synthesis of the copper triflate (II) **119**

Reference: Jenkins, C.L.; Kochi, J.K. *J. Am. Chem.* **1972**, *94*, 843-855



5 g (22.61 mmol, 1 eq.) of cupric carbonate dihydrated was slurried with 200 mL of acetonitrile and 8 mL (90.41 mmol, 4 eq.) of trifluoromethanesulfonic acid was added slowly, as vigorous evolution of carbon dioxide took place. The solution was stirred for 30 min. and filtered; the resulting blue filtrate was concentrated to dryness. The crude salt was rinsed several times with light petroleum ether and then redissolved in acetonitrile. Diethyl ether was added until the solution was cloudy and the solution was allowed to cool to -20°C in a freezer. A light blue precipitate was obtained which was dried under vacuum at 150°C for one night.

R.N. : [34946-82-2]

Physical aspect: white powder

M.F.: $\text{C}_2\text{CuF}_6\text{O}_6\text{S}_2$

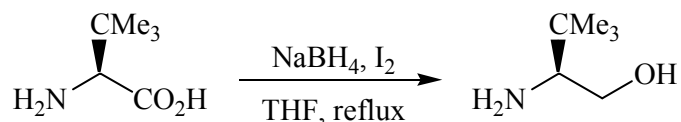
M.W.: 361.67

Yield: 5.7 g (70 %) (lit.: 55 %)

11.1.2 Synthesis of the 2,2-Bis[2-[4(*S*)-*tert*-butyl-1,3-oxazoliny]]propane **120**

11.1.2.1 Synthesis of (*S*)-*tert*-leucinol **122**

Reference: Meyers, A.I.; McKennon, M.J. *J. Org. Chem.* **1993**, *58*, 3568-3571



A three-necked flask, equipped with a mechanical stirrer and an addition funnel, dried under vacuum, was charged with 17.73 g (459.3 mmol, 2.41 eq.) of sodium borohydride and 500 mL of dry THF. The solution was stirred while 25 g (190.6 mmol, 1 eq.) of (*S*)-*tert*-leucine was added in one portion. The flask was cooled to 0°C and fitted with a reflux condenser. The addition funnel was charged with a solution of 48.47 g (190.6 mmol, 1 eq.) of I_2 in 62 mL of THF which was added dropwise to the flask over a 1.5 hour period with considerable gas evolution. The solution was allowed to warm to room temperature. When the brown color had dissipated to give a cloudy white solution, the solution was brought to reflux for 19 hours. The cloudy white suspension was cooled to room temperature with the aid of a water bath. The addition funnel was charged with 46.88 mL of MeOH, which was added dropwise with rapid stirring. Vigorous gas evolution was observed. Small aliquots of MeOH were then

added until all of the solid white material had dissolved. The solution was concentrated by rotary evaporation to give a white pasty oil that was dissolved in 375 mL of 20 % (w/w) aqueous KOH and stirred for 6 h at room temperature. The light green solution was extracted with CH₂Cl₂ (3x450 mL, 1x190 mL). To minimize the emulsion, 60 mL of brine was added to the aqueous layer after extraction. The combined organic extracted were dried over MgSO₄, filtered through glass wool, and concentrated *in vacuo* to give of a white crystalline solid in a thick, slightly yellow oil.

R.N. : [112245-13-3]

Purification: Distillation of the product (70-73 °C/2 mm Hg) furnished the product as a clear oil which solidified upon cooling to room temperature.

Physical aspect: white solid

M.F.: C₆H₁₅NO

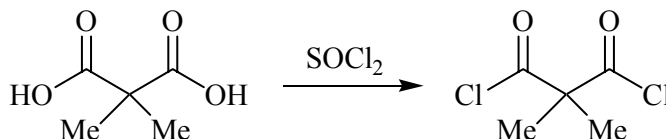
M.W.: 117.19

Yield: 20.77 g (93 %) (lit.: 84 %)

¹H NMR (300 MHz, CDCl₃, T = 25 °C) δ 3.73 (dd, 1H, *J* = 10.3, 3.8 Hz), 3.21 (t, 1H, *J* = 10.3 Hz), 2.51 (dd, 1H, *J* = 10.3, 3.8 Hz), 1.86 (br s, 3H), 0.94 (s, 9H) ppm

11.1.2.2 Synthesis of dimethylmalonyl dichloride **121**

Reference: Evans, D.A.; Woerpel, K.A.; Hinman, M.M.; Faul, M.M. *J. Am. Chem.* **1991**, *113*, 726-728



A flask equipped with an addition funnel and a magnetic stirrer, dried under vacuum, was charged with 10 g (74.18 mmol, 1 eq.) of dimethylmalonic acid and 27.05 mL (370.89 mmol, 5 eq.) of thionyl chloride, was refluxed 24 hours. The excess of thionyl chloride was distilled at atmospheric pressure and the product was distilled under reduced pressure (Eb.t: 75 °C/15 mm Hg).

R.N. : [5659-93-8]

Physical aspect: colorless liquid

M.F.: C₅H₆Cl₂O₂

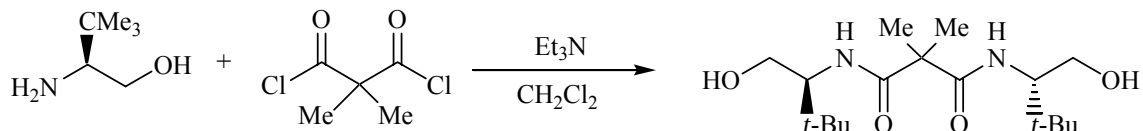
M.W.: 169.00

Yield: 8.99 g (72 %)

¹H NMR (300 MHz, CDCl₃, T = 25 °C) δ 1.70 (s, 6H, (CH₃)₂C) ppm

11.1.2.3 Synthesis of (S)-N,N'-Bis[1-(hydroxymethyl)-2,2-dimethylpropyl]-2,2-dimethyl-1,3-propanediamide **123**

Reference: Evans, D.A.; Peterson, G.S.; Johnson, J.S.; Barnes, D.M.; Campos, K.R.; Woerpel, K.A. *J. Org. Chem.* **1998**, 63, 4541-4544



A three-necked flask, fitted with a magnetic stirrer, dried under vacuum, was charged with a solution of 2.2 g (18.40 mmol, 2 eq.) of (S)-tert-leucinol **122** in 40 mL of CH₂Cl₂. The solution was cooled in an ice bath, and 6.27 mL (45.07 mmol, 4.9 eq.) of triethylamine was added *via* a syringe. A solution of 1.55 g (9.20 mmol, 1 eq.) of dimethylmalonyl chloride **121** in 10 mL of CH₂Cl₂ was slowly added *via* a cannula to the vigorously stirred mixture over 20 minutes. The ice bath was removed, and the thick white suspension was stirred at room temperature for 35 minutes. A few drops of CH₂Cl₂ were added, dissolving most of the white solid. The reaction mixture was washed with 20 mL of 1N HCl, and the aqueous layer was back-extracted with CH₂Cl₂. The combined organic extracts were washed with saturated aqueous NaHCO₃, and the aqueous layer was back-extracted with CH₂Cl₂. The combined organic extracts were dried over MgSO₄, filtered through glass wool, and concentrated *in vacuo* to give a white solid.

R.N. : [131863-76-8]

Physical aspect: white solid

M.F.: C₁₇H₃₄N₂O₄

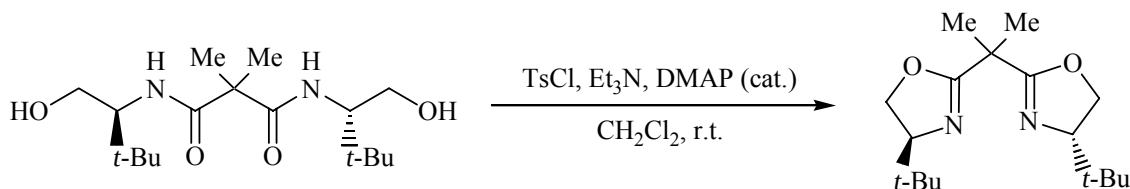
M.W.: 330.46

Yield: 2.42 g (80 %) (lit. : 89 %)

¹H NMR (300 MHz, CDCl₃, T = 25 °C) δ 6.38 (d, 2H, ³J_{HH} = 9.6 Hz, NH), 3.89 (m, 4H, CH₂OH), 3.46 (m, 2H, NHCH), 2.72 (s, 2H, OH), 1.55 (s, 6H, CH₃C), 0.95 (s, 18H, (CH₃)₃C) ppm

11.1.2.4 Synthesis of 2,2-Bis{2-[4(S)-tert-butyl-1,3-oxazolinyl]}propane **120**

Reference: Evans, D.A.; Peterson, G.S.; Johnson, J.S.; Barnes, D.M.; Campos, K.R.; Woerpel, K.A. *J. Org. Chem.* **1998**, 63, 4541-4544



A flask equipped with a magnetic stirrer, was charged with 2.41 g (7.29 mmol, 1 eq.) of dihydroxymalonodiamide, 0.09 g (0.73 mmol, 0.1 eq.) of 4-(dimethylamino)pyridine, and 30 mL of CH₂Cl₂. 4.46 mL (32.09 mmol, 4.4 eq.) of triethylamine was added *via* syringe. The

flask was placed in a room temperature water bath, and a solution of 2.81 g (14.59 mmol, 2 eq.) of *para*-toluenesulfonyl chloride in 10 mL of CH₂Cl₂ was added *via* cannula, followed by one 1 mL CH₂Cl₂ rinse. The bright yellow solution was stirred at room temperature for 27 hours. The solution containing crystalline solid was diluted with 50 mL of CH₂Cl₂, and upon washing with 30 mL of saturated aqueous NH₄Cl, a white solid formed in the aqueous layer. Water (20 mL) was added, the layers were separated, and the aqueous layer was back-extracted with CH₂Cl₂ (3x30 mL). The combined organic extracts were washed with saturated aqueous NaHCO₃. The aqueous layer was back-extracted with CH₂Cl₂ (3x30 mL). The combined organic extracts were dried over MgSO₄, filtered through cotton, and concentrated *in vacuo* to give a yellow-white solid. The resulting solid was triturated with hot pentane (1x50 mL, 1x30 mL, 2x20 mL), followed by hot gravity filtration. The colorless extracts were concentrated *in vacuo* to give a white solid that was recrystallised from pentane to give a white crystalline solid. The mother liquors were purified by flash chromatography (20 % AcOEt/CH₂Cl₂ to 50 % AcOEt/CH₂Cl₂) to give additional product.

R.N. : [131833-93-7]

Physical aspect: white solid

M.F.: C₁₇H₃₀N₂O₂

M.W.: 294.43

Yield: 1.72 g (80.0 %) (lit.: 88 %)

¹H NMR (300 MHz, CDCl₃, T = 25 °C) δ 4.13 (m, 4H, CH₂O), 3.85 (m, 2H, NCH₂*t*-Bu), 1.52 (s, 6H, CH₃C), 0.89 (s, 18H, (CH₃)₃C) ppm

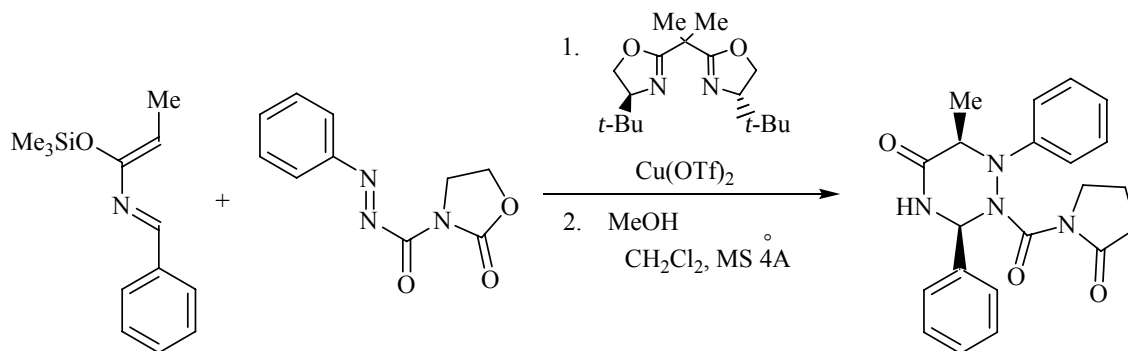
11.2 Catalytic asymmetric [4+2] cycloaddition reactions with azo dienophiles

General procedure

An oven-dried 25 mL round bottom flask containing a magnetic stirring bar and under an inert atmosphere was charged with molecular sieves 4Å in powder, (*S,S*)-*tert*-butylbis(oxazoline) and Cu(OTf)₂. Dry dichloromethane was added *via* syringe and the mixture was stirred for two hours to give a clear green solution.

The green solution was then cooled to -78 °C, and the dienophile in solution in 0.5 mL of dichloromethane was added in one portion *via* syringe. The 2-azadiene was then added *via* syringe through the rubber septum. The solution was stirred at the appropriate temperature during the time required. The reaction mixture was then treated by 2 mL MeOH. After filtration through celite and evaporation of the solvent under reduced pressure, the crude product was purified by flash column chromatography or recrystallization.

11.2.1 Synthesis of (+)-(3*S*,6*R*)-6-methyl-2-[(2-oxo-1,3-oxazolan-3-yl)carbonyl]-1,3-diphenyl-1,2,4-triazinan-5-one **181**



Prepared according to the general procedure with $\text{Cu}(\text{OTf})_2$ (0.020 g, 0.055 mmol, 0.1 eq.), (*S,S*)-*tert*-Bu-box (0.020 g, 0.066 mmol, 0.12 eq.) in 1.5 mL CH_2Cl_2 . Followed by azo compound **168a** (0.12 g, 0.547 mmol, 1 eq.) in 0.5 mL CH_2Cl_2 and azadiene **33b** (0.252 g, 1.095 mmol, 2 eq.), room temperature, 1 h 30.

Purification: flash chromatography (AcOEt)

R_f: 0.4 (AcOEt/cyclohexane: 80/20)

Physical aspect: white crystals

M.P.: 177-178 °C

Yield: 0.198 g (95 %)

M.F.: $\text{C}_{20}\text{H}_{20}\text{N}_4\text{O}_4$

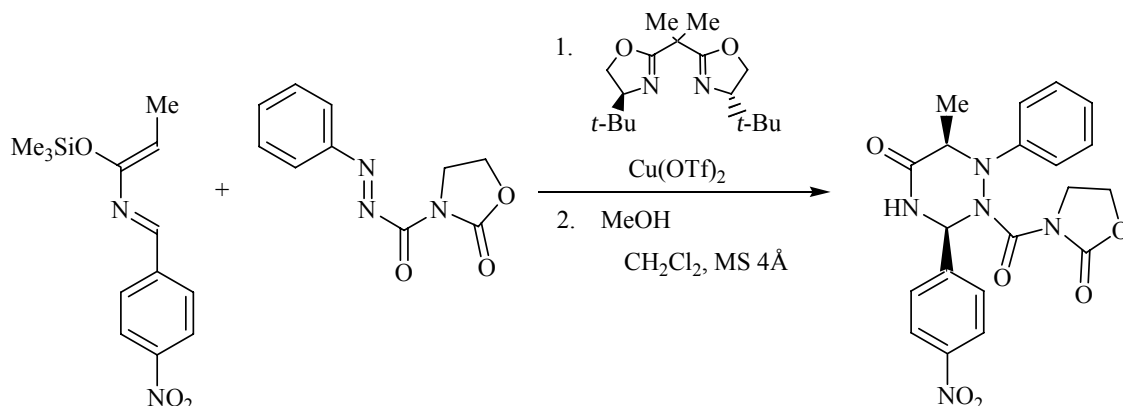
M.W.: 380.4

e.e.: 94 % (Chiralcel AD, EtOH/hexane (13/87), 2 mL/min, $\lambda = 254 \text{ nm}$, $t_{\text{r (maj)}}$ = 13.8 min. and $t_{\text{r (min)}}$ = 19.9 min.)

$[\alpha]_{\text{D}}$ = + 133.3 ° ($c=0.06$, CHCl_3)

The spectroscopic and spectrometric data are described for the thermal reaction.

11.2.2 Synthesis of the (+)-(3*S*,6*R*)-6-methyl-3-(4-nitrophenyl)-2-[(2-oxo-1,3-oxazolan-3-yl)carbonyl]-1-phenyl-1,2,4-triazinan-5-one **183**



Prepared according to the general procedure with $\text{Cu}(\text{OTf})_2$ (0.033 g, 0.091 mmol, 0.1 eq.), (*S,S*)-*tert*-Bu-box (0.032 g, 0.109 mmol, 0.12 eq.) in 1.5 mL CH_2Cl_2 . Followed by azo compound **168a** (0.200 g, 0.91 mmol, 1 eq.) in 0.5 mL CH_2Cl_2 and azadiene **33c** (0.508 g, 1.82 mmol, 2 eq.) dissolved in 1 mL CH_2Cl_2 , room temperature, 2 h 30.

Purification: flash chromatography (AcOEt) followed by recrystallization in AcOEt

Rf: 0.2 (AcOEt)

Physical aspect: beige crystals

M.P.: 130 °C

Yield: 0.304 g (78 %)

M.F.: $\text{C}_{20}\text{H}_{19}\text{N}_5\text{O}_6$

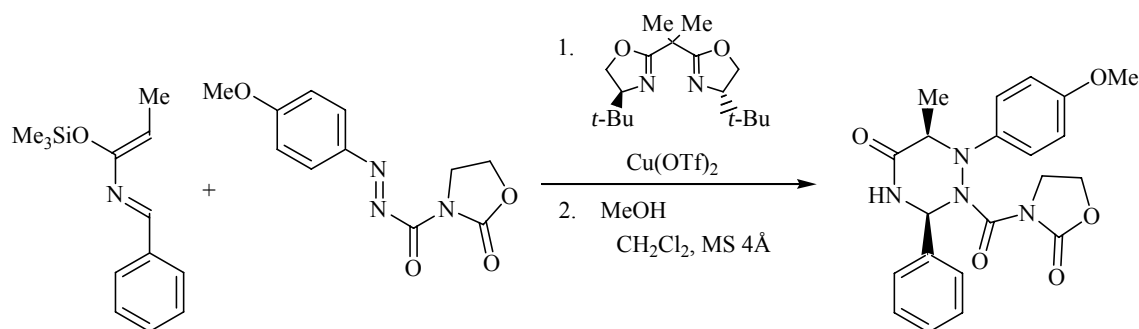
M.W.: 425.4

e.e.: 99 % (Chiralcel AD, *i*-PrOH/hexane (30/70), 1 mL/min, $\lambda = 254$ nm, $t_{\text{r (min)}} = 9.5$ min. and $t_{\text{r (maj)}} = 12.2$ min.)

$[\alpha]_{\text{D}} = +160^\circ$ ($c = 0.6$, CH_2Cl_2)

The spectroscopic and spectrometric data are described for the thermal reaction.

11.2.3 Synthesis of (+)-(3*S*,6*R*)-1-(4-methoxyphenyl)-6-methyl-2-[(2-oxo-1,3-oxazolan-3-yl)carbonyl]-3-phenyl-1,2,4-triazinan-5-one **182**



Prepared according to the general procedure with $\text{Cu}(\text{OTf})_2$ (0.045 g, 0.124 mmol, 0.1 eq.), (*S,S*)-*tert*-Bu-box (0.044 g, 0.149 mmol, 0.12 eq.) in 3.5 mL CH_2Cl_2 . Followed by azo compound **168f** (0.310 g, 1.24 mmol, 1 eq.) in 2 mL CH_2Cl_2 . The mixture is first warmed to 10 °C, and then azadiene **33b** (0.435 g, 1.87 mmol, 1.5 eq.) is added dropwise. After 1 h 30 at room temperature, a second portion of azadiene **33b** (0.435 g, 1.87 mmol, 1.5 eq.) is added. Room temperature, 21 h.

Purification: flash chromatography (AcOEt/cyclohexane: 2/1, then AcOEt, followed by AcOEt +15 % *i*-PrOH)

Rf: 0.56 (AcOEt)

Physical aspect: white solid

M.P.: 118-120 °C

Yield: 0.447 g (87.5 %)

M.F.: $\text{C}_{21}\text{H}_{22}\text{N}_4\text{O}_5$

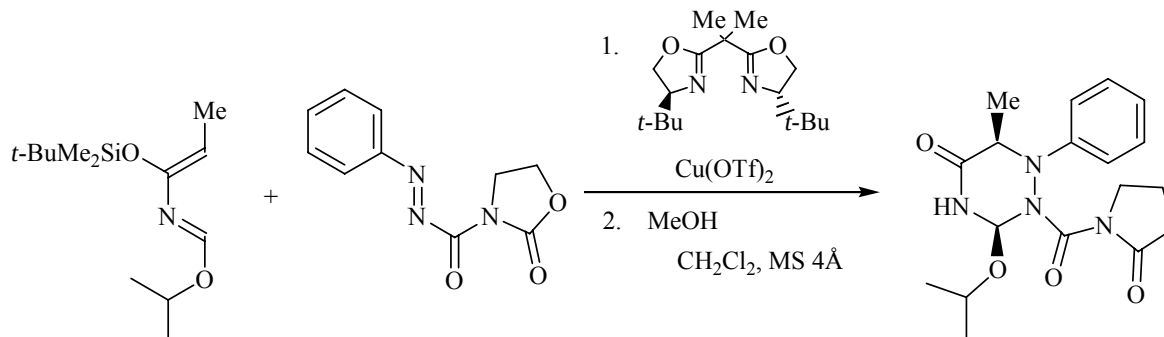
M.W.: 410.42

e.e.: 99 % (Chiralcel AD, *i*-PrOH/hexane (30/70), 1 mL/min, $\lambda = 254 \text{ nm}$, $t_{\text{r}} (\text{min}) = 12.6 \text{ min.}$ and $t_{\text{r}} (\text{maj}) = 16.3 \text{ min.}$)

$[\alpha]_{\text{D}} = +261.5^\circ$ ($c=0.065$, CHCl_3)

The spectroscopic and spectrometric data are described for the thermal reaction.

11.2.4 Synthesis of the (-)-(3*S*,6*R*)-3-isopropoxy-6-methyl-2-[(2-oxo-1,3-oxazolan-3-yl)carbonyl]-1-phenyl-1,2,4-triazinan-5-one **179**



Prepared according to the general procedure with Cu(OTf)₂ (0.033 g, 0.091 mmol, 0.1 eq.), (*S,S*)-*tert*-Bu-box (0.032 g, 0.109 mmol, 0.12 eq.) in 1.5 mL CH₂Cl₂. Followed by azo compound **168a** (0.200 g, 0.91 mmol, 1 eq.) in 0.5 mL CH₂Cl₂ and azadiene **29a** (0.470 g, 1.82 mmol, 2 eq.), -78 °C, 30 min..

Purification: flash chromatography (AcOEt/cyclohexane: 2/1, then AcOEt)

Rf: 0.53 (AcOEt)

Physical aspect: white solid

Yield: 0.26 g (79 %)

M.F.: C₁₇H₂₂N₄O₅

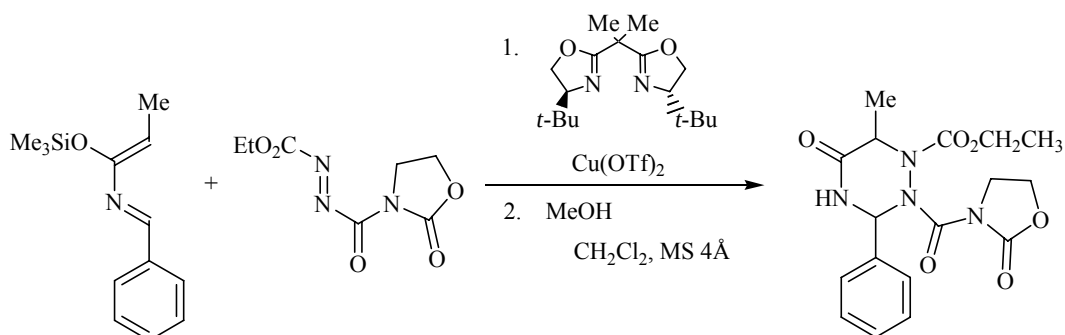
M.W.: 362.38

e.e.: 97 % (Chiralcel AD, *i*-PrOH/hexane (20/80), 2 mL/min, λ = 254 nm, t_r (min) = 8.3 min. and t_r (maj) = 12.8 min.)

[α]_D = -52 ° (c = 0.6, CHCl₃)

The spectroscopic and spectrometric data are described for the thermal reaction.

11.2.5 Synthesis of ethyl 6-methyl-5-oxo-2-[(2-oxo-1,3-oxazolan-3-yl) carbonyl]-3-phenyl-1,2,4-triazinone-1-carboxylate **184**



Prepared according to the general procedure with $\text{Cu}(\text{OTf})_2$ (0.032 g, 0.088 mmol, 0.1 eq.), (*S,S*)-*tert*-Bu-box (0.031 g, 0.106 mmol, 0.12 eq.) in 1.5 mL CH_2Cl_2 . Followed by azo compound **168d** (0.200 g, 0.88 mmol, 1 eq.) in 1.5 mL CH_2Cl_2 and azadiene **33b** (0.412 g, 1.77 mmol, 2 eq.), $-78\text{ }^\circ\text{C}$, 1 h 30.

Purification: Recrystallization in CH_2Cl_2

Rf: 0.54 (AcOEt)

Physical aspect: white solid

M.F.: $\text{C}_{17}\text{H}_{20}\text{N}_4\text{O}_6$

M.W.: 376.36

Yield: 0.160 g (48 %)

e.e.: 0 % (Chiralcel AD, *i*-PrOH/hexane (20/80), 1 mL/min, $\lambda = 220\text{ nm}$, $t_r = 18.5\text{ min.}$ and $t_r = 22.2\text{ min.}$)

The spectroscopic and spectrometric data are described for the thermal reaction.

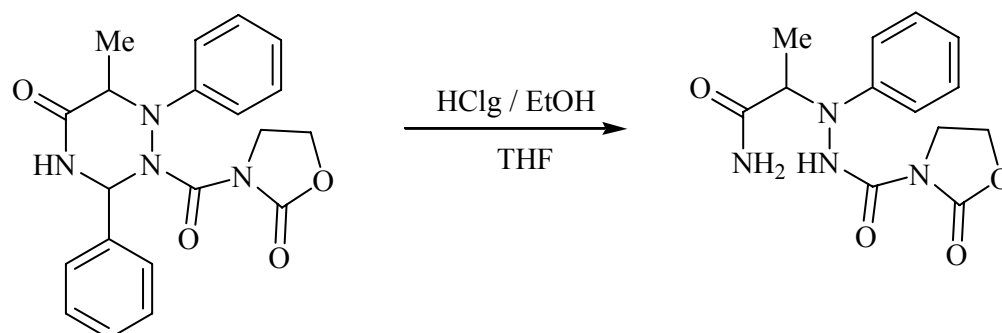
12 Modification of the cycloadducts

12.1 Hydrolysis of the cycloadducts

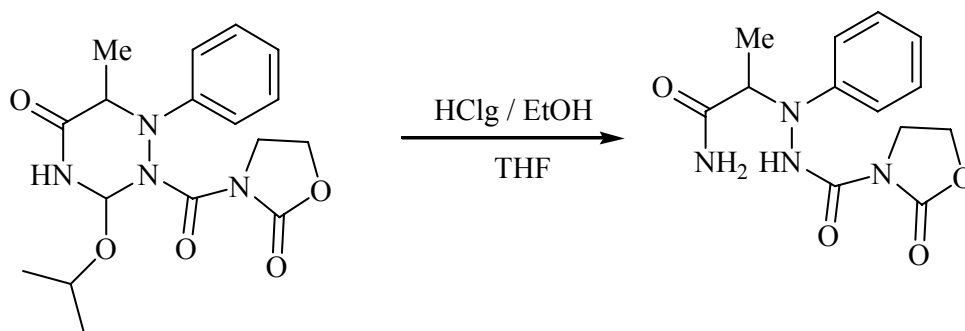
General procedure

A mixture of the cycloadduct (1 eq.) in THF and 4 mL of a 3 M solution of HCl in ethanol was allowed to stay at $80\text{ }^\circ\text{C}$ for several hours. Evaporation of the solvents gave a residue which was purified by flash chromatography on silica gel.

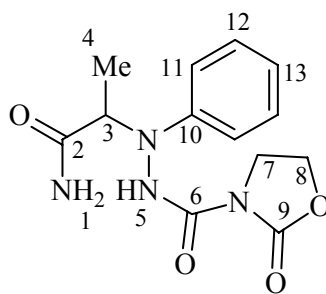
12.1.1 Synthesis of the 2-[*N'*-(2-Oxo-oxazolidine-3-carbonyl)-*N*-phenyl-hydrazino]-propionamide **188** starting from **181**



Prepared according to the general procedure with cycloadduct **181** (0.3 g, 0.789 mmol, 1 eq.) in 1 mL THF, 2.63 mL of a 3 M solution of HCl/EtOH, 15 hours at $80\text{ }^\circ\text{C}$. Purification by flash chromatography (AcOEt, AcOEt + 10 % *i*-PrOH) provided **188** (0.150 g, 65 %).

12.1.2 Synthesis of **188** starting from **179**

Prepared according to the general procedure with cycloadduct **179** (0.170 g, 0.469 mmol, 1 eq.) in 2 mL THF, 1.7 mL of a 3 M solution of HCl/EtOH, 23 hours at room temperature. Purification by flash chromatography (AcOEt, AcOEt + 10 % *i*-PrOH) provided **188** (0.054 g, 39 %).

188

Rf: 0.32 (AcOEt)

Physical aspect: beige solid

M.F.: C₁₃H₁₆N₄O₄

M.W.: 292.29

I.R. (KBr, cm⁻¹): 3434-3296 (st NH and NH₂), 2986 (st alipatic CH), 1761 (st CO oxazolidinone), 1684 (st CO amide and imide), 1501 (st C=C in Arom.)

¹H NMR (500 MHz, DMSO, T = 47 °C)

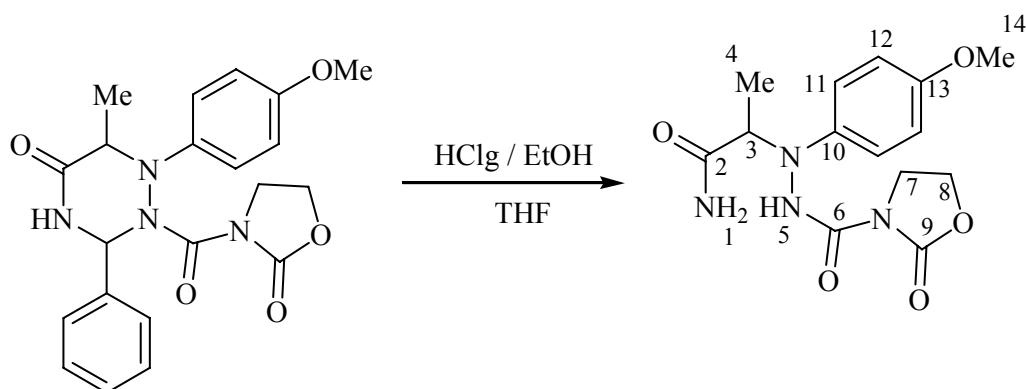
Proton	δ (ppm)	Mult.	Integ.	J (Hz)
5	9.83	br s	1	/
1	7.64	br s	1	/
12	7.20	mult	2	³ J ₁₂₋₁₃ = 8.1
1'	6.96	br s	1	/
11, 13	6.80	m	3	/
8	4.45	t	2	³ J ₈₋₇ = 8.1
3	4.39	q	1	³ J ₄₋₃ = 7.1
7	3.95	t	2	³ J ₇₋₈ = 8.1
4	1.37	d	3	³ J ₄₋₃ = 7.1

^{13}C NMR (125 MHz, DMSO, T = 47 °C) δ 174.8 (C²), 154.8 (C⁹), 128.5 (C¹²), 119.1 (C¹³), 112.9 (C¹¹), 62.9 (C⁸), 42.3 (C⁷), 15.2 (C⁴) ppm (C⁶, C³ and C¹⁰ not seen).

M.S. (C.I./CH₄-N₂O): 293 ([M+H]⁺, 1 %), 163 ([M-C₄H₅N₂O₃]⁺, 14 %), 131 (C₄H₇N₂O₃⁺, 37 %), 88 (C₃H₆NO₂⁺, 77 %)

HRMS: Calculated for C₁₃H₁₇N₄O₄: 293.1245
Found: 293.1250

12.1.3 Synthesis of the 2-[N-(4-Methoxy-phenyl)-N'-(2-oxo-oxazolidine-3-carbonyl)-hydrazino]-propionamide **189**



Prepared according to the general procedure with cycloadduct **182** (0.5 g, 1.218 mmol, 1 eq.) in 13 mL THF, 2.4 mL of a 3 M solution of HCl/EtOH, 15 h 30 at 70 °C.

Purification: flash chromatography (AcOEt, AcOEt + 10 % *i*-PrOH)

R_f: 0.31 (AcOEt)

Physical aspect: white solid

M.P.: 84-85 °C

M.F.: C₁₈H₁₈N₄O₅

M.W.: 322.32

Yield: 0.290 g (74 %)

I.R. (KBr, cm⁻¹): 3295 (st NH and NH₂), 2995 (st alipatic CH), 2925 (st CH in Arom.), 2836 (st OCH₃), 1758 (st CO oxazolidinone), 1683 (st CO amide and imide), 1511 (st C=C in Arom.)

^1H NMR (200 MHz, CDCl₃, T = 25 °C)

Proton	δ (ppm)	Mult.	Integ.	J (Hz)
5	9.51	br s	1	/
1	8.24	br s	1	/
11, 12	6.85	m	4	/

Proton	δ (ppm)	Mult.	Integ.	J (Hz)
1'	5.38	br s	1	/
8	4.54	t	2	$^3J_{8-7} = 8.2$
7, 3	4.11	m	3	/
14	3.76	s	3	/
4	1.45	d	3	$^3J_{4-3} = 7.2$

^{13}C NMR (50 MHz, CDCl_3 , T = 25 °C) δ 176.2 (C^2), 155.7 (C^6), 155.0 (C^9), 153.5 (C^{13}), 141.4 (C^{10}), 116.1 (C^{12}), 115.0 (C^{11}), 63.5 (C^3), 63.4 (C^8), 55.8 (C^{14}), 42.6 (C^7), 13.9 (C^4) ppm

M.S. (C.I./ $\text{CH}_4\text{-N}_2\text{O}$): 351 ($[\text{M}+\text{C}_2\text{H}_5]^+$, 5 %), 323 ($[\text{M}+\text{H}]^+$, 14 %), 322 (M^+ , 23 %), 278 (12 %), 194 ($\text{C}_{10}\text{H}_{14}\text{N}_2\text{O}_2^+$, 45 %), 150 (95 %), 131 ($\text{C}_4\text{H}_7\text{N}_2\text{O}_3^+$, 49 %), 88 ($\text{C}_3\text{H}_6\text{NO}_2^+$, 67 %)

HRMS: Calculated for $\text{C}_{18}\text{H}_{18}\text{N}_4\text{O}_5$: 322.128424

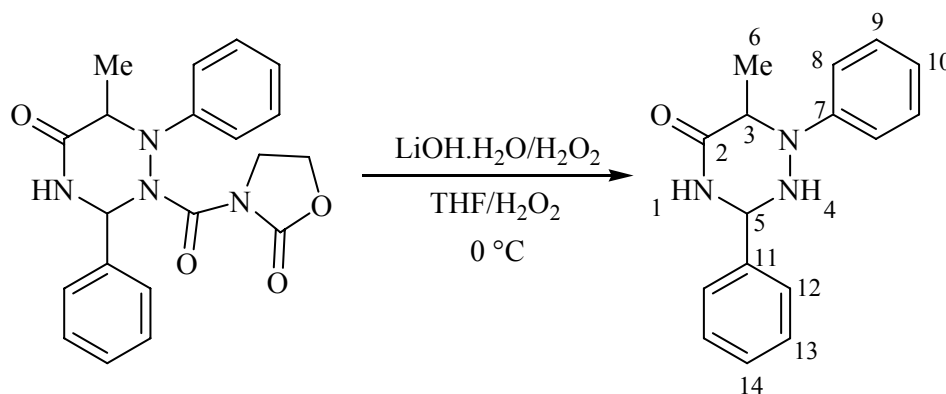
Found: 322.127720

12.2 Cleavage of the acyloxazolidinone group

General procedure

To a solution of the cycloadduct (1 eq.) in THF/ H_2O cooled to 0 °C was added 30 % H_2O_2 (ca. 4 eq.) followed by lithium hydroxide monohydrate (3 eq.). The mixture was stirred at 0 °C for 30 minutes to 1 hour, and then treated with aqueous Na_2SO_3 . Saturated aqueous NH_4Cl was added and the mixture was extracted with CH_2Cl_2 . The organic layer was washed with saturated NaHCO_3 and brine, dried over MgSO_4 , and concentrated to give the product. Purification by flash chromatography afforded the desired product.

12.2.1 Synthesis of 6-Methyl-1,3-diphenyl-[1,2,4]-triazinan-5-one **190**



Prepared according to the general procedure with cycloadduct **181** (0.2 g, 0.526 mmol, 1 eq.) in THF/ H_2O (3 mL/1 mL), H_2O_2 (30 %) (0.211 mL, 2.103 mmol), lithium hydroxide monohydrate (0.045 g, 1.052 mmol, 3 eq.), 45 min. at 0 °C, treated with aqueous Na_2SO_3 (0.3 g in 4 mL H_2O).

Purification: Flash chromatography (AcOEt/cyclohexane: 1/1)

Rf: 0.61 (AcOEt/cyclohexane: 1/1)

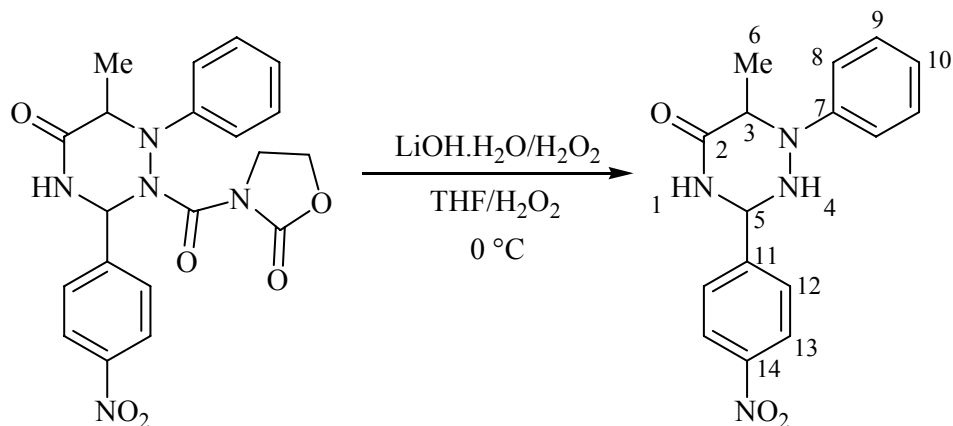
Physical aspect: white solid

M.P.: 155 °C**M.F.:** C₁₆H₁₇N₃O**M.W.:** 267.33**Yield:** 0.081 g (58 %)**I.R.** (KBr, cm⁻¹): 3199 (st NH), 3061-3034 (st aryl-H), 2971, 1671 (st CO lactam), 1598, 1499 (st C=C in Arom.)**¹H NMR** (300 MHz, CDCl₃, T = 25 °C)

Proton	δ (ppm)	Mult.	Integ.	J (Hz)
12, 13, 14	7.6-7.4	m	5	/
8	7.23	mult	2	/
9	7.07	mult	2	/
10	6.85	mult	1	/
1	6.60	br s	1	/
4	5.60	d	1	³ J ₄₋₅ = 11.8
3	4.51	q	1	³ J ₃₋₆ = 7.0
5	3.53	d	1	³ J ₅₋₄ = 11.8
6	1.37	d	3	³ J ₆₋₃ = 7.0

¹³C NMR (50 MHz, CDCl₃, T = 25 °C) δ 172.3 (C²), 147.9 (C⁷), 137.3 (C¹¹), 129.8-130.5 (C⁹ + C¹³ + C¹⁴), 127.5 (C¹²), 120.5 (C¹⁰), 114.6 (C⁸), 71.7 (C⁵), 56.4 (C³), 12.7 (C⁶) ppm**M.S.** (C.I. /CH₄-N₂O): 296 ([M+C₂H₅]⁺, 6 %), 268 ([M+H]⁺, 100 %), 267 (M⁺, 75 %), 223 (25 %)**HRMS:** Calculated for C₁₆H₁₇N₃O: 267.134952

Found: 267.137162

12.2.2 Synthesis of 6-Methyl-3-(4-nitro-phenyl)-1-phenyl-[1,2,4]-triazinan-5-one **191**

Prepared according to the general procedure with cycloadduct **183** (0.1 g, 0.235 mmol, 1 eq.) in THF/H₂O (3 mL/1 mL), H₂O₂ (30%) (0.094 mL, 0.94 mmol), lithium hydroxide monohydrate (0.030 g, 0.705 mmol, 3 eq.), 1 hour at 0 °C, treated with aqueous Na₂SO₃ (0.15 g in 2 mL H₂O).

Purification: Flash chromatography (AcOEt/cyclohexane: 2/1, AcOEt)

Rf: 0.71 (AcOEt)

Physical aspect: orange oil

F.B.: C₁₆H₁₆N₄O₃

M.W.: 312.32

Yield: 0.05 g (68 %)

I.R. (KBr, cm⁻¹): 3201 and 3067 (st NH), 1672 (CO lactam), 1598, 1521 (st N=O)

¹H NMR (500 MHz, CDCl₃, T = 25 °C)

Proton	δ (ppm)	Mult.	Integ.	J (Hz)
13	8.16	m	2	/
12	7.64	m	2	/
9	7.47	m	2	/
5	7.34	m	1	/
10	7.32	m	1	/
8	7.26	m	2	/
4	6.37	br s	1	/
1	5.74	br s	1	/
3	4.51	q	1	³ J ₃₋₆ = 7.4
6	1.60	d	3	³ J ₆₋₃ = 7.4

¹³C NMR (125 MHz, CDCl₃, T = 25 °C) δ 174.55 (C²), 146.83 (C¹⁴), 143.33 (C⁷), 142.01 (C¹¹), 132.66 (C⁵), 129.96 (C⁹), 127.02 (C¹⁰), 125.98 (C¹²), 124.93 (C⁸), 123.94 (C¹³), 63.61 (C³), 15.05 (C⁶) ppm

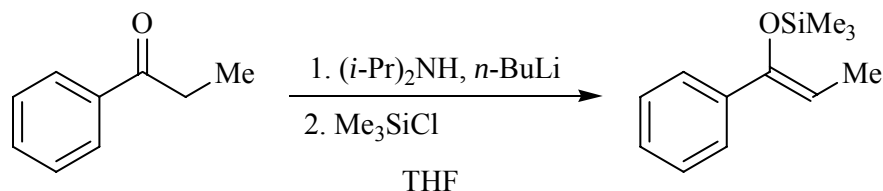
M.S. (C.I. /CH₄-N₂O): 313 ([M+H]⁺, 50 %), 295 (100 %), 195 ([M-C₆H₄NO₂]⁺⁺, 22 %)

13 Electrophilic amination reactions of silyl enols ethers

13.1 Synthesis of the reagents

13.1.1 Synthesis of (Z)-1-Phenyl-1-(trimethylsiloxy)-1-propene **196**

Reference: Heathcock, C. H.; Davidsen, S. K.; Hug, K. T.; Flippin, L. A. *J. Org. Chem.* **1986**, *51*, 3027-37



To a solution of diisopropylamine (12.5 mL, 89.3 mmol, 1.2 eq.) in dry THF (80 mL) cooled to 0 °C was added *n*-BuLi (40.8 mL, 85.6 mmol, 1.15 eq., 2.1 M in hexanes). After 15 min., the mixture was cooled to –78 °C and the propiophenone (10 mL, 74.4 mmol, 1 eq.) was added. After 20 min., chlorotrimethylsilane (11.6 mL, 89.3 mmol, 1.2 eq.) was added. The solution was stirred at –78 °C for 1 hour, and then allowed to warm at room temperature and stirred for 4 hours. A saturated aqueous NH₄Cl solution (pH 8) was added to the reaction mixture, and the aqueous layer was extracted with Et₂O (3X). The combined organic layers were washed with a saturated aqueous NaCl solution, dried over MgSO₄, and concentrated *in vacuo*. Distillation (75 °C/4 10^{–1} mbar) afforded the enolsilane **196**.

R.N.: [66323-99-7]

Physical aspect: clear liquid

M.F.: C₁₂H₁₈OSi

M.W.: 206.35

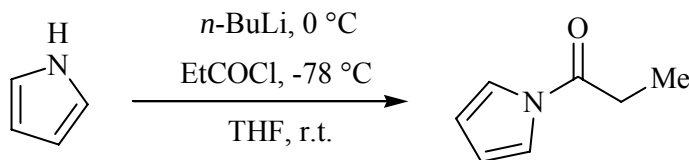
Yield: 10.4 g (68 %)

¹H NMR (200 MHz, CDCl₃, T = 25 °C) δ 7.20-7.48 (m, 5H, CH_{ar}), 5.33 (q, 1H, CHCH₃, ³J = 7 Hz), 1.73 (d, 3H, CHCH₃, ³J = 7 Hz), 0.10 (s, 9H, OSi(CH₃)₃) ppm

13.1.2 Synthesis of (Z)-1-pyrrolyl-1-trimethylsilyloxyprop-1-ene **199**

13.1.2.1 Synthesis of 1-pyrrolylpropan-1-one **200**

Reference: Evans, D. A.; Johnson, D. S. *Org. Lett.* **1999**, *1*, 595-598



To a solution of freshly distilled pyrrole (6.27 mL, 90.32 mmol, 1.05 eq.) in THF (100 mL) cooled to 0 °C, was added *n*-BuLi (36.04 mL, 90.09 mmol, 1.05 eq., 2.5 M in hexanes). After 15 min., the solution was cooled to –78 °C and it became a slurry. The propionyl chloride

(7.45 mL, 85.8 mmol, 1 eq.) was added as a solution in THF (25 mL) quickly *via* cannula and the reaction immediately became homogenous. After 30 min. at $-78\text{ }^{\circ}\text{C}$, the reaction was warmed to room temperature and stirred overnight. The reaction was poured into a separatory funnel containing Et_2O and water. The organic layer was washed with water (2X) and brine (2X), dried over MgSO_4 , and concentrated to give a brown liquid.

Purification: Distillation ($83\text{--}85\text{ }^{\circ}\text{C}$, 16 mm Hg)

R.N.: [59303-16-1]

Physical aspect: clear liquid

M.F.: $\text{C}_7\text{H}_9\text{NO}$

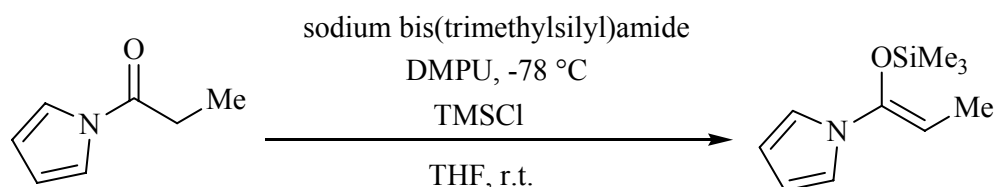
M.W.: 123.15

Yield: 7.12 g (67 %) (lit.: 63 %)

^1H NMR (200 MHz, CDCl_3 , $T = 25\text{ }^{\circ}\text{C}$) δ 7.22 (br s, 2H), 6.20 (t, 2H, $^3J = 2.4\text{ Hz}$), 2.75 (q, 2H, $^3J = 7.4\text{ Hz}$), 1.21 (t, 3H, $^3J = 7.3\text{ Hz}$) ppm

13.1.2.2 Synthesis of (Z)-1-pyrrolyl-1-trimethylsilyloxyprop-1-ene **199**

Reference: Evans, D. A.; Johnson, D. S. *Org. Lett.* **1999**, 1, 595-598



To a solution of sodium bis(trimethylsilyl)amide (27.11 mL, 27.11 mmol, 1.1 eq., 1 M in THF) in THF (10 mL) cooled to $-78\text{ }^{\circ}\text{C}$, was added DMPU (3.91 mL, 32.49 mmol, 1.3 eq.) followed by acylpyrrole **200** (3.04 g, 24.64 mmol, 1 eq.) in THF (8 mL). After 20 min., chlorotrimethylsilane (4.38 mL, 34.5 mmol, 1.4 eq.) was added. The reaction mixture became viscous. After 30 min. at $-78\text{ }^{\circ}\text{C}$, the mixture was allowed to warm to room temperature and stirred overnight. The reaction mixture was partitioned between pentane and pH 7 phosphate buffer. The organic layer was washed with pH 7 phosphate buffer (several times), 0.5 M aqueous CuSO_4 , pH 7 phosphate buffer and brine, dried over Na_2SO_4 , and concentrated *in vacuo*.

Purification: Distillation ($54\text{ }^{\circ}\text{C}$, 2 mm Hg). Unfortunately, a considerable loss of product occurred during the distillation, and some starting material could not be separated.

R.N.: [244091-17-6]

Physical aspect: clear liquid

M.F.: $\text{C}_{10}\text{H}_{17}\text{NOSi}$

M.W.: 195.33

Yield: 3.6 g (45 %) (mixture of **199/200**: 73/27) (lit.: 95 %)

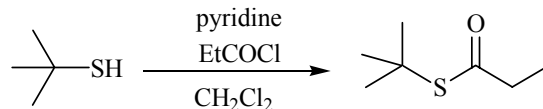
The enolsilane will be used so.

¹H NMR (200 MHz, CDCl₃, T = 25 °C) δ 6.84 (t, 2H, ³J = 2.2 Hz), 6.15 (t, 2H, ³J = 2.2 Hz), 4.71 (q, 1H, ³J = 6.9 Hz), 1.66 (d, 3H, ³J = 6.9 Hz), 0.17 (s, 9H) ppm

13.1.3 Synthesis of (*E*)-1-(*tert*-butylthio)-1-trimethylsilyloxyprop-1-ene **201**

13.1.3.1 Synthesis of the *tert*-butylthiopropionate **202**

Reference: Evans, D. A.; Johnson, D. S. *Org. Lett.* **1999**, 1, 595-598. Gennari, C.; Grazia, Beretta, M.; Bernardi, A. ; Moro, G. ; Scolastico, C. and Todeschini, R. *Tetrahedron* **1986**, 42, 893-909



In a round bottom flask, equipped with septum and an addition funnel, previously dried and placed under an argon atmosphere, 2-methyl-2-propanethiol (10 mL, 87.82 mmol, 1 eq.), and pyridine (7.12 mL, 87.82 mmol, 1 eq.) were added at room temperature. Then propionyl chloride (7.79 mL, 87.82 mmol, 1 eq.) was added dropwise to this mixture at room temperature. The reacting mixture was stirred for two hours at this temperature. The solution was then diluted with dichloromethane and dropped on water. The phases were separated and the aqueous phase was extracted with dichloromethane. The organic layers were washed were combined and washed with 5 % HCl aq., water, brine and dried over Na₂SO₄, and concentrated under reduced pressure. A clear liquid was obtained.

Purification: horizontal distillation (46 °C / 16 mmHg)

R.N.: [61540-13-4]

Physical aspect: colourless liquid

M.F.: C₇H₁₄OS

M.W.: 146.24

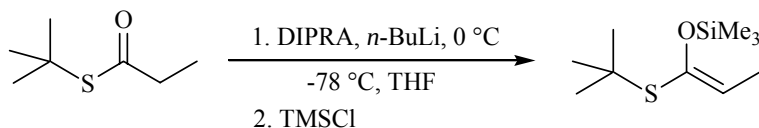
Yield: 7.80 g (61 %)

¹H NMR (200 MHz, CDCl₃, T = 25 °C) δ 2.48 (q, 2H, ³J = 7.6 Hz, CH₂), 1.47 (s, 9H, (CH₃)₃CS), 1.13 (t, 3H, ³J = 7.4 Hz, CH₃) ppm

¹³C NMR (50 MHz, CDCl₃, T = 25 °C) δ 201.7 (SCO), 48.2 (CH₃)₃CS), 38.4 (CH₂), 30.4 (CH₃)₃CS), 10.1 (CH₃) ppm

13.1.3.2 Synthesis of (E)-1-(tert-butylthio)-1-trimethylsilyloxyprop-1-ene **201**

Reference: Evans, D. A.; Johnson, D. S. *Org. Lett.* **1999**, *1*, 595-598. Gennari, C.; Grazia, Beretta, M.; Bernardi, A.; Moro, G.; Scolastico, C. and Todeschini, R. *Tetrahedron* **1986**, *42*, 893-909



To a solution of diisopropylamine (1.40 mL, 10.0 mmol, 1 eq.) in THF (10 mL) cooled to 0 °C was added *n*-BuLi (5.31 mL, 10.0 mmol, 1 eq., 1.88 M in hexanes). After 15 min., the mixture was cooled to –78 °C and HMPA (3.5 mL) was added. Freshly distilled *tert*-butylthiopropionate (2.19 g, 15.0 mmol, 1.5 eq.) was added as a solution in THF (10 mL) and HMPA (3 mL) *via* cannula over 2 minutes. After 20 min., chlorotrimethylsilane (1.52 mL, 12.0 mmol, 1.2 eq.) was added as a solution in hexanes. The solution was stirred at –78 °C for 30 min. and then allowed to warm to room temperature and stir for 2 hours. The reaction mixture was partitioned between pentane and pH 7 phosphate buffer. The organic layer was washed with pH 7 phosphate buffer (3X), 0.5 M aqueous CuSO₄ (5X), pH 7 phosphate buffer (2X) and brine, dried over MgSO₄, and concentrated *in vacuo*. A clear liquid was isolated.

Purification: Distillation (62 °C, 8 mm Hg)

R.N.: [76943-95-8]

Physical aspect: clear liquid

M.F.: C₁₀H₂₂OSSi

M.W.: 218.42

Yield: 1.87 g (85 %)

¹H NMR (200 MHz, CDCl₃, T = 25 °C) δ 5.27 (q, 1H, CH, ³J = 6.8 Hz), 1.62 (d, 3H, CH₃, ³J = 6.8 Hz), 1.35 (s, 9H, (CH₃)₃CS), 0.27 (s, 9H, Me₃Si) ppm

13.2 Catalytic electrophilic amination reactions of silyl enols ethers

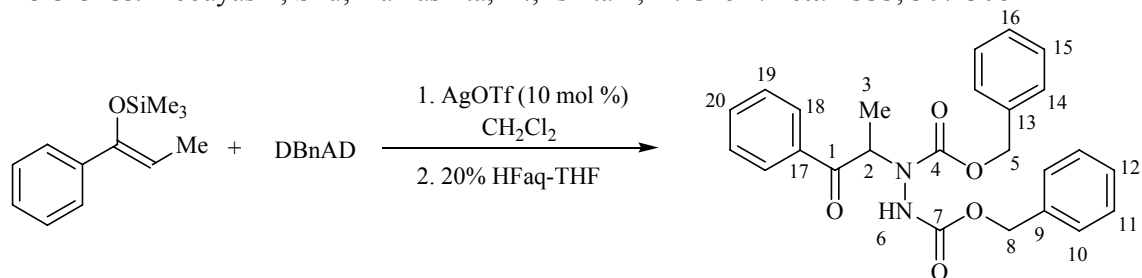
13.2.1 Synthesis of amination products **197** and **204**

General procedure for the synthesis of amination products **197** and **204**

To a stirred suspension of AgOTf (0.1 eq. in CH₂Cl₂) was added the azo compound (1.1 eq. in CH₂Cl₂) at 0 °C. After stirring for 10 min., the silyl enol ether (1 eq. in CH₂Cl₂) was added dropwise, and the mixture was stirred at the temperature and the time described. A 20 % HF_(aq)-THF (1:1) solution was then added and the mixture was stirred for 1 hour at room temperature. After being basified with saturated aq NaHCO₃, the aqueous layer was extracted with CH₂Cl₂. The organic layers were combined and dried over MgSO₄. After filtration and concentration, the residue was purified by flash chromatography to afford the desired product.

13.2.1.1 Synthesis of the dibenzyl *N*-(1-methyl-2-oxo-2-phenylethyl)-*N,N'*-hydrazine-dicarboxylate **197**

Reference: Kobayashi, Shu; Yamashita, Y.; Ishitani, H. *Chem. Lett.* **1999**, 307-308



Prepared according general procedure with AgOTf (0.01 g, 0.04 mmol, 0.1 eq.) in 1 mL CH₂Cl₂, dibenzylazodicarboxylate (DBnAD) (0.140 g, 0.44 mmol, 1.1 eq.) in 0.5 mL CH₂Cl₂. Followed by the silyl enol ether **196** (0.083 g, 0.40 mmol, 1 eq.) in 0.5 mL CH₂Cl₂. 0 °C, 30 minutes. Purification by flash chromatography (AcOEt/petroleum ether: 1/3) afforded adduct **197**.

R.N.: [224427-76-3]

Physical aspect: white solid

M.F.: C₂₅H₂₄N₂O₅

M.W.: 432.47

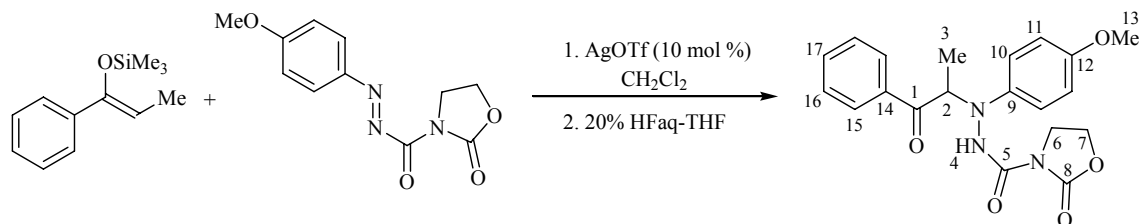
Yield: 0.148 g (86 %) (lit.: 84 %)

¹H NMR (500 MHz, DMSO, T = 70 °C)

Proton	δ (ppm)	Mult.	Integ.	J (Hz)
6	9.49	br s	1	/
18	7.94	d	2	³ J ₁₈₋₁₉ = 8.9
20	7.60	t	1	³ J ₂₀₋₁₉ = 7.3
19	7.46	t	2	³ J ₁₉₋₂₀ = 7.3
10-12, 14-16	7.2-7.4	m	10	/
2	5.62	q	1	³ J ₂₋₃ = 7.0
5, 8	5.08	br s	4	/
3	1.32	d	3	³ J ₃₋₂ = 7.0

¹³C NMR (125 MHz, DMSO, T = 70 °C) δ 196.7 (C¹), 156.1 (C⁷), 154.8 (C⁴), 136.1 (C⁹), 135.7 (C¹³), 135.0 (C¹⁷), 132.7 (C²⁰), 128.2 (C¹⁵), 128.0 (C¹¹), 128.0 (C¹⁸), 127.9 (C¹⁹), 127.5 (C¹²), 127.5 (C¹⁶), 127.2 (C¹⁰), 127.0 (C¹⁴), 67.0 (C⁵), 65.9 (C⁸), 57.7 (C²), 13.3 (C³) ppm

13.2.1.2 Synthesis of *N'*-(4-methoxyphenyl)-*N'*-(1-methyl-2-oxo-2-phenylethyl)-2-oxo-1,3-oxazolidine-3-carbohydrazide **204**



Prepared according to the general procedure with AgOTf (0.021 g, 0.08 mmol, 0.1 eq.) in 2.5 mL CH₂Cl₂, *p*-MeOC₆H₄ azo **168f** (0.22 g, 0.88 mmol, 1.1 eq.) in 3 mL CH₂Cl₂. Followed by the silyl enol ether **196** (0.166 g, 0.80 mmol, 1 eq.) in 2 mL CH₂Cl₂. Room temperature, 1 night.

Purification: Flash chromatography (AcOEt/cyclohexane: 2/1, AcOEt)

Rf: 0.71 (AcOEt)

Physical aspect: beige solid

M.F.: C₂₀H₂₁N₃O₅

M.W.: 383.4

Yield: 0.095 g (31 %)

HPLC: Chiralcel AD, *i*-PrOH/hexane (100/0), 0.5 mL/min., λ = 254 nm, T = 25°C, t_r = 17.25 min. and t_r = 22.66 min.

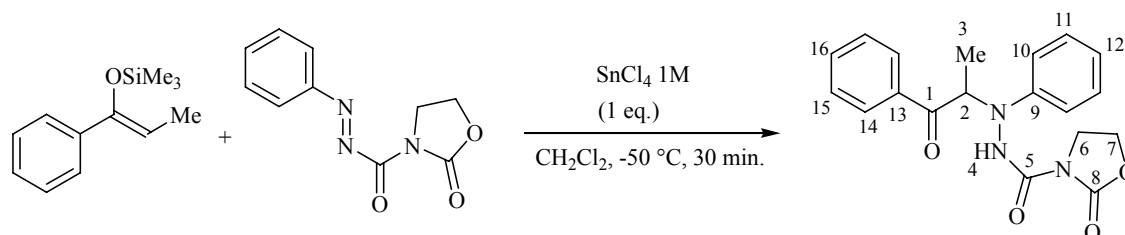
¹H NMR (200 MHz, CDCl₃, T = 25 °C)

Proton	δ (ppm)	Mult.	Integ.	J (Hz)
4	10.24	br s	1	/
15	7.99-7.95	mult	2	/
16, 17	7.61-7.45	m	3	/
10	6.92	mult	2	/
11	6.76	mult	2	/
2	5.52	q	1	³ J ₂₋₃ = 7.16
7	4.51	t	2	³ J ₇₋₆ = 8.1
6	4.13	t	2	³ J ₆₋₇ = 8.1
13	3.71	s	3	/
3	1.63	d	3	³ J ₃₋₂ = 7.16

¹³C NMR (50 MHz, CDCl₃, T = 25 °C) δ 187.0 (C¹), 155.5 (C⁵), 154.8 (C⁸), 152.7 (C¹²), 142.8 (C⁹), 135.0 (C¹⁴), 134.0 (C¹⁷), 129.1 (C¹⁵), 128.5 (C¹⁶), 121.3 (C¹¹), 114.7 (C¹⁰), 68.9 (C²), 63.0 (C⁷), 55.7 (C¹³), 42.8 (C⁶), 16.1 (C³) ppm

M.S. (C.I./CH₄-N₂O): 282 ([M+H-4-MeOC₆H₄]⁺, 5 %), 254 ([M+2H-CH₃O-C₆H₅CO]⁺, 40 %), 142 (C₄H₄NO₃NHNH₃⁺, 13 %)

13.2.2 Synthesis of *N'*-(1-methyl-2-oxo-2-phenylethyl)-2-oxo-*N'*-phenyl-1,3-oxazolidine-3-carbohydrazide **203**



In a round-bottom flask, dried and placed under argon atmosphere, azo compound **168a** (0.075 g, 0.34 mmol, 1 eq.) was dissolved in CH₂Cl₂ (0.7 mL), then enolsilane **196** (0.07 g, 0.34 mmol, 1 eq.) in CH₂Cl₂ (1 mL) was added *via* cannula. The mixture was cooled to -50 °C, and tin (IV) chloride (0.34 mL, 0.34 mmol, 1 eq., 1 M in CH₂Cl₂) was added. The mixture was allowed to react at this temperature during 30 minutes. The mixture was then diluted with CH₂Cl₂, and a saturated aqueous solution of NaHCO₃ was added. The aqueous layer was extracted with CH₂Cl₂ and the organic layers were combined. The organic layer was washed with an aqueous solution of NaHCO₃, brine, and dried over MgSO₄. After filtration and concentration, a crude solid was isolated.

Purification: flash chromatography (AcOEt/cyclohexane: 2/1, AcOEt)

Rf: 0.33 (AcOEt/cyclohexane: 2/1)

Physical aspect: white solid

M.P.: 155-157 °C

M.F.: C₁₉H₁₉N₃O₄

M.W.: 353.37

Yield: 0.076 g (63 %)

HPLC: Chiralcel AD, *i*-PrOH/hexane (20/80), 2 mL/min, λ = 254 nm, T = 25 °C, t_r = 19.1 min. and t_r = 29.3 min.

I.R. (KBr, cm⁻¹): 3320 (st NH), 2995, 2924, 1768 (st CO oxazolidinone), 1718 (st CO imide), 1685 (st CO aryl ketone), 1509 (C=C st in Arom.)

¹H NMR (300 MHz, CDCl₃, T = 25 °C)

Proton	δ (ppm)	Mult.	Integ.	J (Hz)
4	10.13	br s	1	/
14	7.99	d	2	³ J = 7.2
16	7.61	t	1	³ J = 7.5
15	7.50	t	2	³ J = 7.2
10	7.20	t	2	³ J = 7.8
11, 12	6.89	m	3	/
2	5.66	q	1	³ J ₂₋₃ = 7.2
7	4.52	t	2	³ J ₇₋₆ = 8.1

Proton	δ (ppm)	Mult.	Integ.	J (Hz)
6	4.13	t	2	$^3J_{6-7} = 8.1$
3	1.65	d	3	$^3J_{3-2} = 7.2$

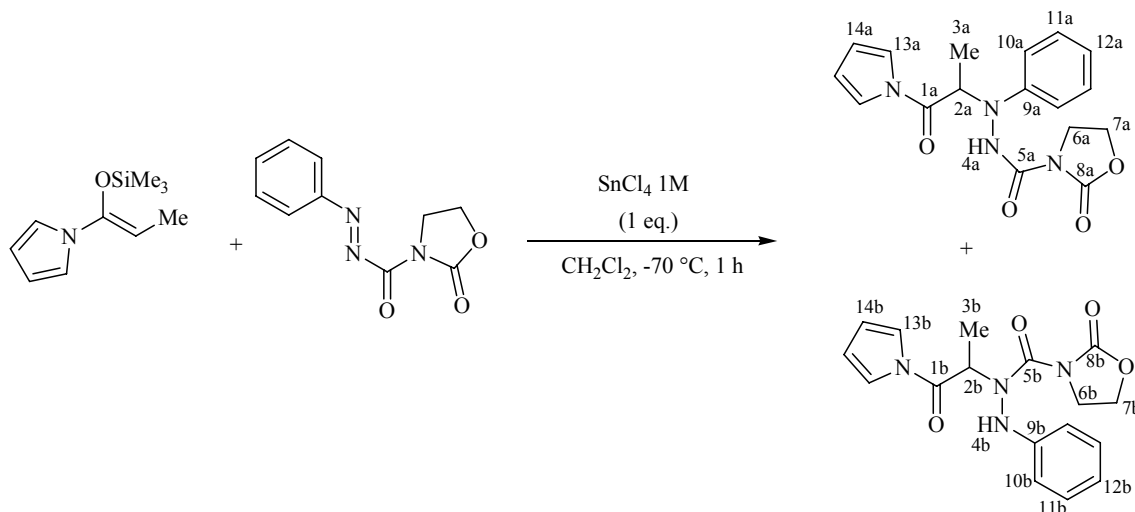
^{13}C NMR (50 MHz, CDCl_3 , T = 25 °C) δ 189.8 (C^1), 155.5 (C^5), 152.9 (C^8), 148.7 (C^9), 135.0 (C^{13}), 134.1 (C^{16}), 129.5 (C^{11}), 129.2 (C^{14}), 128.5 (C^{15}), 121.4 (C^{12}), 114.8 (C^{10}), 63.1 (C^2), 60.1 (C^7), 42.8 (C^6), 15.9 (C^3) ppm

M.S. (E.I.+Q1MS) : 353 (M^+ , 2 %), 248 ($[\text{M}-\text{C}_7\text{H}_5\text{O}]^+$, 20 %), 221 ($\text{C}_{10}\text{H}_{11}\text{N}_3\text{O}_3^+$, 100 %), 166 (56 %), 161 (100 %) 133 ($\text{C}_9\text{H}_9\text{O}^+$, 73 %), 105 (PhN_2^+ , 100 %), 77 (C_6H_5^+ , 100 %)

HRMS: Calculated for $\text{C}_{19}\text{H}_{20}\text{N}_3\text{O}_4$: 354.146545

Found: 354.145381

13.2.3 Synthesis of *N'*-[1-methyl-2-oxo-2-(1*H*-pyrrol-1-yl)ethyl]-2-oxo-*N'*-phenyl-1,3-oxazolidine-3-carbohydrazide **206a** and *N*-[1-methyl-2-oxo-2-(1*H*-pyrrol-1-yl)ethyl]-2-oxo-*N'*-phenyl-1,3-oxazolidine-3-carbohydrazide **206b**



In a round-bottom flask, dried and placed under argon atmosphere, azo compound **168a** (0.15 g, 0.68 mmol, 1 eq.) was dissolved in CH_2Cl_2 (1.4 mL), then enolsilane **199** (0.32 g, 0.72 mmol, 1.05 eq., 73 % purity) in CH_2Cl_2 (2 mL) was added *via* cannula. The mixture was cooled to $-70\text{ }^\circ\text{C}$, and tin (IV) chloride (0.68 mL, 0.68 mmol, 1 eq., 1 M in CH_2Cl_2) was added. The mixture was allowed to react at this temperature during 1 hour. The mixture was then diluted with CH_2Cl_2 , and a saturated aqueous solution of NaHCO_3 was added. The aqueous phase was extracted with CH_2Cl_2 and the organic layers were combined. The organic layer was washed with a aqueous solution of NaHCO_3 , brine, and dried over MgSO_4 . After filtration and concentration, a crude solid was isolated.

Purification: Purification by flash chromatography (AcOEt/cyclohexane: 1/1, then 3/1) afforded a mixture of two regioisomers **206a** and **206b** (59/41) which were not separated.

Rf: 0.46 (AcOEt/cyclohexane: 2/1)

Physical aspect: white solid

M.F.: C₁₇H₁₈N₄O₄

M.W.: 342.35

Yield: 0.13 g: 0.076 g **206a** (32 %)
0.054 g **206b** (23 %)

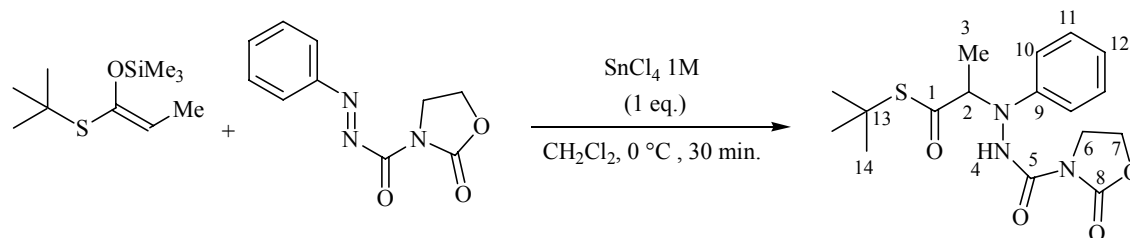
HPLC: Chiralcel AD, *i*-PrOH/hexane (20/80), 2 mL/min, λ = 254 nm, T = 25°C, t_r = 22.2 min. and t_r = 29.8 min. for **206a**

¹H NMR (200 MHz, CDCl₃, T = 25 °C)

Proton	δ (ppm)	Mult.	Integ.	J (Hz)
4a	10.14	br s	1	/
4b	9.33	br s	1	/
10a, 11a + 10b, 11b	7.35-7.16	m	4 + 4	/
12a, 13a + 12b, 13b	6.96-6.80	m	3 + 3	/
14a	6.34	t	2	$^3J_{14a-13a} = 2.2$
14b	6.20	t	2	$^3J_{14b-13b} = 2.1$
2a	5.30	q	1	$^3J_{2a-3a} = 7.0$
7a + 7b	4.56-4.46	m	2 + 2	/
2b	4.28	q	1	$^3J_{2b-3b} = 6.9$
6a + 6b	4.18-4.02	m	2 + 2	/
3a	1.73	d	3	$^3J_{3a-2a} = 7.2$
3b	1.54	d	3	$^3J_{3b-2b} = 6.9$

For the other spectrometric data, see at point 13.3.2.3.

13.2.4 Synthesis of the (*tert*-butyl)2-{2-[(2-oxo-1,3-oxazolidin-3-yl)carbonyl]-1-phenylhydrazino}propanethioate **205**



In a round-bottom flask, dried and placed under argon atmosphere, azo compound **168a** (0.1 g, 0.46 mmol, 1 eq.) was dissolved in CH₂Cl₂ (3 mL), then (*E*)-1-(*tert*-butylthio)-1-trimethylsilyloxyprop-1-ene **201** (0.20 g, 0.91 mmol, 2 eq., 73 % purity) in CH₂Cl₂ (2 mL) was added *via* a cannula. The mixture was cooled to 0 °C, and tin (IV) chloride (0.46 mL, 0.46 mmol, 1 eq., 1 M in CH₂Cl₂) was added. The mixture was allowed to react at this temperature during 30 minutes. The mixture was then diluted with CH₂Cl₂, and a saturated aqueous solution of NaHCO₃ was added. The aqueous layer was extracted with CH₂Cl₂ and the organic phases combined. The organic layer was washed with a aqueous solution of NaHCO₃, brine, and dried over MgSO₄. After filtration and concentration, a crude solid was isolated.

Purification: flash chromatography (AcOEt/cyclohexane: 1/1)

Rf: 0.70 (AcOEt)

Physical aspect: white solid

M.F.: C₁₇H₂₃N₃O₄S

M.W.: 365

Yield: 0.12 g (72 %)

¹H NMR (200 MHz, CDCl₃, T = 25 °C)

Proton	δ (ppm)	Mult.	Integ.
4	9.32	br s	1
11	7.17	d	2
10	6.81	d	2
12	5.90	br s	1
7	4.51	t	2
6	4.09	t	2
2	3.71	q	1
3	1.43	s	3
14	1.40	s	9

¹³C NMR (50 MHz, CDCl₃, T = 25 °C) δ 190.3 (C¹), 156.1 (C⁵), 153.2 (C⁸), 147.5 (C⁹), 129.3 (C¹¹), 114.4 (C¹⁰), 63.8 (C⁷), 54.5 (C²), 48.5 (C¹³), 43.1 (C⁶), 30.4 (C¹⁴), 19.2 (C³) ppm

M.S. (C.I./CH₄-N₂O): 394 ([M+C₂H₅]⁺, 4 %), 367 (M⁺ (³⁴S), 10 %), 366 (M⁺ (³³S), 31 %), 365 (M⁺ (³²S), 26 %), 276 ([M (³²S)-C₄H₉S]⁺, 7 %), 248 ([M (³²S)-C₄H₉SCO]⁺, 76 %), 205 ([M (³³S)-C₄H₉S-C₆H₅]⁺, 21 %)

13.3 Catalytic asymmetric electrophilic amination reactions of silyl enols ethers

13.3.1 Preparation of 2,2,2-Trichloroethyl {[(2-oxo-1,3-oxazolidin-3-yl)carbonyl] diazenyl} formate **198**

13.3.1.1 Synthesis of trichloroethyl carbazate **219**

Reference: Johnson, D. S. and Evans, D. A. *Org. Lett.* **1999**, *1*, 595-598



To a mixture of hydrazine (1 M solution in THF) (3.1 mL, 63.1 mmol, 2.9 eq.) in CHCl₃ (200 mL) cooled to -10 °C was added trichloroethylchloroformate (3.06 mL, 21.8 mmol, 1 eq.) as a solution in CHCl₃ (30 mL) via an addition funnel over 2 hours. A white precipitate formed as each drop was added. After the addition was complete, H₂O (80 mL) was added and the precipitate dissolved. The aqueous layer was acidified with 10 % aqueous HCl (40 mL) and the layers were separated. The organic layer was washed with 10 % aqueous HCl. The

organic layer contained diacylated material. The combined aqueous layers were neutralised with solid NaHCO_3 and extracted with CHCl_3 several times. The organic layer was washed with saturated aqueous NaHCO_3 and brine, dried over MgSO_4 and concentrated to give **219**. The yellow oil was engaged without any further purification.

R.N.: [31434-96-5]

Physical aspect: yellow oil

M.F.: $\text{C}_3\text{H}_5\text{N}_2\text{O}_2\text{Cl}_3$

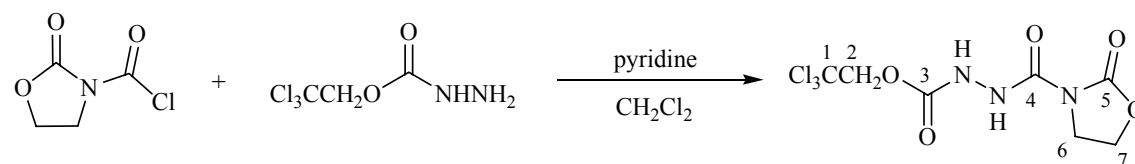
M.W.: 207.44

Yield: 3.84 g (85 %) (lit.: 82 %)

^1H NMR (200 MHz, CDCl_3 , $T = 25\text{ }^\circ\text{C}$) δ 6.74 (br s, 1H, NH), 4.79 (s, 2H, CH_2), 3.88 (br s, 2H, NH_2) ppm

13.3.1.2 Synthesis of the (2-oxo(1,3-oxazolidin-3-yl))-N-[(2,2,2-trichloroethoxy)carbonylamino]carboxamide **220**

Reference: Johnson, D. S. and Evans, D. A. *Org. Lett.* **1999**, 1, 595-598



To a solution of trichloroethyl carbazate **219** (2.85 g, 13.05 mmol, 1.05 eq.) in CH_2Cl_2 (20 mL) cooled to $0\text{ }^\circ\text{C}$ was added pyridine (1.06 mL, 13.05 mmol, 1.05 eq.). 2-Oxo-1,3-oxazolidine-3-carbonyl chloride **171b** (1.86 g, 12.43 mmol, 1 eq.) was added as a solution in CH_2Cl_2 (10 mL) *via* cannula. The reaction was allowed to warm to room temperature and stir for 2 hours. The mixture was diluted with CH_2Cl_2 and poured into H_2O . The layers were separated and the aqueous layer was extracted with CH_2Cl_2 . The combined organic layers were washed with 5 % aqueous HCl , H_2O and brine, dried over MgSO_4 , and concentrated to give the hydrazide.

Purification: Recrystallization in CH_2Cl_2

R.N.: [244091-07-4]

Physical aspect: white solid

M.F.: $\text{C}_7\text{H}_8\text{N}_3\text{O}_5\text{Cl}_3$

M.W.: 320.51

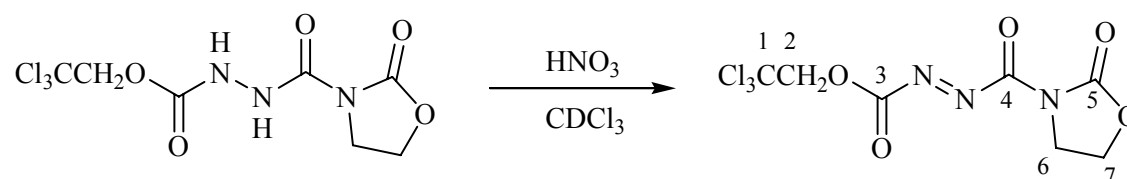
Yield: 3.7 g (93 %) (lit.: 96 % after a column chromatography)

^1H NMR (300 MHz, CDCl_3 , T = 25 °C) δ 9.37 (br s, 1H, $\text{Cl}_3\text{CCH}_2\text{ONH}$), 6.76 (s, 1H, NHCO(oxaz)), 4.80 (s, 2H, $\text{Cl}_3\text{CCH}_2\text{O}$), 4.52 (t, 2H, OCH_2 , $^3J = 8$ Hz), 4.10 (t, 2H, NCH_2 , $^3J = 8$ Hz) ppm

^{13}C NMR (75 MHz, CDCl_3 , T = 25 °C) δ 155.2 (C^4), 154.5 (C^3), 152.0 (C^5), 94.7 (C^1), 75.1 (C^2), 63.2 (C^7), 42.4 (C^6) ppm

13.3.1.3 Synthesis of 2,2,2-Trichloroethyl {[[(2-oxo-1,3-oxazolidin-3-yl)carbonyl]diazenyl}formate **198**

Reference: Johnson, D. S. and Evans, D. A. *Org. Lett.* **1999**, *1*, 595-598



To a solution of hydrazide (2.5 g, 7.80 mmol, 1 eq.) in 40 mL CDCl_3 * cooled to 0 °C was added fuming nitric acid (90 %) (2.18 mL, 46.80 mmol, 6 eq.) via an addition funnel. The reaction was stirred at 0 °C for 2 hours and then warmed to room temperature for approximately 8 hours. The reaction started to turn orange as it was warmed to room temperature and after about 4 hours the flask was filled with an orange gas. The mixture was poured into ice. The layers were separated and the aqueous layer was extracted with CHCl_3 . The organic layer was washed with saturated aqueous NaHCO_3 , H_2O (2X), and brine, dried over MgSO_4 , and concentrated to give an orange oil which solidified *in vacuo*.

* alternatively, CHCl_3 washed with H_2O , dried over CaCl_2 and distilled to remove EtOH stabilizer can be used.

Purification: Recrystallisation from CH_2Cl_2 /hexane

R.N.: [244091-10-9]

Physical aspect: orange solid

M.F.: $\text{C}_7\text{H}_6\text{N}_3\text{O}_5\text{Cl}_3$

M.W.: 318.50

Yield: 1.08 g (43.5 %) (lit.: 72 % in CHCl_3)

^1H NMR (200 MHz, CDCl_3 , T = 25 °C) δ 5.06 (s, 2H, $\text{Cl}_3\text{CCH}_2\text{O}$), 4.64 (t, 2H, $^3J = 8.1$ Hz, OCH_2), 4.24 (t, 2H, $^3J = 8.1$ Hz, NCH_2) ppm

^{13}C NMR (50 MHz, CDCl_3 , T = 25 °C) δ 159.6 (C^4), 158.3 (C^3), 151.5 (C^5), 93.5 (C^1), 77.0 (C^2), 63.7 (C^7), 42.6 (C^6) ppm

13.3.2 Catalytic asymmetric amination reaction

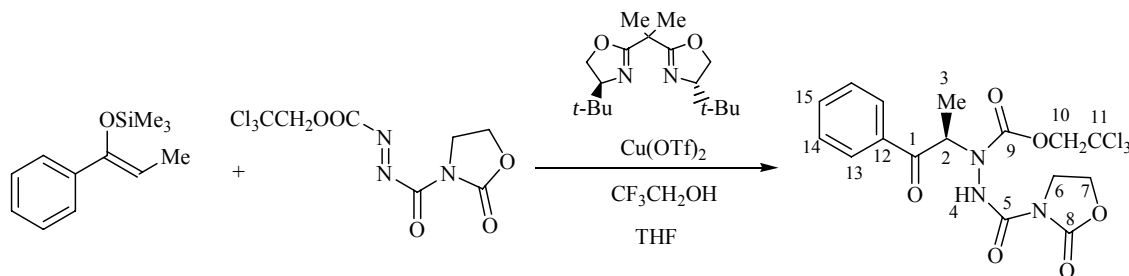
General procedure

In an oven-dried schlenk, equipped with magnetic stirring bar and a septum, placed under argon atmosphere, Cu(OTf)₂, (S,S)-*tert*-Bu-box and THF were added. The green solution was stirred during 2 hours at room temperature.

In a round bottom flask, equipped with a magnetic stirring bar and a septum, dried and placed under argon atmosphere, the azo compound and THF were added. The catalyst solution was added to this mixture cooled to -78°C via a cannula, followed by trifluoroethanol and the enolsilane. The reacting mixture was stirred during the time and temperature required. The mixture was then diluted with CH₂Cl₂, and a saturated aqueous solution of NaHCO₃ was added. The aqueous layer was extracted with CH₂Cl₂ and the organic layers were combined. The organic layer was washed with an aqueous solution of NaHCO₃, brine, and dried over MgSO₄.

13.3.2.1 Synthesis of *N*-((1*R*)-1-methyl-2-oxo-2-phenylethyl)-*N*-[(2-oxo(1,3-oxazolidin-3-yl))carbonylamino](2,2,2-trichloroethoxy)carboxamide **221**

Reference: Johnson, D. S. and Evans, D. A. *Org. Lett.* **1999**, *1*, 595-598



Prepared according to the general procedure with: Cu(OTf)₂ (0.018 g, 0.050 mmol, 0.1 eq.), (S, S)-*tert*-Bu-box (0.015 g, 0.050 mmol, 0.1 eq.) and 1.5 mL THF. Azo compound **198** (0.160 g, 0.502 mmol, 1 eq.) in 1 mL THF, trifluoroethanol (0.036 mL, 0.502 mmol, 1 eq.) and enolsilane **196** (0.155 g, 0.754 mmol, 1.5 eq.). 1 hour at -78°C .

Purification: Flash chromatography (AcOEt/hexane: 1/1)

R.N.: [244091-24-5]

Physical aspect: white solid

M.F.: C₁₆H₁₆N₃O₆Cl₃

M.W.: 452.67

Yield: 0.212 g (93 %) (lit.: 95 %)

¹H NMR (200 MHz, CDCl₃, T = 25 °C)

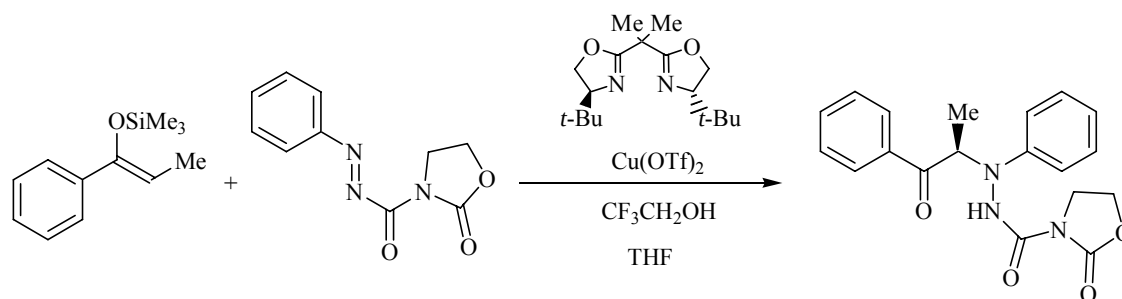
Proton	δ (ppm)	Mult.	Integ.	J (Hz)
4	9.76	br d	1	/
13	7.96	mult	2	/
14, 15	7.53	m	3	/

Proton	δ (ppm)	Mult.	Integ.	J (Hz)
2	5.89	q	1	$^3J_{2-3} = 7.3$
10	4.75	mult	2	/
7	4.50	br t	2	$^3J_{7-6} = 8.1$
6	4.07	br t	2	$^3J_{6-7} = 8.1$
3	1.54	d	3	$^3J_{3-2} = 7.3$

^{13}C NMR (50 MHz, CDCl_3 , T = 25 °C) δ 198.7 (C^1), 155.1 (C^5), 154.1 (C^8), 152.1 (C^9), 134.5 (C^{12}), 133.8 (C^{15}), 128.9 (C^{13}), 128.6 (C^{14}), 94.8 (C^{11}), 75.7 (C^{10}), 63.0 (C^7), 58.4 (C^2), 42.5 (C^6), 14.5 (C^3) ppm

e.e.: 99 % (Chiralcel AD column, 20% *i*-PrOH/hexane, 1 mL/min., 254 nm, $t_{\text{r (maj)}}$ = 26.7 min., $t_{\text{r (min)}}$: not seen (normally: 36 min.)

13.3.2.2 Synthesis of (-)-*N'*-((1*R*)-1-methyl-2-oxo-2-phenylethyl)-2-oxo-*N'*-phenyl-1,3-oxazolidine-3-carbohydrazide **203**



Prepared according to the general procedure with: $\text{Cu}(\text{OTf})_2$ (0.019 g, 0.054 mmol, 0.1 eq.), (*S,S*)-*tert*-Bu-box (0.019 g, 0.064 mmol, 0.12 eq.) and 1.0 mL THF. Azo compound **168a** (0.12 g, 0.54 mmol, 1 eq.) in 1 mL THF, trifluoroethanol (0.039 mL, 0.54 mmol, 1 eq.) and enolsilane **196** (0.17 g, 0.80 mmol, 1.5 eq.). 1 hour at -78°C .

Purification: Flash chromatography (AcOEt/hexane: 1/1), followed by recrystallization from AcOEt/hexane

Rf: 0.33 (AcOEt/cyclohexane: 2/1)

Physical aspect: beige crystals

M.P.: 155-157 °C

M.F.: $\text{C}_{19}\text{H}_{19}\text{N}_3\text{O}_4$

M.W.: 353.37

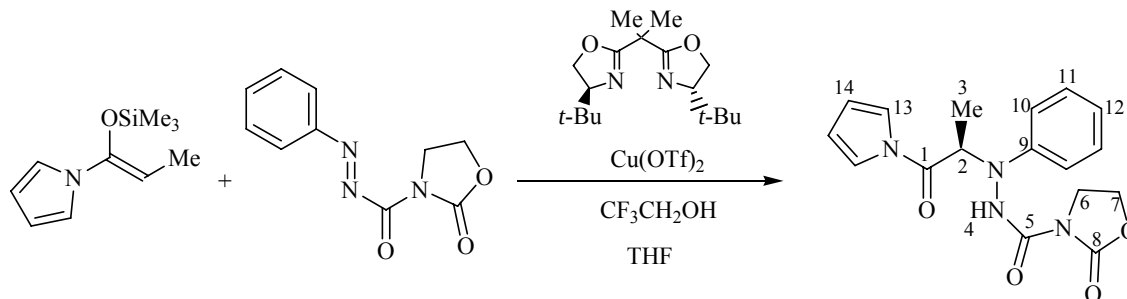
Yield: 0.17 g (89 %)

e.e. > 99.5 % (Chiralcel AD, *i*-PrOH/hexane (20/80), 2 mL/min, $\lambda = 254$ nm, T = 25°C, $t_{\text{r (maj.)}}$ = 19.6 min. and $t_{\text{r (min.)}}$ = 28.5 min.)

$[\alpha]_{\text{D}}$ = -70.1° ($c=0.16$, CHCl_3)

The spectroscopic and spectrometric data are described for the thermal reaction.

13.3.2.3 Synthesis of (-)-N'-[(1R)-1-methyl-2-oxo-2-(1H-pyrrol-1-yl)ethyl]-2-oxo-N'-phenyl-1,3-oxazolidine-3-carbohydrazide **206a**



Prepared according to the general procedure with: Cu(OTf)₂ (0.019 g, 0.054 mmol, 0.1 eq.), (*S, S*)-*tert*-Bu-box (0.019 g, 0.064 mmol, 0.12 eq.) and 1.0 mL THF. Azo compound **168a** (0.12 g, 0.54 mmol, 1 eq.) in 1 mL THF, trifluoroethanol (0.039 mL, 0.54 mmol, 1 eq.) and enolsilane **199** (0.36 g, 0.80 mmol, 1.5 eq., 73 % purity). The reacting mixture was allowed to warm to room temperature and maintained 2 h 30 under agitation.

Purification: Flash chromatography (AcOEt/hexane: 2/1)

Rf: 0.33 (AcOEt/cyclohexane: 2/1)

Physical aspect: white solid

M.F.: C₁₇H₁₈N₄O₄

M.W.: 342.35

Yield: 0.165 g (90 %)

I.R. (KBr, cm⁻¹): 3296 (st NH), 2988, 2924, 1762 (CO oxazolidinone), 1714 (CO imide), 1599, 1513, 1470, 1278

¹H NMR (200 MHz, CDCl₃, T = 25 °C)

Proton	δ (ppm)	Mult.	Integ.	J (Hz)
4	10.14	br s	1	/
10, 11	7.35-7.21	m	4	/
12, 13	6.92	m	3	/
14	6.34	t	2	³ J ₁₄₋₁₃ = 2.1
2	5.30	q	1	³ J ₂₋₃ = 7.2
7	4.53	dd	2	³ J ₇₋₆ = 8.2, ³ J _{7-7'} = 0.9
6	4.14	dd	2	³ J ₆₋₇ = 8.7, ³ J _{6-6'} = 1.2
3	1.73	d	3	³ J ₃₋₂ = 7.1

¹³C NMR (50 MHz, CDCl₃, T = 25 °C) δ 171.5 (C¹), 155.8 (C⁵), 152.7 (C⁸), 148.2 (C⁹), 129.7 (C¹¹), 122.0 (C¹²), 119.2 (C¹³), 115.1 (C¹⁰), 114.2 (C¹⁴), 63.1 (C⁷), 58.1 (C²), 42.8 (C⁶), 16.2 (C³) ppm

M.S. (C.I./CH₄-N₂O): 343 ([M+H]⁺, 53 %), 342 (M⁺, 5 %), 276 ([M-C₄H₄N]⁺, 4 %), 248 ([M-C₄H₄NCO+H]⁺, 57 %), 233 ([M-C₄H₄NO₃]⁺, 20 %), 205 ([M-C₄H₄N-C₆H₅]⁺, 12 %)

E.A. :

Element	% calculated	% found	Δ
C	59.64	59.18	0.46
H	5.30	5.37	0.07
N	16.36	15.92	0.44

e.e. 96 % (Chiralcel AD, *i*-PrOH/hexane (20/80), 2 mL/min, λ = 254 nm, T = 25 °C, t_r (maj.) = 21.7 min. and t_r (min.) = 29.3 min.)

[α]_D = -141.7 ° (c=0.12, CHCl₃)